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An evaluation of continuous-flow left ventricular assist devices and the incidence of stroke in patients awaiting heart transplantation

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SCHOOL OF MEDICINE

Thesis

**AN EVALUATION OF CONTINUOUS-FLOW LEFT VENTRICULAR ASSIST
DEVICES AND THE INCIDENCE OF STROKE IN PATIENTS AWAITING
HEART TRANSPLANTATION**

by

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B.S., Stonehill College, 2013

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ABSTRACT

Continuous-flow left ventricular assist devices provide mechanical circulatory assistance for patients suffering from end-stage heart failure that are awaiting or ineligible for heart transplantation. Although actuarial survival and quality of life with these devices is comparable to allograft transplant, they are associated with severe adverse events, including cerebrovascular accidents. Recent advances in continuous-flow technology aim to mitigate the risk of stroke by including design features that minimize flow stasis, turbulence and endothelial dysfunction, as well as promote near-normal pulse pressures. The proposed study is a multicenter, prospective, randomized clinical trial that aims to compare the stroke-free survival and associated incidence and risk of cerebrovascular accidents between three continuous-flow left ventricular assist devices in patients with refractory, end-stage heart failure planning to undergo bridge-to-transplant or destination therapy. Patients will be randomized to receive one of three devices (HeartMate II, Thoratec Corporation, Pleasanton, CA; HeartWare HVAD, HeartWare International Inc., Framingham, MA; HeartMate III, Thoratec Corporation, Pleasanton, CA). Patients will be monitored for stroke-free survival and incidence of cerebrovascular accident for 24 months post-implantation. Investigators will compare stroke-free survival with Kaplan-Meier survival curves and log-rank testing; in addition, investigators will

examine each device's level of risk for causing a cerebrovascular accident with chi square and odds ratio analysis. The data from this study will be used to guide treatment paradigms, device assignment and future development of technologies that mitigate stroke risk in this high-risk population.

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LIST OF ABBREVIATIONS

ACCF	American College of Cardiology Foundation
ACE-I	Angiotensin Converting Enzyme Inhibitor
ADVANCE	Evaluation of HeartWare Left Ventricular Assist Device for Treatment of Advanced Heart Failure
AHA	American Heart Association
ARB	Angiotensin Receptor Blocker
AvWS	Acquired von Willebrand Syndrome
BNP	Brain Natriuretic Peptide
BSA	Body Surface Area
BTC	Bridge-to-Candidacy
BTR	Bridge-to-Recovery
BTT	Bridge-to-Transplant
CE Mark	Conformite Europeen Mark
CF-LVAD	Continuous-Flow Left Ventricular Assist Device
CHF	Congestive Heart Failure
CVA	Cerebrovascular Accident
DT	Destination Therapy
ENDURANCE	A Clinical Trial to Evaluate HeartWare Ventricular Assist Device
ESHF	End-Stage Heart Failure
FDA	Food and Drug Administration
HF	Heart Failure

HFSS	Heart Failure Survival Score
HITs	High Intensity Signal
ICD	Implantable Cardiac Defibrillator
INR	International Normalized Ratio
INTERMACS	Interagency Registry for Mechanical Assist Devices Classification System
IP	Implanted Pneumatic
ISHLT	International Society for Heart & Lung Transplantation
LVAD	Left Ventricular Assist Device
MAP	Mean Arterial Pressure
MCS	Mechanical Circulatory Support
MELDS	Model for End-Stage Liver Disease Score
MES	Microembolic Signal
MOMENTUM 3	Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with the HeartMate 3
NHLBI	National Heart, Lung and Blood Institute
NIH	National Institute of Health
NYHA	New York Heart Association
OPTN	Organ Procurement and Transplantation Network
PCWP	Pulmonary Capillary Wedge Pressure
REMATCH	Randomized Evaluation of Mechanical Assistance for Treatment of Congestive Heart Failure

SHFM	Seattle Heart Failure Model
TCD	Transcranial Doppler
TIA	Transient Ischemic Attack
VAD	Ventricular Assist Device
VE	Vented Electric
vWF	von Willebrand Factor

INTRODUCTION

Background

Congestive heart failure (CHF) affects nearly 6 million people over the age of 20 in this country. The National Heart, Lung and Blood Institute (NHLBI) estimates 870,000 cases are diagnosed every year. The prevalence of heart failure (HF) in the United States across all age groups is forecast to rise at an unprecedented rate due in part to the growing obesity epidemic and aging population. Patients with the severest level of disease per the New York Heart Association (NYHA) Functional Classification System for Heart Failure, tiered by degree of symptomology and functional impairment, face the direst outcomes. For patients classified as NYHA IIIb/IV, or end-stage heart failure (ESHF), medical management alone may only provide temporary benefit. Heart transplantation is the definitive treatment for ESHF in patients whose course is refractory to medical and nonsurgical management.

The Organ Procurement and Transplantation Network (OPTN), of the U.S. Department of Health and Human Services, reports 4,164 candidates currently wait on the list for cardiac transplant. In contrast, the OPTN notes 2,804 heart transplantations were performed in 2015, and only 246 transplants were completed through April 2016. Heart transplants are designated for those who meet strict eligibility criteria. Moreover, the donor pool for cardiac transplants lags behind the need for organs; the obvious discrepancy between supply and demand for cardiac allografts has left some ESHF patients wanting, and unfortunately, unlikely to receive a life-saving heart.

Since the 1960s, mechanical circulatory support (MCS) devices have provided exogenous means of sustaining cardiac output in failing hearts. Companies have extensively invested into the development of ventricular assist devices (VADs), which are implantable mechanisms that replace native heart function. In 2001, the Randomized Evaluation of Mechanical Assistance for Treatment of Congestive Heart Failure (REMATCH) trial demonstrated that a first-generation left ventricular assist device (LVAD) had significant survival benefit at 2 years compared to medical therapy in ESHF patients ineligible for transplant. The REMATCH results beautifully illustrated the concept of destination therapy for this population. Destination therapy (DT) refers to the use of a MCS system, typically a LVAD, for long-term cardiac support for those ineligible for transplant. The REMATCH trial established DT as a FDA-approved treatment for ESHF patients contraindicated for transplantation.

LVADs are not without their risks; first-generation LVADs were notable for high rates of infection, bleeding, as well as a high likelihood for device failure necessitating replacement within 2 years after implantation. In addition, these initial devices demonstrated significant rates of cerebrovascular accidents (CVAs). The development of second-generation LVADs, described as continuous-flow mechanisms (CF-LVADs), brought about a new age in MCS technology. Second-generation LVADs utilize rotary pump mechanisms that provide linear blood flow at a constant pressure; these models are also smaller in design, more durable and have a decreased incidence of adverse events. However, the overall incidence of stroke was not significantly different from previous models. Third-generation CF-LVADs utilize centrifugal rotary systems to spin blood

tangentially via magnetic or hydrodynamically levitated impellers and have the potential for reduced risk of thrombus formation. Advanced-third generation CF-LVADs, which combine centrifugal rotary mechanisms based on magnetic levitation technology with programmed pulsatile settings, are the newest models on the VAD market. Although the use of CF-LVADs has demonstrated an overall reduction in adverse events, morbidity due to ischemic and hemorrhagic stroke remains a serious complication in this group.

Statement of the Problem

As DT becomes more prevalent for ESHF patients ineligible for transplant, CF-LVADs promise higher long-term functional status and overall improved quality of life. The success of CF-LVADs regarding device durability and survival has spurred research aiming to further reduce adverse outcomes, such as bleeding, thromboembolism, and ultimately, stroke. Multiple studies have indicated that patients with CF-LVADs have alterations in their coagulation and hemostatic pathways.¹ Such abnormalities relate to an intrinsic coagulopathy secondary to the device itself, leading to hypercoagulability, fibrinolysis and platelet dysfunction.² To complicate management further, CF-LVADs require long-term anticoagulation therapy, which predisposes patients to hemorrhage. Optimum anticoagulation protocols suffer inter-facility and inter-patient variability.^{2,3} By understanding the physiologic effects of rotary pump systems companies can develop technologies that decrease the inherent mechanical factors that place individuals at higher-risk for stroke.

Sparse data is available comparing advanced third-generation CF-LVADs to previous second-generation or third-generation devices, specifically in regards to rates of ischemic and hemorrhagic stroke.

Hypothesis

An advanced third-generation CF-LVAD, the HeartMate III (Thoratec Corporation, Pleasanton, CA), will have greater stroke-free survival and lower associated incidence of stroke compared with a second-generation (HeartMate II, Thoratec Corporation, Pleasanton, CA) or third-generation CF-LVAD (HeartWare HVAD, HeartWare International Inc., Framingham, MA).

Objectives and specific aims

Since the REMATCH trial in 2001, advances in long-term MCS technologies have allowed ESHF patients a higher quality of life without transplant. Destination therapy with CF-LVADs may supplement the increasing need for donor hearts. However, patients with long-term use of CF-LVADs are at elevated risk for adverse outcomes, including stroke. Cerebrovascular accidents in this population are associated with increased morbidity and mortality, and decreased likelihood of receiving a transplant.^{4,5} This study proposes to further explore the association between individual continuous-flow devices and stroke by comparing stroke-free survival across three device cohorts through a prospective randomized clinical trial. Additional aims of this proposed study include:

- To determine a strength of association between each device mechanism and stroke
- To compare the overall incidence of cerebrovascular accidents in three CF-LVAD models
- To examine the odds ratio for stroke in three different CF-LVAD models
- To characterize stroke type in three CF-LVAD models

REVIEW OF THE LITERATURE

Overview of Mechanical Circulatory Support

Estimates based off of population growth indicate that by the year 2030, the total number of CHF cases is expected to increase by 46% in the United States. By that same year, more than 8 million patients will be diagnosed with HF. Heart failure is most common amongst the elderly, and by 2050, approximately 20% of the population will be greater than 65 years of age.⁶ The total direct cost of HF will rise 3-fold over the next fifteen years, increasing to approximately \$160 billion dollars annually, assuming a continued rate of inflation for medical care.⁷ Although treatment paradigms have improved over time, current overall 5-year mortality rates from the time of diagnosis approach 50%; moderate to severe HF patients suffer worse outcomes, with 1-year mortality rates remaining as high as 20-50%.^{6,8}

Per the 2013 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Guideline for Heart Failure Management, HF is a clinical syndrome caused by any disorder effecting cardiac structure or function, and hallmarked typically by left ventricular myocardial dysfunction.⁶ More common causes of HF are ischemic heart disease, uncontrolled hypertension and diabetes mellitus, as well as various cardiomyopathies, myocarditis, toxins, untreated arrhythmias or valvular disease.⁹ Physiologic compensatory processes, namely volume expansion and neurohormonal activation, aim to increase the rate of blood flow at the expense of elevated filling pressures within the heart.¹⁰ Hypertrophic factors, i.e. mechanical strain, angiotensin, cytokines and oxidative stress, caused or released by the compensatory

mechanisms lead to myocardial changes known as maladaptive compensation.¹¹

Ultimately, mechanical and biochemical maladaptive processes lead to pathologic cardiac remodeling, further decreasing cardiac function.

Symptoms of HF directly result from the maladaptive physiologic processes at play: volume expansion and neurohormonal activation.¹⁰ These processes directly affect fluid shifts in the intravascular space, leading to fluid retention. As a result, the patient may complain of dyspnea, fatigue, angina, palpitations and/or peripheral edema which may culminate into exercise intolerance.^{6,8} Since HF is a clinical diagnosis, the patient's symptomology and level of function compared to baseline are critical in staging the severity of the disease.

The NYHA Functional Classification System for Heart Failure was first used to describe symptomatic functional impairment secondary to HF in 1928. For decades, researchers have used this system to subjectively differentiate and track patients' disease process based on functional capacity.¹² The NYHA classification system can readily discern between mild and severe cases of HF, but does not definitively distinguish moderate and advanced-staged disease.¹² The ACCF/AHA Stages of HF also describes the progression of disease, but incorporates important goals of care based on the severity of the patients' HF.⁶ Table 1 compares the ACCF/AHA staging and NYHA classification system. Where the NYHA system depicts the spectrum of disease, the ACCF/AHA stages provide a definitive separation between potentially reversible HF and advanced HF requiring more invasive therapy.

Table 1. Comparison of ACCF/AHA Stages of Heart Failure and NYHA Functional Classification System for Heart Failure.

ACCF/AHA Stages of Heart Failure		NYHA Functional Classification System	
A	-At high risk for HF, no structural heart disease or symptoms -Modify Risk Factors	None	---
B	-Structural heart disease, w/o symptoms -Treat structural disease	I	No functional limitation; ordinary ADLs cause no HF symptoms
C	-Structural heart disease, w/ prior or current symptoms -Reduce morbidity and mortality	I	No functional limitation; ordinary ADLs cause no HF symptoms
		II	Slight functional limitation; comfortable at rest; ADLs cause symptoms of HF
		IIIa/b	Marked functional limitation; comfortable at rest; ADLs cause symptoms of HF
		IV	Severe functional limitation; symptoms occur at rest
D	-Refractory HF -Invasive interventions to reduce morbidity and mortality	IV	Severe functional limitation; HF symptoms occur at rest

ACCF (American College of Cardiology Foundation); AHA (American Heart Association); ADL (activities of daily living); HF (heart failure); IIIa/b (continuum of disease, with 'b' representing more severe HF); Adapted from Yancy CW, Jessup M, Bozkurt B, et al. 2013

Medical management in HF begins by identifying patients with critical risk factors: hypertension, diabetes mellitus, metabolic syndrome and atherosclerotic disease. Patients with ACCF/AHA Stage A or B disease will receive a wide range of medications that target these predisposing factors. Angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), statins and beta blockers, as well as satisfactory

glycemic control are recommended for mild to moderate HF. Serial evaluations of volume status – weight, jugular venous pressure, and peripheral edema – as well as serial echocardiographic imaging assess and plot cardiac function. As patients suffer worsening HF, Stage C disease or NYHA II-III, they may require an implantable cardiac defibrillator (ICD), stringent diet and sodium restriction, diuretics, nitrates and/or aldosterone antagonists to maintain desired blood pressures. In addition, patients with comorbid arrhythmias or ischemic disease may require some combination of revascularization, antithrombotic therapy, anti-arrhythmic medication, pacemaker/defibrillator implantation, or cardioversion.⁶

Stage D HF describes patients with advanced or end-stage disease whose course may be refractory to previous medical and invasive management. Patients may exhibit NYHA III or IV symptoms, have reduced ejection fraction (EF) below 30%, elevated pulmonary capillary wedge pressures (PCWP), and severely impaired functional capacity with multiple hospitalizations within 6 months.⁶ Appendix I contains a complete definition of advanced heart failure. ESHF patients may be candidates for specialized treatments, including continuous IV inotropic support, short or long-term MCS or cardiac transplantation. Heart transplant is considered the definitive, gold standard treatment for ESHF, capable of reversing the progression of disease.^{6,13}

It is crucial to rule out other etiologies for refractory HF, including malignancy, concomitant pulmonary disease, toxins, reversible ischemic disease or noncompliance when evaluating patients for more intensive therapies. Table 2 lists major selection criteria and indications for cardiac transplant.

Table 2. Selection Criteria for Cardiac Transplantation.

Absolute Indications	Relative Indications	Insufficient Indications
-Hemodynamic compromise <ul style="list-style-type: none"> - Refractory cardiogenic shock - Documented IV inotropic support dependence - Peak $V_{O_2} < 10$ ml/kg/min -Severe ischemic symptoms at rest not amendable to revascularization -Recurrent, refractory and symptomatic ventricular arrhythmias	-Peak V_{O_2} 11-14 ml/kg/min (55% of predicted) with marked ADL limitation -Recurrent unstable ischemia not amendable to interventions -Recurrent fluid imbalance or renal dysfunction not due to medical non-compliance	-Low left ventricular ejection fraction -History of NYHA III or IV symptoms alone -Peak $V_{O_2} > 15$ ml/kg/min (greater 55% of predicted) in the absence of other indications

ADL (activities of daily living); Peak V_{O_2} (peak volume of oxygen); Adapted from Friedrich EB, Böhm M. et al., 2007

Although cardiac transplant has been found to improve exercise capacity, quality of life and survival compared to established therapies, not every ESHF patient is a likely candidate for the operation.⁸ Patients who are greater than 70 years old, those who have severe systemic (i.e. neoplastic) disease or advanced comorbidities or are morbidly obese have poor outcomes following transplant. Untreated psychiatric disease, mental retardation or poor social support are also considered relative contraindications.¹⁴

Appendix II provides a complete list of contraindications for heart transplant. Stringent eligibility criteria, in conjunction with a national shortage of available donor hearts, leave

many critically ill ESHF patients without the chance for a life-saving organ. For this underserved population, advances in medical technology may provide the heart they so desperately require.

In 1963, the first MCS system was implanted in a post-cardiotomy cardiac shock patient to provide exogenous circulatory assistance.¹⁵ The era of MCS was born out of federal research interest in developing short and long-term cardiac assistance modalities that could mitigate the high death rates on the transplant list and long wait times for donor identification.¹⁶ By 1978, the first LVAD was used as a temporary intervention to prepare a patient for cardiac transplant. By the 1990s, first-generation LVADs, utilizing volume displacement technologies, were introduced to clinical practice. Although these devices improved survival in ESHF patients, they were larger, bulkier and suffered severe adverse events, including thrombosis and device failure.¹⁶ Current devices utilize variations of rotary mechanisms, which propel blood at a near-constant pressure. These machines are smaller and allow increased survival with less adverse events. Future development will focus on device durability and biocompatibility.¹⁷ Increased survival with these mechanisms provides promise for ESHF patients ineligible for transplant.

MCS systems, in particular LVADs, have been designated for one of four device strategies: bridge-to-recovery (BTR), bridge-to-candidacy (BTC), bridge-to-transplant (BTT) and destination therapy (DT). Table 3 compares the goals of each treatment paradigm. The latter two strategies are critical to ESHF patients in the modern era of MCS utilization, as evidence has indicated improved survival while awaiting transplant.^{16,18}

Table 3. Mechanical Circulatory Support (MCS) Device Strategies

Device Strategy	Definition	Percentage (%) of Patients Enrolled in Strategy (2012)
Bridge-to-Recovery (BTR)	Patient requires temporary support; expected cardiac recovery; no transplant indicated	1.0
Bridge-to-Candidacy (BTC)	Patient not actively listed for transplant. Potential for recovery unclear; no absolute contraindication for transplant	33.1
Bridge-to-Transplant (BTT)	Patient actively listed for transplant. Will not survive without MCS/LVAD.	21.0
Destination Therapy (DT)	Patient is ineligible for transplant and will not survive without MCS; has absolute contraindication for transplant.	44.0

MCS (mechanical circulatory support); LVAD (left ventricular assist device); Adapted from Rodriguez et al., 2013

As VAD technology has improved, the goals of newer devices are to mitigate adverse events and readmission rates, while sustaining patients for longer-durations.¹⁹ As of 2012, amongst ESHF patients ineligible for transplant, DT is the most common device strategy and is employed in 44% of patients requiring LVAD placement.¹⁷ Researchers have found that patients in DT are experiencing similar 1 and 2-year survival-rates as those with heart transplant.²⁰ Implant strategies, however, are not inflexible treatment modalities; rather they represent modes of therapy for a spectrum of potential outcomes based on patient characteristics, severity of HF and likelihood of receiving a transplant or

becoming eligible for the waiting list. In fact, nearly 30% of patients chosen for BTT strategy were found in one study to be on support 2 years post-implantation.²¹ As LVADs are increasingly used for long-duration, or even permanent therapy, decision for device strategy will have to address patients' clinical need for circulatory support rather than their probability for receiving a new heart.

Selection criteria for MCS will naturally parallel those of heart transplant. The authors of the 2013 International Society of Heart and Lung Transplantation (ISHLT) Guidelines for Mechanical Circulatory Support recommend long-term MCS for patients whose ventricular function is deemed unrecoverable, or who cannot be weaned from inotropic support but have the capacity for a meaningful recovery. Inotrope-dependent individuals, who are not in cardiogenic shock, represent a high-mortality group that may also benefit from MCS. Any ESHF patient with high risk for 1-year mortality should be referred for MCS or transplantation consult.²²

The decision for LVAD implantation is multi-faceted, comprised of a patient's surgical-candidacy, transplant status and potential survival benefit. Patient selection is critical to successful operational outcomes²³; various risk stratification tools have been developed to classify ESHF patients according to surgical benefit. One of the most critical risk stratification tools relevant to MCS patient selection is the National Institute of Health (NIH) Interagency Registry for Mechanical Assist Devices (INTERMACS) Classification System. INTERMACS organizes refractory HF patients into more precise profiles, thereby identifying more appropriate MCS candidates.²⁴ Table 4 illustrates the INTERMACS profiles and Appendix III provides more detailed descriptions.

Table 4. The INTERMACS Classification Profiles

Profile	Description/Status	Time-Frame for Intervention
1	Critical cardiogenic shock	Hours
2	Progressive decline	Days to 1 week
3	Stable, inotrope-dependent	Weeks
4	Recurrent advanced HF, resting-symptoms	Weeks to few months, if baseline function restored
5	Exertion intolerant	Weeks to months; variable urgency
6	Exertion limited	Months, if nutrition and activity maintained; variable urgency
7	Advanced NYHA III	Transplant or MCS may not be currently indicated

HF (heart failure); NYHA (New York Health Association); MCS (mechanical circulatory support); Adapted from Mancini and Lietz, 2010

Patients in cardiogenic shock (INTERMACS 1) or patients with worsening ESHF symptomology (INTERMACS 2) are the sickest patients presenting for transplant or MCS consult. Due to the intense acuity of this population, assessment for transplant or emergent MCS implantation must be performed within hours. These patients may even receive an intra-aortic balloon pump or short-term MCS for days to weeks while the decision is made to pursue transplant or long-term LVAD therapy. A Futile Implant Score (Appendix IV), based off various individual characteristics and laboratory data, has been developed to determine beneficence of LVAD placement in high-risk operative patients. High-scoring patients (> 16) were found to have 1-year survival of less than

28%, and very-high scoring patients (>19) have 1-year survival less than 11%.²³ No standardized protocols exist to guide elective device placement in this critically ill population.²⁵ Parenteral inotrope-dependent patients whose disease process remains stable (INTERMACS 3) have 1-year survival outcomes of 23%, indicating necessity for MCS implantation, if transplant must be delayed.^{18,25} For INTERMACS 1-3 patients especially, MCS device strategies must be readily discussed given their high acuity. Destination therapy can be considered in those who are contraindicated for transplant, but bridge therapies represent more immediate treatment options for this population. Appendix V illustrates factors critical to the decision for MCS bridging therapy.

ESHF patients with NYHA IIIb/IV symptoms who are not inotrope dependent (INTERMACS 4-6) represent the ambulatory cohort of transplant/MCS candidates.²⁵ Physiologic parameters, such as cardiopulmonary stress testing and peak V_{O_2} measurements, identify patients needing invasive intervention. Prognostic evaluation tools, like the Heart Failure Survival Score (HFSS) and the Seattle Heart Failure Model (SHFM), quantify the patient's physiologic and clinical status.^{25,26,27} The individual can then be ranked according to disease severity, and thereby, their appropriateness for transplant listing or MCS management. Both tools' analysis allows providers to estimate a patient's 1 and 2-year survival with medical management, which is crucial to the LVAD implantation decision.²⁸

Once an appropriate patient for MCS therapy is identified, the cardiac surgical team, in conjunction with heart transplant specialists, can move forward with LVAD implantation. Over the decades, various types of VADs have been developed, with

multiple devices available within each generational class. It is crucial to understand how each VAD system functions, as each is associated with particular advantages and disadvantages that may affect the course of therapy. In this paper, we will discuss each generation of VADs broadly and refer only to select models approved for BTT and/or DT as representatives of their respective generational class. Figure 1 on the following page illustrates the classifications of MCS devices through the generations.

In 1994, the U.S. FDA approved a first-generation LVAD for BTT therapy. The first-generation devices, also known as pulsatile LVADs, attempted to mimic normal ventricular contractility using volume displacement technology.¹⁷ Pulsatile LVADs utilize pneumatic or electrically powered pumps designed with pusher-plate mechanisms. The HeartMate I (Thoratec Corporation, Pleasanton, CA), available as an implantable pneumatic [IP] or vented electric [VE] device, was the first to receive international marketing approval in the 1990s.²⁹ An inflow conduit, attached at the apex of the heart, connects the left ventricle to the device pump. Sensors connected to the external control system regulate the pusher-plate, increasing or decreasing the rate of pulsation (volume displacement) in response to blood flow (i.e. higher rates at higher flows).²⁹

A diaphragm separates two chambers; one chamber houses the motor unit and the other houses blood. The motor compresses the diaphragm with the pusher-plate, causing increased pressure within the chamber, thereby ejecting blood through the outflow conduit anastomosed to the ascending aorta. Diastolic refilling is mimicked by a recoil property of the diaphragm. As the diaphragm re-expands, negative pressure draws blood

from the ventricle into the blood chamber, even in the setting of a flaccid left ventricle.^{29,30}

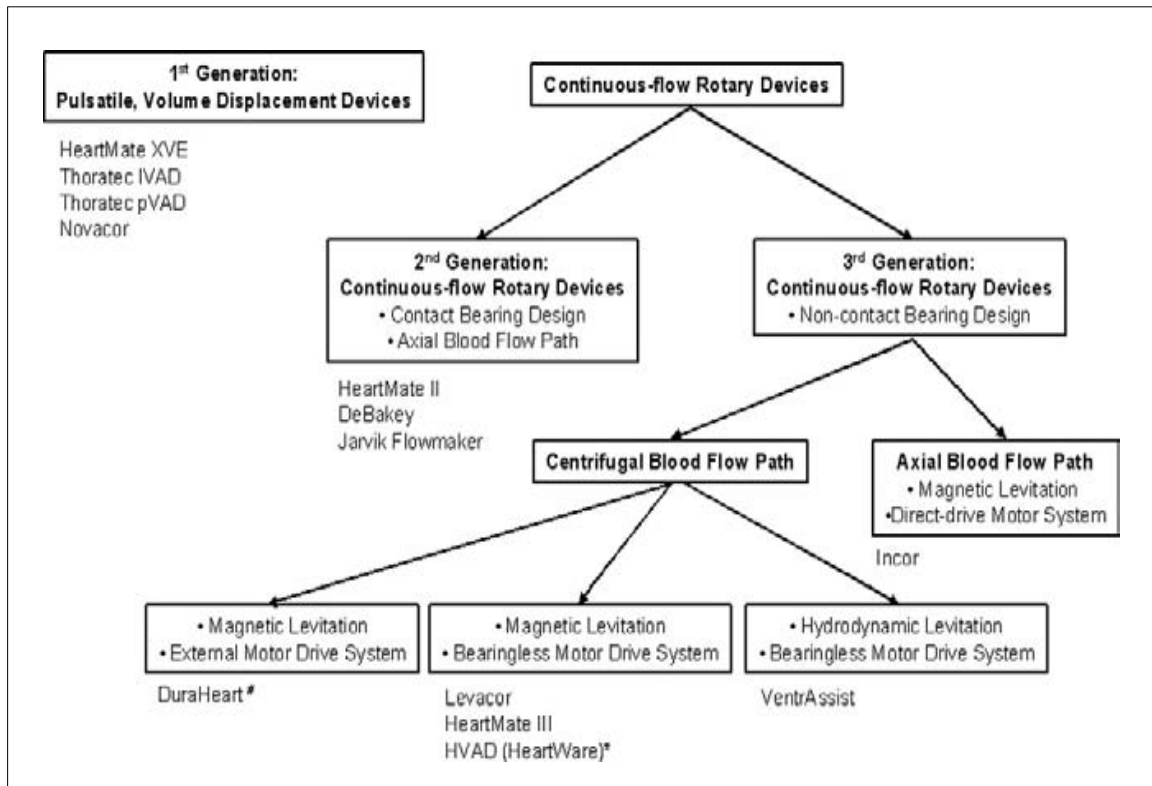


Figure 1: Generational Classification of VADs³¹

To maintain proper motor unit functionality, a percutaneous driveline – containing an electric cable and air vent – leads from the device to the external controller; this prevents overheating and maintains atmospheric pressures within the motor chamber. Porcine valves ensure unidirectional flow. Biocompatible textured materials – titanium microspheres and polyurethane – promote deposition of natural endothelia.¹⁵ Creation of a so-called pseudointima decreases device thrombogenicity and eliminates need for

anticoagulation.^{29,30} Figure 2 provides a schematic of a pulsatile LVAD similar to the HeartMate I.

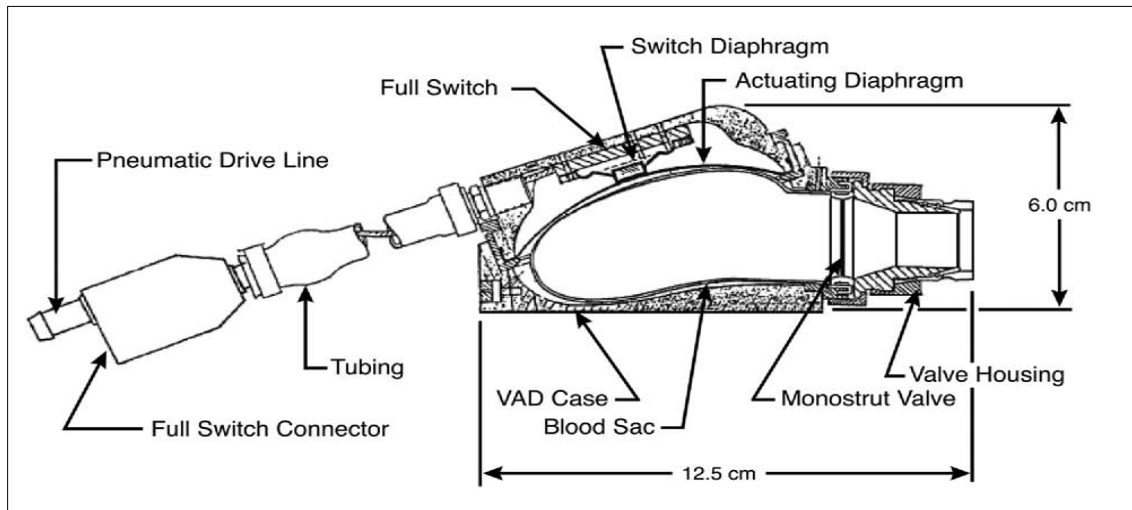


Figure 2: Schematic of a Pulsatile LVAD.³⁰

In 2001, the REMATCH trial demonstrated that a first-generation LVAD had significant survival benefit compared to medical therapy alone, 52% vs. 25% one-year survival respectively, for long-term management of patients not eligible for transplant.¹⁸ The trial indicated the clinical success of first-generation LVAD therapy outside of short-duration support, and validated the concept of DT. The device functionally replaces the failing left ventricle, providing pulsatile blood flow at levels up to 12 liters per minute.³² Researchers have shown that pulsatile LVADs unload strain from the left ventricle, promoting reverse remodeling and improved hemodynamics; some patients even recovered to NYHA I symptomology.^{32,33} The pseudointima created using textured biocompatible lining reduced anticoagulation needs.

REMATCH's landmark findings notwithstanding, pulsatile LVAD therapy was complicated by severe morbidity and mortality. The mechanism's large size required invasive median sternotomy and sub-diaphragmatic implantation, with creation of a peritoneal pocket. Only large patients, with body surface area (BSA) greater than 1.5 square meters could be implanted with the device.¹⁵ REMATCH noted patients with first-generation LVADs were twice as likely to suffer a serious adverse event compared to those who underwent medical therapy alone.¹⁸ Pulsatile LVADs predisposed patients to higher risks of infection/sepsis, thrombus formation and hemolysis. Within the first 60 days after implantation, patients experienced bleeding, infection and arrhythmias at rates of 36-48%; greater than 60 days post-implant, neurologic events, respiratory issues and tamponade occurred at rates of 24-31%.³⁴ Pulsatile LVADs were also associated with an increased risk for CVA, with 14-47% of patients suffering a stroke.³⁵ Additionally, first-generation LVADs were likely to suffer catastrophic device failure, requiring potentially emergent replacement; most devices required reoperation between 18-24 months post-implant.³⁶ First-generation LVADs' survival benefit for patients ineligible for transplant was in stark contrast to their high rate of associated complications.

Cerebrovascular Accidents & Left Ventricular Assist Devices

Cerebrovascular accidents exist as a persistent source of morbidity and mortality in the VAD patient population; pre-transplant strokes are major contraindications for subsequent transplant, and may predispose successful transplant recipients to worse outcomes.^{5,35} VADs represent a foreign substrate in the body, and as such represent a

procoagulant stimulus in the coagulation cascade. Multiple studies have been performed to demonstrate how VADs affect the hematologic state of the body.

Spanier et al. conducted a study in a population using pulsatile VADs to illustrate how the device activates coagulation and fibrinolytic pathways. The researchers noted that VAD patients had elevated baseline levels of thrombin anti-thrombin complex and prothrombin activation peptide, two markers denoting production of thrombin and an overall procoagulant state. In addition, these respective markers were significantly elevated compared to those measured in patients with ESHF without VAD therapy. Furthermore, patients with an implanted VAD demonstrated significantly elevated fibrin degradation products and D-dimers compared to medically managed ESHF patients. VADs stimulate coagulation as well as secondary fibrinolysis.³⁷

Similar results were found in additional studies with focus on later generation VADs with continuous-flow mechanics. John et al. studied 21 second-generation LVAD recipients for changes in endothelial and coagulation function. Compared to a control, non-LVAD cardiac surgery population, VAD patients revealed increased serum markers for endothelial dysfunction (i.e. tissue factor, E-selectin) as well as increased markers for coagulation and fibrinolysis (von Willebrand antigen, thrombin/antithrombin III).³⁸ Ultimately the studies noted, regardless of pulsatile or continuous-flow mechanics, the device, with associated altered fluid dynamics, lead to constant activation of the extrinsic coagulation cascade with subsequent rheologic changes. Spanier et al describe a compensated coagulopathy that supports thrombosis via sustained endothelial dysfunction.^{37,38} Abnormalities in endothelia and hemostasis lead to increased

inflammation, molecule aggregation and adhesion, all processes common to potentially embolic disease.³⁸

Transcranial Doppler (TCD) is a noninvasive test that uses ultrasound of the basal cerebral arteries, particularly the middle cerebral artery, to accurately visualize emboli traveling into the cerebral vasculature.³⁹ High intensity signals (HITs), also known as microembolic signals (MES), are dynamic changes in flow velocity that are typically transient, unidirectional and short in duration. Figure 3 illustrates a MES waveform suggestive of embolus. VADs represent an obvious source for cardiac emboli. Studies on prosthetic valves and structural heart disease have noted that patients with a known cardiac source have higher levels of MES than patients who do not, and this may predict higher risks for recurrent stroke, transient ischemic attacks (TIAs) or mortality.³⁹

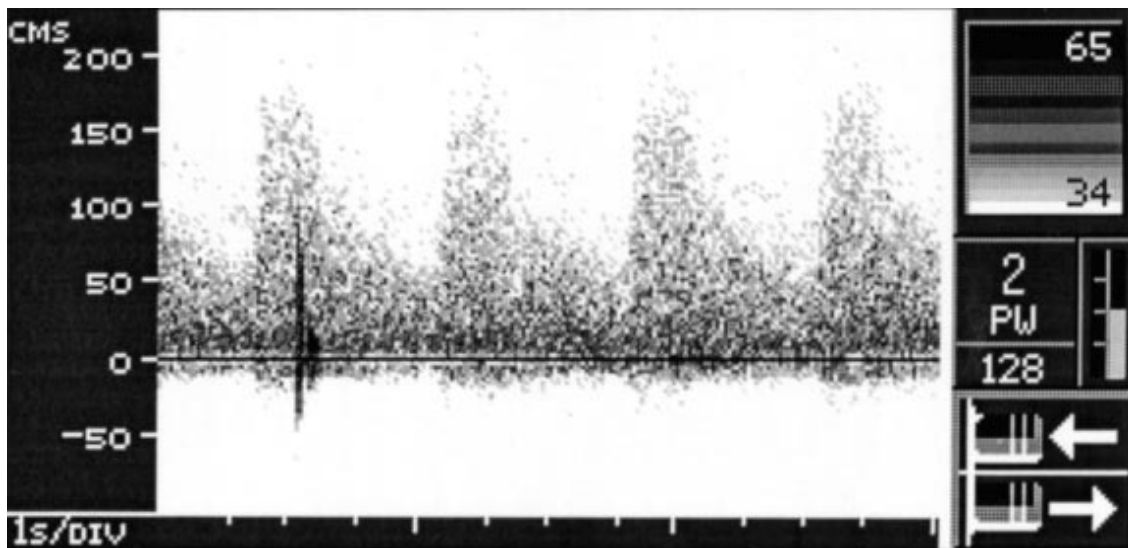


Figure 3: Illustration of a Microembolic Signal (MES)³⁹

Data regarding VADs, microembolism and clinically significant neurologic events is variable. In former pulsatile models, one study noted early TCD findings of significantly elevated MES detections on days with clinically-evident embolic events compared to days without events.⁴⁰ A study of 23 patients implanted with a continuous, axial-flow LVAD noted 10 clinically evident thromboembolic complications in 34.8% of patients, while overall MESs were detected in 87% of subjects.⁴¹ In this study, researchers found no statistical association between MES activity and the thromboembolic events. Regardless of pulsatile or continuous-flow mechanics, LVADs promote a hypercoagulable state and their effect on fluid dynamics plays a role in the generation of microemboli.^{40,41}

The incidence of stroke in the LVAD population is difficult to assess given variable patient and device characteristics, antithrombotic medication status and compliance. In one study of 230 patients implanted with a second-generation CF-LVAD, the overall incidence of stroke was 17%.² In separate studies, authors report an overall stroke incidence in continuous-flow devices ranging 10 – 18%, with some studies indicating this could be as high as 25%.^{4,42} Ischemic strokes may occur due in part to deposition of fibrin or protein throughout the device, closure of the aortic valve and increased length of the inflow/outflow grafts.^{5,43} A patient history of previous CVAs, heart failure, atrial fibrillation and arrhythmias, diabetes mellitus, as well as increased duration of intraoperative aortic-cross clamping and increased duration of VAD support all stand as major risk factors for stroke.^{5,42,44} In the largest study of 956 patients for pre-operative risk factors for stroke in patients receiving a CF-LVAD, ischemic strokes were

more likely when patients exhibited higher platelet counts, lower international normalized ratio (INR), lower partial thromboplastin time and lower Model for End-Stage Liver Disease (MELD) score.⁴⁵

An important risk factor for stroke in LVAD patients that deserves special mention is infection. In CF-LVAD patients, pneumonia, sepsis and percutaneous site infections of the driveline are the most common infectious etiologies. A persistent bacteremia lasting more than 72 hours is a critical factor in predisposing patients to CVA.⁴⁶ *Staphylococcus* and *Pseudomonas* species are the most likely infectious organisms. Both species produce biofilms that adhere to the driveline and device itself, spreading deeper into the machine and surrounding tissues, potentially forming an abscess.⁴⁶ Ultimately, infection exacerbates the already taxed inflammatory state of the VAD patient. Platelet activation, further endothelial dysfunction, systemic inflammation and even septic embolic seeding of the brain can occur. In one study, post-operative infection was the single independent risk factor for neurologic complications and CVA, with an odds ratio of 4.24.⁴

Hemorrhagic CVAs are devastating neurologic complications in the VAD population. The overall incidence of hemorrhagic events is variable, occurring at a similar or decreased rate as ischemic strokes. The etiology for hemorrhagic CVAs in CF-LVADs is multifactorial: fibrinolysis, acquired hematologic deficiencies and use of antithrombotic therapy all heighten the risk of intracranial bleeding. As noted previously, studies have elucidated that CF-LVAD recipients have increased fibrin degradation products in circulation at baseline; this is likely due to an over activated coagulation

cascade and the body's attempt to break down the increased thrombosis. In addition, fibrinolysis can be attributed to the high shear stress on blood product due to the moving rotors of the device. Resultant hemolysis increases fibrinolysis and contributes to thrombocytopenia.⁴⁷

The major risk factors for hemorrhagic stroke are systemic infection and supratherapeutic INRs.⁵ Endocarditis and mycotic aneurysms secondary to *Pseudomonas* infection have been implicated in hemorrhagic CVAs.^{5,46} Elevated INRs are not always predictive of intracranial bleeding, as patients can have hemorrhages even when INRs are normal. Additional factors, such as hemostatic abnormalities and reduced pulsatility, may cause bleeds. CF-LVADs' known association with endothelial dysfunction may play a role in both ischemic and hemorrhagic strokes.⁵ Hemorrhagic conversion of ischemic strokes is likely to occur in patients with cardioembolic sources as well as large infarction size.⁵

High shear forces caused by the spinning rotors in CF-LVADs also lead to an acquired von Willebrand's factor deficiency, similar in pathophysiology to Heyde's syndrome in aortic stenosis.^{47,48} Acquired von Willebrand's Syndrome (AvWS) is caused by a loss of larger von Willebrand factor (vWF) monomers secondary to structural changes in the multimer.⁴⁸ These multimers play a critical role in primary hemostasis by binding to glycoprotein receptors.⁴⁹ Patients are thereby susceptible to bleeding, especially gastrointestinal bleeds. Interestingly, researchers found that AvWS is reversible, with multimers returning to normal size and function with removal of the VAD.⁴⁸ AvWS was first noted in axial-flow devices, but was later identified to occur in

centrifugal-flow devices as well.⁴⁹ AvWS has not been proven to directly cause cerebral hemorrhagic events in the VAD population, but the syndrome complicates antithrombotic therapy.

Antithrombotic regimens for CF-LVAD patients are necessary due to the fact that all foreign, implanted substances, regardless of biocompatibility, are not fully biologically inert. Therefore, blood-thinning medications are prescribed to mitigate thromboembolism and hemolysis.⁵⁰ All therapies include a vitamin K antagonist (i.e. warfarin) and an antiplatelet medication (i.e. aspirin). Additional antiplatelet therapy with dipyridamole or clopidogrel, may be necessary if there is significant hemolysis to reduce platelet aggregation.⁵⁰ Table 5 lists antithrombotic therapies with goal INRs for several VAD models.

Table 5. FDA Approved Ventricular Assist Device Antithrombotic Therapies

Ventricular Assist Device	Aspirin	Dipyridamole	Vitamin K Antagonist	Goal INR
Heartmate XVE	81 mg daily	---	---	---
HeartMate II	81 mg daily	75 mg BID	Warfarin	1.5 – 2.0 2.0 – 2.5 2.5 – 3.0
HeartWare HVAD	325 mg daily	---	Warfarin	2.5 – 3.0
HeartMate III	100 mg daily	---	Warfarin	2.0 – 3.0

Adapted from Von Ruden et al., 2012, Netuka, 2015

Due to the high risk of bleeding in CF-LVADs, which occurs in up to 50% of patients, studies have been performed to observe the effects of less aggressive

antithrombotic therapy.⁵¹ Boyle et al. found in a study of 331 patients implanted with a second-generation LVAD that thromboembolic events were more likely when INR was less than 1.5, while hemorrhage was more likely if INR was greater than 2.5.⁵² Further, these researchers noted infrequent thromboembolic events at INRs greater than 1.5, and suggested that in patients prone to bleeding, a less aggressive goal INR was appropriate.⁵² Katz et al. noted a 6% overall incidence of thromboembolic events with less aggressive antithrombotic therapy.⁵³ Due to a growing body of evidence for the existence of AvWS in CF-LVAD patients, antithrombotic therapies are not standardized. Antithrombotic regimens are titrated based on an individual's risk for thromboembolism or hemorrhage, surgeon's preference and manufacturer suggestions.⁵⁰

Second Generation CF-LVAD: HeartMate II

The development of continuous-flow devices (CF-LVADs) provided answers to a multitude of problems presented by the pulsatile mechanisms. Due to the importance of increasing device durability, manufacturers aimed to reduce the number of moving parts within an LVAD system; companies focused on rotary pump designs with a single moving part. Second-generation devices, also known as axial flow CF-LVADs, utilize an internal rotor pump suspended within the blood pathway; blood-immersed bearings hold the pump in place. CF-LVADs eliminated the multi-chamber design and use of valves to reduce sites of thrombus formation. Single pump, direct-contact design (i.e. the pump is actively exposed to blood) minimizes device wear-and-tear. Like the first-generation pumps, an inflow conduit leads from the apex of the left ventricle into the device, with an

outflow graft anastomosed to the ascending aorta.¹⁷ Figure 4 provides an illustration of the HeartMate II (Thoratec Corporation, Pleasanton, CA), a second-generation LVAD. An external control device, connected via a driveline, responds to changing physiologic demands by adjusting motor speed to maintain optimal flow. The impeller continuously rotates typically at 8,000-12,000 rpm, and up to 15,000 rpm, creating a near-constant pressure that moves blood from the ventricle through the aorta at a rate of 3-10 liters per minute.^{16,17,29} The HeartMate II also implements the use of textured biocompatible material to create a pseudointima on blood-contacting surfaces.

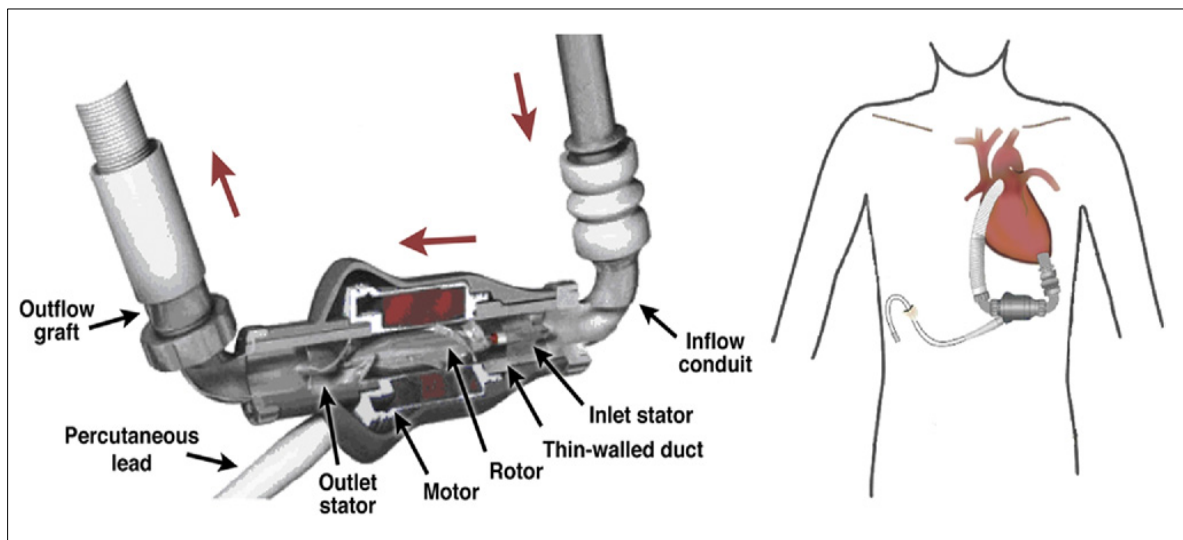


Figure 4: Diagram of the HeartMate II – A Second-Generation Axial Continuous-Flow LVAD.³⁰

The HeartMate II is implanted similarly to first-generation LVADs, placed in a sub-diaphragmatic position within a surgically created peritoneal pocket; second-generation models, however, are much smaller than pulsatile LVADs, allowing patients with a BSA

less than 1.5 square meters to undergo placement. Due to the device's smaller size, the operation may require a median sternotomy or left thoracotomy technique.

Miller et al. studied the efficacy of the HeartMate II in providing circulatory support to patients awaiting cardiac transplant. Researchers noted that 75% of patients reached primary experimental end-points – successful transplantation, cardiac recovery or survival – at 180 days. In addition, patients supported with a second-generation CF-LVAD had a 1-year actuarial survival of 68%.⁵⁴ Similarly, Pagani et al. evaluated the HeartMate II for BTT indication, finding that 79% of enrolled patients received a transplant, underwent LVAD removal or were living with ongoing support at 18 months post-implant.³ Slaughter and colleagues found that the second-generation CF-LVADs had significantly improved actuarial survival at 2-year follow-up compared to pulsatile LVADs (58% vs. 24%, respectively).⁵⁵ Figure 5 provides Kaplan-Meier survival curves comparing the HeartMate II and a pulsatile device. In addition, researchers noted significant reduction in the overall incidence of adverse events in patients randomized to the CF-LVAD group.⁵⁵ The Slaughter study established HeartMate II and second-generation CF-LVADs as viable devices for long-duration therapy, leading to FDA approval of the HeartMate II for DT in 2010.

The HeartMate II is the most commonly used LVAD internationally, with approximately 13,000 implantations since 2000.¹⁶ The success of the axial flow CF-LVAD model is due in part to its smaller size, simplistic design and increased durability. In one study analyzing 100 patients implanted with the HeartMate II, no catastrophic

mechanical failures were reported; 2 non-fatal malfunctions occurred, while only 1 patient underwent device replacement due to thrombus formation.¹

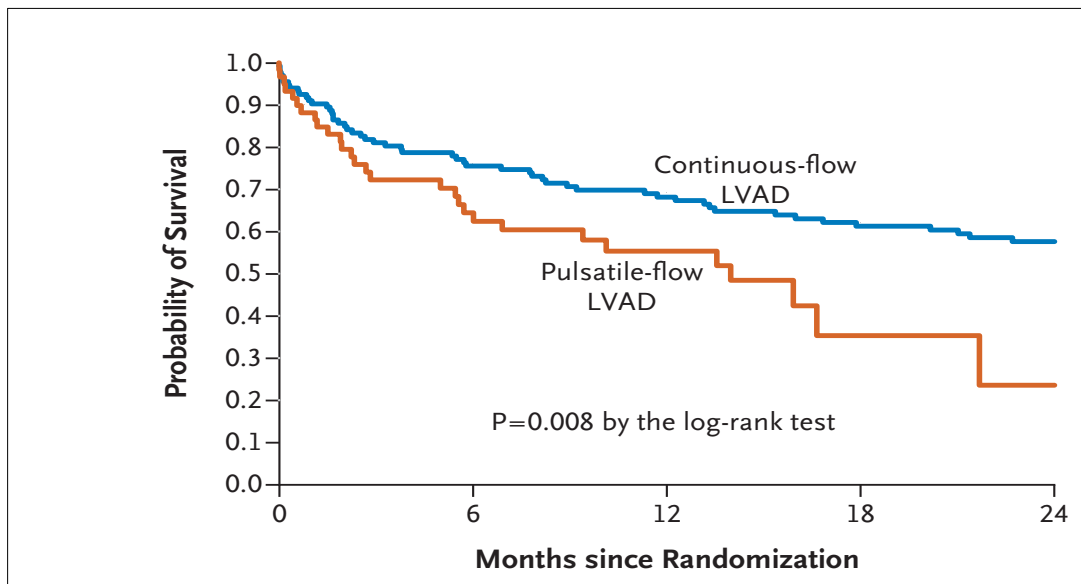


Figure 5: Comparison of Kaplan-Meier Estimates of Survival Between CF-LVAD and Pulsatile LVAD⁵⁵

The HeartMate II is one of the most extensively studied CF-LVADs available; data about the device points to significantly improved patient hemodynamics, quality of life and functional capacity.⁵⁵

Albeit the HeartMate II represented a leap forward in MCS, the second-generation devices are associated with new challenges. Continuous-flow models unload the left ventricle throughout the cardiac cycle, delivering blood systemically at reduced pulse pressures.⁵⁶ Absence of pulsatile hemodynamics has led to concerns about CF-LVADs' effects on myocardial recovery, ventricular unloading and the adequacy of end-organ

perfusion. Researchers have noted the HeartMate II has poorer myocardial recovery compared to pulsatile VADs, with increased levels of heart failure biomarkers, such as brain natriuretic peptide (BNP).^{56,57} Right heart failure caused by a lateral shift in the interventricular septum secondary to left ventricular unloading may contribute to this phenomenon.²⁴ Management of CF-LVADs requires mean arterial blood pressures (MAP) to be maintained by vasoactive and inotropic medications, along with careful fluid volume control; MAP should be measured at 70-80 mmHg, and never exceed 90 mmHg.²⁸ Such reduced pressures, often requiring a Doppler to identify pulses, cause theoretical concern for end-organ hypoperfusion. However, Kamdar et al. report that serum creatinine and urea nitrogen levels compared between pulsatile and continuous-flow devices do not differ significantly; hepatic function values decreased or remained within normal range over a three-month duration.⁵⁸ The HeartMate II provides adequate end-organ perfusion, without detriment to end-organ function.

Overall adverse event rates are reduced in second-generation devices compared to pulsatile devices, but complications associated with the HeartMate II can cause severe morbidity and mortality. Reduced pulse pressures have been implicated as a cause for the development of arteriovenous malformations and gastrointestinal bleeds; hematologic abnormalities, like acquired von Willebrand disease, complicate antithrombotic therapy.²⁴ One meta-analysis noted aortic valve insufficiency, due to increased afterload pressures in the aorta, which predispose to regurgitant flow; while decreased pulse pressure for prolonged durations may lead to leaflet fusion.⁵⁷ Both may occur in the HeartMate II, leading to flow stasis and potential thrombus formation. In addition, the

HeartMate II is associated with embolic and hemorrhagic stroke. According to Slaughter et al., there was no significant difference in incidence of stroke with the HeartMate II compared to pulsatile models, occurring in 17% of study patients. The leading cause of death in the study population was hemorrhagic stroke, occurring in 9% of patients.⁵⁵ The overall incidence of stroke in continuous-flow devices varies between 6-17%, dependent on variables like individual pump-characteristics, patient-related factors, and anticoagulation status.²⁴ Appendix VI denotes adverse events rates from the Slaughter et al, 2009 trial.

Third Generation CF-LVAD: HeartWare HVAD

As survival with LVADs increases and long-duration therapy is implemented more frequently, research continues to reduce adverse events and improve device durability. Third-generation LVADs replaced axial design with centrifugal continuous-flow mechanics, where the rotary pump is levitated using hydrodynamic or magnetic forces, or a combination of the two systems.¹⁶ The HeartWare HVAD (HeartWare International Inc., Framingham, MA) is an example of a centrifugal pump; the design incorporates passive magnets and hydrodynamic thrust bearings which allow the rotary pump to float – or levitate – in the blood pathway, minimizing the occurrence of prothrombotic sites.^{17,59} Spinning blades throw blood tangentially to produce adequate flow.⁶⁰ As the blades spin, blood flows across the surfaces, creating lift; constant flow generates a cushioned space between the impeller and motor housing.⁵⁹ Levitation technology, in theory, allows wider gaps for flow, reducing shearing forces on the blood

cells, while also decreasing device wear-and-tear.¹⁶ In addition, these models are smaller compared to axial flow devices, allowing for advances in surgical implantation techniques. Figure 6 depicts an illustration of the HeartWare HVAD.

The HeartWare HVAD can be placed in an intrapericardial position, eliminating the peritoneal pocket and reducing surgical complications.¹⁷ The inflow conduit is implanted directly within the left ventricle, while the outflow graft is anastomosed to the ascending aorta. A subcutaneous driveline connects to an external control system, which regulates a fixed pump rotational speed. Centrifugal pumps produce cardiac output up to 10 liters per minute at lower operational speeds; reduced rotational speeds of 1,800 – 3,200 rpm allow for increased pump efficiency compared to axial designs.^{17,59,61}

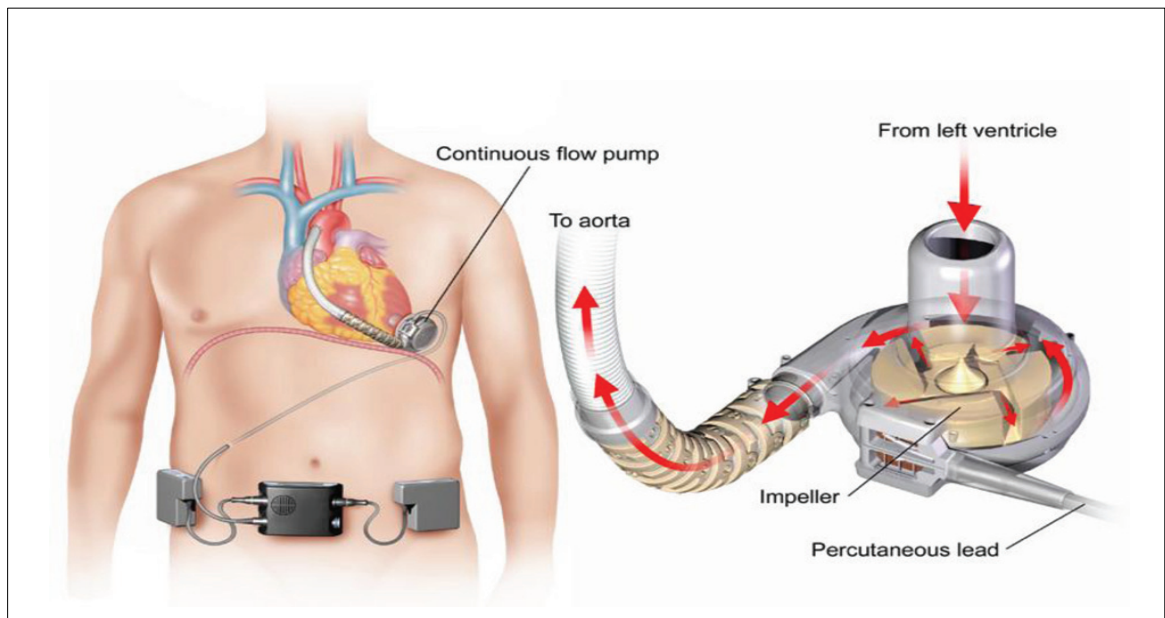


Figure 6: Illustration of the HeartWare HVAD⁶¹

Dell'Aquila et al. and researchers initial experience with the HeartWare HVAD system noted similar survival curves compared to John et al.'s early findings in the HeartMate II (77.9% versus 78.8% overall 1-year survival).⁵⁹ The ADVANCE trial conducted in 2012 demonstrated non-inferiority of the HeartWare HVAD for BTT device strategy. Researchers compared the HVAD to INTERMACS control device data, mostly made up of HeartMate II implantations. Investigators noted 86% 1-year survival with the Heartware HVAD, compared to 85% 1-year survival in the control group.⁶¹ The ADVANCE trial enabled FDA approval of the HeartWare HVAD for BTT, which is the only third-generation device approved for this indication.¹⁶ The ENDURANCE trial, an on-going project evaluating the HVAD for DT indication in 446 patients randomized to MCS support with the HVAD or HeartMate II, recently reached primary study end-points. HeartWare International Inc. published a memorandum stating of those enrolled between 2010-2012, 55% experienced stroke-free survival at 2 years while supported with the HeartWare HVAD, compared to 57.4% who attained the same end-point with the HeartMate II.⁶² These initial results suggest non-inferiority in terms of mitigating stroke for the HVAD in long-term circulatory assistance for refractory ESHF patients.

Although overall and stroke-free survival curves for the HeartWare HVAD suggest that the third-generation device may exist as a viable device option for ESHF patients, adverse events persist. A retrospective cohort study compared 46 patients implanted with a HeartWare HVAD or HeartMate II over a six-year timeframe noted similar complication rates across groups. Right ventricular failure, liver or renal dysfunction as well as thromboembolism, infection and bleeding occurred similarly in

either cohort. However, researchers noted patients with the HVAD suffered a 44% incidence of stroke compared to 10% in those supported with the HeartMate II, with a trend favoring higher incidence of hemorrhagic stroke. In addition, the same researchers noted a significant increase in GI bleeding with the HVAD.⁶³ Preliminary results from the ENDURANCE trial noted an overall elevated risk of stroke in the newer model, likely due to poor blood pressure control in the investigational cohort.^{64,62}

Axial versus Centrifugal CF-LVAD Physiology

Thrombosis results from the pathologic mechanisms of hypercoagulability, endothelial dysfunction and variation in hemodynamic performance, namely flow stasis or turbulence. VAD mechanisms contribute to each of these three processes, as a foreign object within the body, disrupting natural endothelia and altering fluid dynamics. As advanced third-generation centrifugal designs come to fruition, we can see the focus on LVAD development set upon decreasing hindrances to flow, producing more normalized pulsatile function and incorporating biocompatible materials. Although the bioengineering principles of VADs are outside the scope of this paper, it is crucial to understand basic elements of continuous flow mechanics in order to appreciate how advanced third-generation designs function.

By analyzing axial versus centrifugal continuous flow mechanics, we can make inferences into advantages of advanced third-generation designs. Table 6 lists a summary of physiologic differences between the two mechanisms. The means by which VADs produce flow, manipulate blood and respond to physiologic demands, contributes to the

inherent coagulopathogenicity of the device. A device’s flow pulsatility, inlet suction predisposition, pre-load and after-load sensitivity, susceptibility to infection, biocompatibility, tendency for hemolysis and anticoagulation protocols can create an environment conducive for thromboembolism.

Table 6. Summary of Physiologic Differences Between Centrifugal and Axial CF-LVAD Designs

Pump Characteristics	Centrifugal vs. Axial	Summary of Comparison
Flow Pulsatility	C > A	Centrifugal VADs have higher flow pulsatility
Inlet Suction	A > C	Centrifugal VADs have significantly lower inlet suction events at low flow conditions
Pre-Load Sensitivity	A = C	Axial and Centrifugal VADs have low pre-load sensitivity, relative to native LV and pulsatile VADs
After-Load Sensitivity	C > A	Centrifugal > Axial > Native LV/Pulsatile VADs in terms of after-load sensitivity
Susceptibility to Infection	A = C	No difference
Biocompatibility	A = C	No difference
Hemolysis	A = C	Not enough clinical data to suggest superiority
Anticoagulation	A = C	Not enough clinical data to suggest superiority

A (axial); C (centrifugal); VADs (ventricular assist devices); LV (left ventricle); Adapted from Moazami, N et al., 2013

CF-LVADs are conduits which mediate a pressure gradient between the failing native left ventricle and the aorta. The pressure across the inlet and outlet of these hydrodynamic pumps – the pressure head or delta P – illustrates the relationship between

pump flow and pressure at a given operating speed.⁶⁰ Centrifugal systems have a flat pressure head curve, whereas axial designs have a steep pressure head. Centrifugal pumps exhibit a wide variation in operational flows over small changes in the pressure gradient, while axial flows do not vary significantly with changes in delta P.

The implications of this are twofold: a) centrifugal pumps function with a higher degree of “pulsatility” through the cardiac cycle compared to axial devices b) centrifugal flows can better adapt to changing physiologic demands without causing structural change to the interventricular septum.⁶⁰ On the following page, Figure 7 displays a visual schematic of the pressure heads of axial versus centrifugal machines. Inlet suction events occur more frequently in axial devices in low flow states, where the negative pressure generated by the rotor mechanism causes a leftward shift of the septum; this causes right heart dilatation, decreased device efficiency and may lead to other problems with device function. In centrifugal designs, the relative increased pulsatility and decreased inlet suction events thereby lessen flow stasis and mitigate the occurrence of ventricular arrhythmias and right heart dysfunction, which can predispose to thrombus formation.

Pre-load and after-load are hemodynamic conditions that contribute to overall cardiac output. In MCS devices, pre-load refers to the relationship between the left ventricular filling pressures and left ventricular stroke volume.⁶⁰ Continuous flow pumps have a reduced internal volume, by nature of their size compared to the native ventricle, and therefore have a limited pre-load sensitivity. CF-LVADs have a restricted output response to variations in venous return, which makes maintenance of euvolemia challenging. However, continuous flow devices demonstrate higher after-load sensitivity

compared to the normal human heart. After-load in MCS refers to the pressure gradient between the systemic vasculature and the device's outlet.

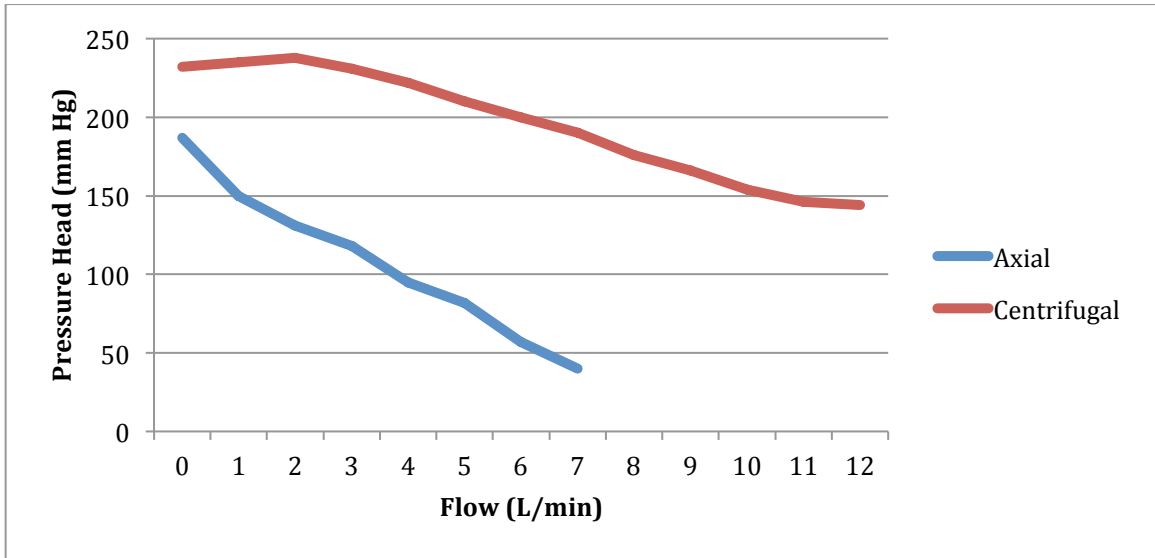


Figure 7: Example Pressure Head Curves of Axial and Centrifugal Devices

In order to maintain normal function of the rotor system, mean arterial pressures must be kept for all continuous flow devices strictly between 70-90 mmHg.^{22,60} Centrifugal devices, due to their flat head curve, are especially susceptible to deleterious effects on output flow in response to increased systemic vascular resistance; axial devices are less susceptible to after-load variation and can maintain adequate pressures due to a steeper delta P. Although axial devices can maintain a more constant flow to overcome increased vascular resistance, this predisposes to inlet suction events, arrhythmias and hemolysis, if venous return is not sufficient.⁶⁰

Hemolysis results from blood shearing effects of the rotor mechanism due to high rotational speed and is related to the volume of space for blood to pass through the device. Axial-flow VADs have smaller clearances around the rotor blades, which spin at higher operational speeds; this creates high shearing forces on red blood cells compared to centrifugal devices. Hemolysis occurs in both centrifugal and axial designs, and there is a lack of evidence to suggest hemolysis secondary to pump design is a major clinical problem in MCS devices. However, hemolysis can be the harbinger of future morbidity, such as outflow graft misalignment or significant thrombus formation.⁶⁰ Deposition of fibrin clots typically occurs due to increased turbulence or stasis in “poor wash” areas, or sections of the device that are not exposed to adequate flow.⁶⁰ Centrifugal devices like the advanced third-generation mechanisms, with increased clearance between the blades for flow, have highly washed surfaces that are protective against stasis.^{60,65}

Advanced Third Generation CF-LVAD: HeartMate III

A particular advanced third-generation device, the HeartMate III (Thoratec Corporation, Pleasanton, CA), combines successful aspects of previous generation design. Figure 8 illustrates the HeartMate III, a more compact centrifugal pump with a solely magnetically levitated rotor system; the rotation and levitation of the rotor is made possible by a simplistic design. A single stationary component – made up of iron poles, copper coils and position sensors – allows for a miniaturized mechanism that eliminates the need for mechanical or fluid bearings like those used in earlier VADs.¹⁶ The magnet-based system prevents movement of the motor housing no matter what the relationship of

the device to the body, which decreases likelihood of device displacement. Without the bearings, mechanical wear-and-tear secondary to friction and device breakdown is no longer an issue. In addition, there are increased gaps for flow that are 10-20 times greater than those in hydrodynamic bearing systems, like the HeartWare HVAD.^{16,66} As previously noted, larger clearance areas for fluid movement favors laminar versus static flow. The system allows for high wash areas while maintaining flows between 2-10 liters per minute, while minimizing shear forces on blood product.^{16,65} Furthermore, the magnetic system maintains large gaps for flow to increase pump efficiency, permitting higher flows at lower rotational speeds between 3,000-4,000 rpm.

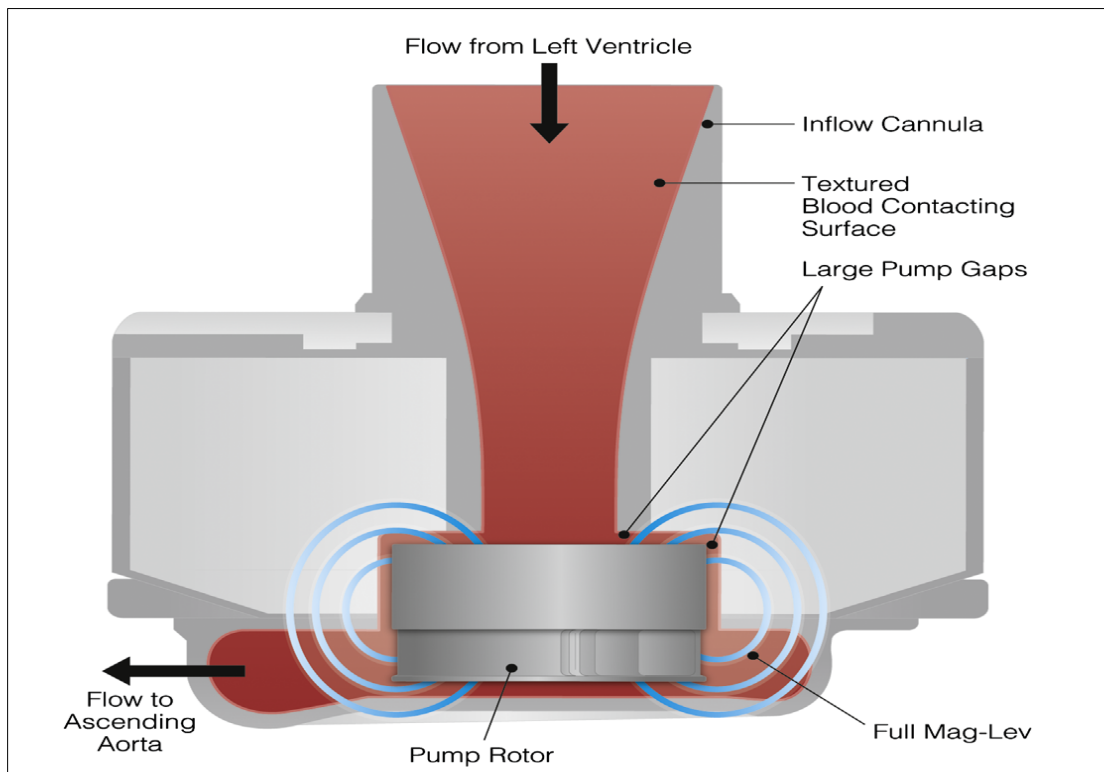


Figure 8: Internal Mechanics of the HeartMate III⁶⁶

The HeartMate III revolutionizes MCS design, not only for its use of magnetism, but also for implementing an element that harkens back to the first-generation models: pulsatile flow. Although the HeartMate III is classified as a CF-LVAD, the rotor mechanism will depart from its designated operational speed at periodic intervals, creating flow disruption. Regular, brief pauses in flow will act as a mechanized heartbeat, imitating natural cardiac contractility similar to volume-displacement technology. The artificial pulse may occur up to 30 times per minute, separate from the heart's natural rhythm.¹⁶ During development, the artificial pulse mode was tested in sheep where the speed of the device fluctuated between 1,500 and 5,500 rpm at 60 beats per minute; researchers noted that the estimated equivalent pressure (a measure of pulsatility) rose significantly when pulse pressures were subsequently increased. The enhanced pulsatility function promotes myocardial recovery and regeneration of tissue, as well as improves wash area coverage to decrease thrombus formation.⁶⁵ In computational fluid dynamic trials, researchers tested the HeartMate III at flows between 0-12 L/min to observe evidence of stasis or turbulence. The authors noted clean fluid dynamics over the range of operating speeds, while no thrombus was observed at normal or low flow conditions with little evidence of stasis.⁶⁷

The HeartMate III incorporates textured titanium microspheres on all the blood-contacting surfaces of the device, with the exception of the rotor and rotor well. Like the HeartMates XVE and II, this biocompatible material promotes the growth of natural endothelia to create a pseudointima.^{16,65} The resulting biologic lining reduces the need for

anticoagulation therapy. In combination with larger clearance areas due to the use of the magnetic-levitation system, the biocompatible material further promotes a low thrombogenic environment.

The HeartMate III is implanted adjacent to the heart in a supradiaphragmatic position typically via median sternotomy. The inflow conduit is placed in an intrapericardial position, with the outflow graft anastomosed to the ascending aorta.^{66,68}

Although the HeartMate III has been studied in animal models since the early 2000s, it was first implanted in humans in Germany in 2014. The patient was a 55-year-old gentleman with a history of dilated cardiomyopathy and ESHF with ejection fraction of 10-15%. The procedure was performed without incident and the patient recovered well post-operatively. Nine months after implantation, the patient's functional status had recovered to NYHA I disease.⁶⁶

Little clinical study data is published about the HeartMate III, but what is available holds promise. The HeartMate 3 CE Mark Trial was the first prospective, non-randomized multi-center trial in humans that tested device performance and safety compared to the HeartMate II. Fifty patients from six European countries were implanted for DT or BTT between June and November 2014. The study's primary endpoint for overall survival at six months was set at a performance goal of 88%, based on the HeartMate II. The study found the HeartMate III exceeded the performance goal, with 92% overall survival at six months. The HeartMate III demonstrated no evidence of significant hemolysis, pump thrombosis or device failure necessitating pump exchange.⁶⁹ In addition, researchers noted stroke occurred in 12% of patients implanted with the

HeartMate III (8% ischemic, 4% hemorrhagic). The authors noted difficulties with intraoperative placement, infection and reaction to contrast media might have played a role in the incident of stroke. The trial exhibited increased survival and improved functional outcomes at six months with the HeartMate III, while adverse events occurred at similar or reduced rates than expected.⁶⁹ The MOMENTUM 3 clinical trial has enrolled 1,028 patients since September 2014 to evaluate the HeartMate III for safety and effectiveness compared to the HeartMate II for ESHF. Researchers' primary endpoints include overall short and long-term survival, as well as composite survival to transplant or adverse event (i.e. stroke) at 6 and 24 months post-implant. Primary data collection will be complete in November 2018.

METHODS

Study design

The CON-FLOW STROKE clinical trial will be a multicenter, prospective, randomized study examining the difference in performance of three CF-LVAD devices in terms of stroke-free survival as well as their respective incidence and risk of cerebrovascular accidents.

Study population and sampling

The study population will be selected from 59 cardiac transplant/mechanical circulatory support centers in the United States (Appendix VII). Eligible candidates for this study will have been diagnosed with advanced heart failure, classified as NYHA IIIb (dyspnea with mild physical activity) or end-stage, NYHA IV disease that is refractory to medical management. Patients meeting inclusion criteria will be enrolled regardless of individual device strategy (BTT or DT).⁷⁰ Appendix VIII provides a complete list of inclusion and exclusion criteria.⁷⁰ A sample size of 291 patients per cohort, totaling a population of 873 patients, will be enrolled in the study. Sample size will be calculated assuming a CVA incidence of 20% in the standard VAD population. We will aim to observe a 50% risk reduction in the interventional cohort, and will assume a confidence level of 95% to produce a study with 80% power. Patients will be considered a part of the study population upon signing informed consent; all consented patients will be included in the intent-to-treat analysis.

Intervention

The proposed study will have three arms; one study arm will be randomized to implantation with the HeartMate II (Thoratec Corporation, Pleasanton, CA), one arm will receive the HeartWare HVAD (HeartWare International Inc., Framingham, MA) and the final treatment group will be implanted with the HeartMate III (Thoratec Corporation, Pleasanton, CA). Eligible candidates will be randomized 1:1:1 between the three device groups. Randomization will be stratified by study center and blocked to maintain a 1:1:1 ratio over time. The randomization process will be conducted using an electronic data capture system (Merge Healthcare, Morrisville, NC).⁷⁰ In addition, each study center will be limited to a maximum of 50 randomized patients to control for geographic and demographic differences across regions. All study patients, regardless of device, will be managed in accordance to the current standards of care set forth by the International Society for Heart and Lung Transplant Guidelines for Mechanical Circulatory Support.²²

HeartMate II

The HeartMate II is a second generation, continuous-flow left ventricular assist device designed with an internal axial-flow, direct-contact blood pump. The HeartMate II is connected to an external power source and controller unit via a percutaneous driveline. The axial rotor system produces flow by spinning at 8,000 – 12,000 rpm. The device is implanted in a subdiaphragmatic position, within an artificially made peritoneal pocket. A textured biocompatible material is incorporated in the design to promote growth of natural endothelia. Patients will be treated with an antithrombotic regimen, consisting of a vitamin K antagonist and antiplatelet medications.

HeartWare HVAD

The HeartWare HVAD is a third generation, continuous-flow left ventricular assist device designed with an internal, centrifugal blood pump that incorporates passive magnets and hydrodynamic thrust bearings to produce tangential flow. The HeartWare HVAD rotor system implements levitation technology.¹⁶ The HeartWare HVAD is implanted in an intrapericardial position, in contrast to the second-generation device. The centrifugal pump rotors spin to produce flow at 1,800 – 3,200 rpm. Patients will be treated with an antithrombotic regimen, consisting of a vitamin K antagonist and antiplatelet medications.

HeartMate III

The HeartMate III is an advanced third generation, continuous-flow left ventricular assist device designed with a more compact centrifugal pump with a solely magnetic levitated rotor system. The device has increased gaps for flow that are 10-20 times greater than those in hydrodynamic bearing systems.^{16,66} The rotor mechanism will depart from its designated operational speed at periodic intervals, creating flow disruption, acting as a mechanized heartbeat. The artificial pulse may occur up to 30 times per minute, separate from the heart's natural rhythm.¹⁶ Flow is produced at a rotor speed of 3,000 – 4,000 rpm. The device is implanted in an intrapericardial position. A textured biocompatible material promotes growth of natural endothelia. Patients will be treated with an antithrombotic regimen, consisting of a vitamin K antagonist and antiplatelet medications.

Study variables and measures

Study variables of interest include stroke-free survival over a 24-month, post-implantation period. In addition, the incidence of cerebrovascular accidents – whether ischemic or hemorrhagic – will be documented within the same study period.

Stroke-free survival will be defined as the period of time post-implantation in which a patient is without debilitating or lethal CVA while on LVAD support. CVA will be defined in accordance to the INTERMACS definition: any new focal or global neurologic deficit ascertained by a standard neurologic examination (via a neurologist or qualified provider) and documented with appropriate diagnostic tests and consultation notes.^{2,71}

Incidence of CVA will be calculated as a percentage of the total number of observed, new CVAs in the total study population at sequential post-implantation time periods: 6, 12 and 24 months.

Recruitment

Patients will be obtained primarily via provider referral from cardiology and cardiac surgery practices around the 59 cardiac transplant/mechanical circulatory support centers in the United States. In addition, ambulatory INTERMACS profiles 4-6 patients will be sent letters of notice via contact information listed with the INTERMACS national registry. High-risk, acute patients ranked as INTERMACS profiles 1-3 will be assessed for study eligibility pending clinical status by the appointed study investigator or their representative team at each respective center.

Data collection

Data will be collected via prospective review of each center's daily medical record in the immediate post-implantation period during their inpatient stay. Official neurology consultation notes will be reviewed for report findings from diagnostic imaging and testing. Upon discharge following surgery, patients will be sent home with visiting nursing three days per week for an additional 4 weeks, and then tapered to once weekly and finally, as often as the patient requires. Once discharged, CVA events will be monitored as they occur through visiting nurse and emergency department records. Any and all CVAs will be noted for date and time for each patient. In addition, CVAs will be documented for stroke type: ischemic or hemorrhagic. Additional data, including coagulation study values at the time of stroke, current antithrombotic regimen dosing and presence of concurrent infection will be documented. Stroke-free survival and incidence of CVA will be reported at 6, 12 and 24-months post-implantation.

Data analysis

A statistician group consulted by the clinical trial investigators will perform all data analysis using a statistical computing program (i.e. SPSS). Stroke-free survival will be calculated using log-rank tests and reported using Kaplan-Meier survival curves. In addition, the mean time to stroke in months will be calculated using a three-way analysis of variance to observe for significant difference in time across all treatment-arms. If a significant mean time to stroke is identified, a Tukey method will be used to further identify significance between one or more of the treatment arms. Chi-square and odds ratio analysis will be performed for incidence of stroke and to determine likelihood of

CVA event with each device. Correlation between each device and incidence of stroke will be analyzed using a Pearson's correlation coefficient. An additional Chi-square analysis will be performed to characterize likelihood of CVA type – ischemic or hemorrhagic – in each treatment arm.

Timeline and resources

Personnel:

- Study coordinator at each respective center
- Primary investigator at each respective center
- MCS/VAD coordinator
- Heart Transplant/MCS clinician teams
- Thoratec Corporation, HeartWare International Inc. representatives
- Cardiac Surgery/Cardiac Critical Care medical and nursing specialists accustomed to the management needs of MCS patients
- Neurology consulting team
- Statistician consulting group

Special Resources:

- HeartMate II CF-LVADs
- HeartWare HVAD CF-LVADs
- HeartMate III CF-LVADs

Timeline: see Table 7 on the following page

Table 7. Timeline for CON-FLOW Clinical Trial

May – September 2016	<ul style="list-style-type: none">- IRB proposal submitted/approved
September 2016 – September 2017	<ul style="list-style-type: none">- Contact and recruit study centers for participation- Contact ambulatory MCS patients via INTERMACS registry- Identification of study subjects
September 2016 – September 2019	<ul style="list-style-type: none">- Device implantation and monitoring- Stroke-free survival and incidence of CVA calculated at 6, 12 and 24 months post-implantation
September – October 2019	<ul style="list-style-type: none">- Completion of data collection period
October 2019 – October 2020	<ul style="list-style-type: none">- Data consolidation and analysis- Preparation and submission of manuscript

Institutional Review Board

A proposal will be submitted for IRB approval. CON-FLOW STROKE is a randomized clinical trial. Enrolled patients, given their general higher acuity and the nuances of MCS management, are subject to greater than minimal risk, and therefore this study will warrant full board review.

CONCLUSION

Discussion

To date, this investigator was unable to find study data comparing stroke-free survival, incidence and associated risk of CVA between three top-market CF-LVADs: HeartMate II, HeartWare HVAD and HeartMate III. Several major trials only investigated two of the devices in question. There have been no multicenter, prospective, randomized studies completed that specifically explore continuous-flow device design features and associated incidence and risk for CVA.

The proposed study is limited in regards to its ability to assess the effect of each device design without confounding variables. The exclusion criteria were designated to eliminate patients whose clinical status has a high likelihood for peri-/post-operative morbidity and mortality. However, patients who are eligible but categorized as INTERMACS profiles 1 and 2 represent a highly acute population, at higher risk for 30-day and 1-year mortality, based on Futile Implant Scores.²³ Critical patients are at increased risk for systemic inflammation and therefore at greater risk for a procoagulant state. Other confounding factors include medical non-compliance with anticoagulation protocols as well as concurrent infection, which may place patients at risk for CVA. Aortic cross-clamping times will suffer interpersonal variability based on intraoperative technical difficulty. As a result, patients may be at greater risk for cerebral hypoperfusion and CVA in the immediate post-operative period secondary to increased cross-clamp times and ventricular air emboli due to cardiopulmonary bypass. In addition, complications from the surgery may pose risk for CVA; investigators will be unable to

differentiate etiology of stroke due to device or procedure. Patient's suffering high intraoperative blood losses necessitating multiple blood cell transfusions are at higher risk for stroke; investigators would be unable to differentiate the etiology of stroke between device or transfusion.⁷² Blood pressure controls would aim to maintain MAP between 70-80 mm Hg; patients experiencing CVA at pressures above 90 mm Hg may confound evidence to support CVA was caused by the device or due to hypertensive state.

The generalizability of this study will be based on the large sample size, collected from all regions in the USA. In addition, the results of this study can be applied to acute and ambulatory patients eligible for implantation according to the INTERMACS profiling system, regardless of planned device strategy (BTT or DT).

The greatest strength of this study is that it is a prospective, randomized trial comparing three CF-LVAD models in terms of performance regarding prevention of CVA. It will be one of the first trials to specifically analyze data regarding CVA in CF-LVADs on such a widespread scale.

Summary

Patients suffering from refractory, ESHF suffer 1-year mortality rates as high as 20-50%.^{6,8} Heart transplantation is the definitive treatment for ESHF. Cardiac transplant has been found to improve quality of life and survival compared to established therapies, but not every ESHF patient is a likely candidate due to strict eligibility criteria.⁸ Long-duration mechanical circulatory assistance, via BTT or DT, can provide cardiac output support in patients who are ineligible for or awaiting transplant. Continuous-flow

technology has shown significantly improved actuarial survival at 2-year follow-up compared to pulsatile LVADs.⁵⁵ However, CF-LVADs are associated with reduced pulse pressure, hemolysis, bleeding and thromboembolic events. Cerebrovascular accidents have persisted as one of the major causes for morbidity and mortality in the CF-LVAD population. LVADs are associated with endothelial dysfunction and promote a procoagulant state. Associated antithrombotic regimens predispose to hemorrhagic CVAs. An advanced third-generation CF-LVAD, the HeartMate III, utilizes magnetic levitation technology, boasts wider gaps for flow, incorporates biocompatible textured materials and has clean fluid dynamics with little evidence for flow stasis. Preliminary results from a European study noted a 12% overall incidence of stroke in the HeartMate III.⁶⁹

This study will provide data supporting or refuting the stroke-free survival performance status of an advanced third-generation CF-LVAD in comparison to previous LVAD models currently FDA approved for BTT and DT. Evidence from this trial can be used to provide information about the relative risk for CVA for each device, and guide future research into the efficacy of magnetic levitation technology.

Clinical and/or public health significance

MCS mechanisms allow ESHF patients to live fuller lives. CF-LVADs have provided similar survival and quality of life outcomes compared to allograft transplant. However, stroke remains a leading cause of morbidity in this patient population and limited data exists about the long-term morbidity and mortality of stroke in CF-LVADs.⁵ This study aims to provide widely generalizable evidence about a device's associated incidence and

risk of CVA. The results may help to guide treatment paradigms, device assignment and future development of technologies that mitigate stroke risk in this high-risk population.

APPENDIX I

Definition of Advanced/End-Stage Heart Failure

1. Severe symptoms of HF with dyspnea, and/or fatigue at rest or with minimal exertion (NYHA III or IV)
2. Episodes of fluid retention (pulmonary and/or systemic congestion, peripheral edema) and/or of reduced cardiac function output at rest (peripheral hypoperfusion)
3. Objective evidence of severe cardiac dysfunction, shown by at least one of the following:
 - a) A low LVEF (<30%)
 - b) A severe abnormality of cardiac function on Doppler echocardiography with a pseudo-normal or restrictive mitral flow pattern
 - c) High LV filling pressures (mean PCWP > 16 mmHg and/or mean RAP >12 mmHg by pulmonary artery catheterization)
 - d) High BNP or NT-proBNP plasma levels, in the absence of non-cardiac causes
4. Severe impairment of functional capacity shown by one of the following:
 - a) Inability to exercise
 - b) 6-MWT distance < 300 meters or less in females or patients greater than or equal to 75 years of age
 - c) Peak V_{O_2} < 12-14 ml/kg/min
5. History of 1 or more HF hospitalizations within previous 6 months
6. Presence of all of the above listed features despite attempts to optimize therapy with diuretics, RAA system inhibitors and beta blockers, unless these interventions are poorly tolerated or contraindicated, and CRT, when indicated

HF (heart failure); NYHA (New York Health Association); LVEF (left ventricular ejection fraction); PCWP (pulmonary capillary wedge pressure); RAP (right atrial pressure); BNP (brain natriuretic peptide); NT (N-terminal); 6-MWT (6-minute walk test); VO_2 (oxygen consumption); RAA (renin-angiotensin-aldosterone); CRT (cardiac resynchronization therapy); Adapted from Kyo, 2014

APPENDIX II

Contraindications for Cardiac Transplantation

Absolute Contraindications

Systemic illness with a life expectancy < 2 years despite HT, including:

- Active or recent solid organ or blood malignancy within 5 years
- AIDS with frequent opportunistic infections
- SLE, sarcoid or amyloidosis that has multisystem involvement and is still active
- Irreversible renal or hepatic dysfunction in patients considered only for HT
- Significant obstructive pulmonary disease ($F_{EV1} < 1$ L/min)

Fixed Pulmonary Hypertension

- Pulmonary artery systolic pressure > 60 mm Hg
- Mean transpulmonary gradient > 15 mm Hg
- Pulmonary vascular resistance > 6 Wood units

Relative Contraindications

Age > 72 years

Any active infection (except for device-related infection in VAD recipients)

Active peptic ulcer disease

Severe diabetes mellitus with end-organ damage

Severe peripheral vascular disease or cerebrovascular disease

- PVD not amendable to surgical or percutaneous therapy
- Symptomatic carotid stenosis
- Ankle brachial index < 0.7
- Uncorrected abdominal aortic aneurysm > 6 cm

Morbid obesity ($BMI > 35$ kg/m²) or cachexia ($BMI < 18$ kg/m²)

Creatinine > 2.5 mg/dL or creatinine clearance < 25 ml/min*

Bilirubin > 2.5 mg/dL, serum transaminases > 3-times normal, INR > 1.5 off warfarin

Severe pulmonary dysfunction with $F_{EV1} < 40\%$ normal

Recent pulmonary infarction within 6 to 8 weeks

Difficult-to-control hypertension

Irreversible neurological or neuromuscular disorder

Active mental illness or psychosocial instability

Drug, tobacco, or alcohol abuse within 6 months

Heparin-induced thrombocytopenia within 100 days

*Potentially suitable for HT if inotropic support and hemodynamic management produce a creatinine < 2 mg/dL and creatinine clearance > 50 ml/min; combined heart-kidney transplantation may be advised

AIDS (acquired immunodeficiency syndrome); HT (heart transplant); SLE (systemic lupus erythematosus); F_{EV1} (forced expiratory volume in 1 second); VAD (ventricular assist device); PVD (peripheral vascular disease); BMI (body mass index); Adapted from Mancini and Lietz, 2010

APPENDIX III

INTERMACS Classifications

Profile	Status	Description	Time-frame for Intervention
1	Critical Cardiogenic Shock	Life-threatening hypotension despite escalating inotropic support, hypoperfusion, worsening acidosis and/or lactate levels	Definitive therapy indicated within hours
2	Progressive Decline	Declining function despite IV inotropic support with worsening renal function, nutritional status, volume imbalance; may be unable to tolerate inotropes	Definitive therapy indicated within days
3	Stable, Inotrope- dependent	Stable blood pressures, organ function, nutrition and symptoms on continuous IV inotropic support and/or temporary circulatory support device for weeks to months. Repeated failure to wean from support due to hypotension or renal dysfunction	Definitive therapy indicated; elective intervention within weeks to a few months
4	Resting- symptoms	Stabilized close to normal volume status with daily symptoms at rest or during ADL; diuretic dosing fluctuates; more intensive therapy or surveillance should be considered; interchange with profile 5	Definitive therapy indicated; elective intervention within weeks to a few months
5	Exertion Intolerant	Comfortable at rest and with ADLs; can not engage in any other activity; home-bound; refractory elevated volume status and renal dysfunction may occur, which predisposes patient to worsening disease (profile 4 or greater). Nutritional and organ function may be marginal; may require definitive intervention.	Variable urgency; intervention predicated on nutritional status, organ function and activity level
6	Exertion Limited	No evidence of volume overload, comfortable at rest, with ADLs and minor activities outside the home. Fatigues with minimal, meaningful activity. Cardiopulmonary and physiologic testing required to confirm severity of cardiac dysfunction	Variable urgency; intervention predicated on nutritional status, organ function and activity level
7	Advanced NYHA III HF	Patients without current or recent episodes of fluid imbalance, live comfortable with meaningful activity, but limited to mild exertion.	Transplant or MCS may not be currently indicated

ADL (activities of daily living); IV (intravenous); MCS (mechanical circulatory support);
Adapted from Kyo, 2014

APPENDIX IV

Lietz-Miller Score for Pre-operative Evaluation/Futile Implant Score

Patient Characteristic	Weighted Risk Score
Platelet count <148,000 uL	7
Serum albumin < 3.3 g/dL	5
INR > 1.1	4
Vasodilator therapy	4
Mean pulmonary arterial pressure < 25 mmHg	3
Aspartate aminotransferase > 45 U/mL	2
Hematocrit < 34%	2
Blood urea nitrogen > 51 U/dL	2
No intravenous inotropes	2
Score Interpretation – 1-Year Survival % with LVAD Implant ^{28,73}	
Low-risk (0-8)	81.2%
Medium-risk (9-16)	62.4%
High-risk (17-19)	27.8%
Very high-risk (>19)	10.7%

INR (international normalized ratio); LVAD (left ventricular assist device); Adapted from Lietz et al., 2007, Slaughter et al., 2010, Peura et al., 2012

APPENDIX V

Factors Determining Placement of MCS for Bridge Strategy

Severity of CHF

- INTERMACS profile I-IV
- Seattle Heart Failure Model with 1-year mortality > 25%
- Heart Failure Survival Score, high-risk group

Feasibility of LVAD Placement

- Cardiac anatomy (aortic insufficiency, congenital heart disease, restrictive cardiomyopathy, prosthetic valve)
- Perioperative Score
 - Futile Implant Score
 - Coagulopathic, RA pressures, infection status

Need for BiVAD

- RVSWI
- University of Michigan RVAD Score

Estimated Wait-list Time for Transplant

- Blood type
- Sensitization
- Weight

CHF (congestive heart failure); RA (right atrial); BiVAD (biventricular assist device); RVSWI (right ventricular stroke work index); RVAD (right ventricular assist device); Adapted from Mancini and Lietz, 2010

APPENDIX VI

Comparison of Adverse Events in Continuous-Flow and Pulsatile LVADs

Subgroup	Continuous-Flow LVAD (N=133) (211 patient-yr)		Pulsatile-Flow LVAD (N=59) (41 patient-yr)		Relative Risk (95% CI)	P Value for Interaction
	no. (%)	no. of Events/ Patient-Yr	no. (%)	no. of Events/ Patient-Yr		
Pump replacement	12 (9)	0.06	20 (34)	0.51		<0.001
Stroke	24 (18)	0.13	8 (14)	0.22		0.21
Ischemic	11 (8)	0.06	4 (7)	0.10		0.38
Hemorrhagic	15 (11)	0.07	5 (8)	0.12		0.33
LVAD-related infection	47 (35)	0.48	21 (36)	0.90		0.01
Local non-LVAD infection	65 (49)	0.76	27 (46)	1.33		0.02
Sepsis	48 (36)	0.39	26 (44)	1.11		<0.001
Bleeding						
Bleeding requiring PRBC	108 (81)	1.66	45 (76)	2.45		0.06
Bleeding requiring surgery	40 (30)	0.23	9 (15)	0.29		0.57
Other neurologic event	29 (22)	0.17	10 (17)	0.29		0.14
Right heart failure						
Managed with extended use of inotropes	27 (20)	0.14	16 (27)	0.46		<0.001
Managed with RVAD	5 (4)	0.02	3 (5)	0.07		0.12
Cardiac arrhythmia	75 (56)	0.69	35 (59)	1.31		0.006
Respiratory failure	50 (38)	0.31	24 (41)	0.80		<0.001
Renal failure	21 (16)	0.10	14 (24)	0.34		<0.001
Hepatic dysfunction	3 (2)	0.01	0	0.00		
LVAD thrombosis	5 (4)	0.02	0	0.00		
Rehospitalization	107 (94)	2.64	42 (96)	4.25		0.02

0.0 0.5 1.0 1.5

← Continuous-Flow Better Pulsatile-Flow Better →

LVAD (left ventricular assist device); RVAD (right ventricular assist device); Adapted from Slaughter et al., 2009

APPENDIX VII

List of Cardiac Transplant/Mechanical Circulatory Support Centers in the United States

<i>State</i>	<i>Center</i>
Arkansas	Baptist Health Medical Center
California	Cedars Sinai Medical Center
	University of California, San Diego
	Sharp Memorial Hospital
	Stanford University
Colorado	University of Colorado Hospital
Connecticut	Yale New Haven Hospital
District of Columbia	MedStar Washington Hospital Center
Florida	Shands Hospital at University of Florida
	Florida Hospital
	Tampa General Hospital
Georgia	Piedmont Heart Institute
Illinois	Northwestern Memorial Hospital
	University of Chicago Medical Center
	Advocate Christ Medical Center
Indiana	IU Health/Methodist Hospital
	St. Vincent Hospital
Iowa	University of Iowa Hospitals and Clinics
Kentucky	Jewish Hospital

<i>State</i>	<i>Center</i>
Louisiana	Ochsner Medical Center
Massachusetts	Brigham & Women's Hospital
Michigan	University of Michigan
	Henry Ford Hospital
	Spectrum Health Butterworth Hospital
Minnesota	University of Minnesota Medical Center
	Mayo Clinic Rochester
Missouri	Barnes Jewish Hospital
Nebraska	University of Nebraska Medical Center
New Jersey	Newark Beth Israel Medical Center
New York	Montefiore Medical Center
	Mt. Sinai Medical Center
	Columbia University Medical Center
	University of Rochester Medical Center
North Carolina	University of North Carolina at Chapel Hill
	Carolinas Medical Center
	Duke University
Ohio	Cleveland Clinic Foundation
	Ohio State University Medical Center
Oklahoma	INTEGRIS Baptist Medical Center

<i>State</i>	<i>Center</i>
Oregon	Oregon Health and Science University
Pennsylvania	Hershey
	Hospital of the University of Pennsylvania
	Thomas Jefferson University Hospital
	Allegheny General Hospital
South Carolina	Medical University of South Carolina
Tennessee	Vanderbilt University Medical Center
	St. Thomas West Hospital
Texas	Baylor Research Institute
	Memorial Hermann Health Systems
	Methodist Houston
	Texas Heart Institute
Virginia	University of Virginia Medical Center
	Inova Fairfax Hospital
	Sentara Norfolk General Hospital
	Bon Secours St. Mary's Hospital
	Virginia Commonwealth University
Washington	University of Washington Medical Center
Wisconsin	St. Luke's Medical Center
	University of Wisconsin Hospitals and Clinics

APPENDIX VIII

CON-FLOW STROKE Inclusion and Exclusion Criteria

Inclusion Criteria

1. Subject must be at least 18 years of age at enrollment.
2. Patient or legally authorized representative has signed the informed consent form.
3. Body surface area (BSA) greater than or equal to 1.2 m²
4. NYHA Class III with dyspnea upon mild physical activity or NYHA Class IV, refractory to medical management (see item #6)
5. LVEF less than or equal to 25%
6. Inotrope dependent or cardiac index < 2.2 L/min/m² while not on inotropes but meets one of the following additional requirements:
 - a. On optimal medical management, based on current heart failure practice guidelines for at least 45 of the last 60 days but are failing to respond
 - b. Advanced heart failure diagnosed for at least 14 days AND dependent on intra-aortic balloon pump (IABP) for at least 7 days
7. Patient meets United Network for Organ Sharing (UNOS) Status 1A or 1B listing criteria, if planned device strategy is bridge-to-transplant (BTT).

Exclusion Criteria

1. Existence of any ongoing mechanical circulatory support other than IABP.
2. History of previous organ transplant.
3. History of confirmed, unrepaired abdominal aortic aneurysm > 5 cm.
4. Cardiothoracic surgery within 30 days of enrollment.
5. Acute myocardial infarction within 14 days of implant as diagnosed by ST or T wave changes, diagnostic biomarkers, ongoing pain and hemodynamic abnormalities.
6. On ventilator support >72 hours within the four days immediately prior to study enrollment.
7. Pulmonary embolus within three weeks of enrollment, as documented by computed tomography scan or nuclear scan.
8. Pregnancy, confirmed by serum or urine human chorionic gonadotropin (hCG) test if of childbearing age.
9. Technical obstacles, which pose an inordinately high surgical risk, in the judgment of the center investigator, cardiac surgery, and mechanical circulatory support and transplant team consensus.
10. Psychiatric disease/disorder, irreversible cognitive dysfunction or psychosocial issues are likely to impair study compliance and LVAD management.
11. Presence of active, uncontrolled infection.
12. Intolerance to anticoagulant or antiplatelet therapies or any other peri-/post-operative therapy the investigating team will required based on clinical status of the patient.

NYHA (New York Health Association); LVEF (left ventricular ejection fraction);
Adapted from Heatley, MS et al., 2016, Aaronson, KD et al., 2012

Exclusion Criteria Continued:

13. Presence of any one of the following risk factors for severe end-organ dysfunction/failure:
 - a. An INR > 2.0 not due to anticoagulation therapy
 - b. Total bilirubin > 43 umol/L (2.5 mg/dl), shock liver or biopsy proven liver cirrhosis
 - c. History of chronic obstructive pulmonary disease (COPD) defined by FEV1/FVC < 0.7, and FEV1 < 50% predicted.
 - d. Fixed pulmonary hypertension with a most recent PVR greater than or equal to 8 Woods units that is unresponsive to pharmacologic intervention.
 - e. History of stroke within 90 days of enrollment or history of severe cerebrovascular disease and/or significant, uncorrected carotid stenosis (> 80%)
 - f. Serum creatinine > 221 umol/L (2.5 mg/dl) or the need for chronic renal replacement therapy
 - g. Significant peripheral vascular disease (PVD) accompanied by pain at rest or extremity ulceration.
14. Patient has moderate to severe aortic insufficiency without plans or correction during implantation procedure.
15. Patients with mechanical, animal or human tissue heart valves are excluded.
16. Pre albumin < 150 mg/L (15 mg/dL) or Albumin < 30g/L (3 g/dL) [if only one value available]; Pre albumin < 150 mg/L (15 mg/dL) and Albumin < 30g/L (3 g/dL) [if both values available]
17. Planned biventricular assist device (Bi-VAD) support prior to enrollment.
18. History of known hypo- or hyper-coagulable states such as disseminated intravascular coagulation (DIC) and heparin induced thrombocytopenia (HIT)
19. Participation in any other clinical investigation that is likely to confound study results or affects the study.
20. Any condition other than HF that could limit survival to less than 24 months.

INR (international normalized ratio); FEV1 (forced expiratory volume after 1 second); FVC (forced vital capacity); Adapted from Heatley, MS et al., 2016, Aaronson, KD et al., 2012

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CURRICULUM VITAE

Douglas-Jarrett Cole Turno B.S., M.S., PA-S III

1991

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Education

Boston University School of Medicine Physician Assistant Program - Boston, MA 2014-2016

Master of Science

Thesis: An Evaluation of Continuous-Flow Left Ventricular Assist Devices and the Incidence of Stroke in Patients Awaiting Heart Transplantation

Stonehill College - North Easton, MA 2009-2013

Bachelor of Science

Major: Neuroscience

Minor: Healthcare Administration

Work Experience

Newton-Wellesley Hospital: Outpatient Surgery Center

November 2013 – April 2014

Operating Room Assistant

Responsible for assisting with day-to-day nursing work flow of an outpatient orthopedic surgical center; act as a pre-op aide and anesthesia technologist to monitor vitals, assist with nerve blocks and prepare patients for procedures; act as an operating room aide to assist with surgical turnover, help staff with final preparations and sterilization before surgery as well partake in patient positioning; work as a PACU aide to assist nursing staff in monitoring a patient throughout post-op recovery

Signature Healthcare Brockton Hospital

March 2013 – October 2013

Clinical Care Assistant, A-2 Inpatient Floor

Responsible for assisting nursing staff with daily patient care services including: monitoring vitals, bathing, toileting, feeding, wound care, patient observation and/or restraint, laboratory sample transport, and assist with any other services as requested by nursing staff

- Employee of the Month September 2013: recognized for performing life-saving Heimlich maneuver on fellow employee

Stonehill College EMS

November 2010 – May 2013

Emergency Medical Technician

Responsible for provision of medical care as a MA State certified EMT-B for intramural and club-sporting events hosted at Stonehill College

Boston Children's Hospital

November 2010 – March 2013

Boston Adult Congenital Heart Service (B.A.C.H)

Administrative Assistant, Clinical Observer

Responsible for a wide-variety of administrative duties including organization, distribution and processing of patient data, in addition to assisting on-going research projects and managing patient-exercise initiatives.

Relevant Certification

Physician Assistant License, State of Massachusetts <i>pending</i>	2016 – Present
Certification by the National Commission on Certification of Physician Assistants <i>pending</i>	2016 – Present
Advanced Cardiac Life Support Certification	February 2015
Emergency Medical Technician – Mass BLS Certification	September 2010, April 2013

Leadership Positions/Opportunities

<u>AAPA Leadership and Advocacy Summit – Alexandria, VA</u>	March 2015
Selected by PA program faculty to attend leadership and legislative focused conference; learn and cultivate skills in addressing state and federal congressional officials on physician assistant-related policy issues; networking opportunity with PAs and PA students from across the country	
<u>Massachusetts Association for Physician Assistants (MAPA)</u>	2014 – 2015
<u>Student Representative for BUSM Physician Assistant Program</u>	
Elected board member of the Carl Toney Student Society – Student leadership	

Community Service

<u>Boston Healthcare for the Homeless – Fall Women’s Health Fair</u>	October 2014
Responsible for assisting BHCH dentists with oral health examinations and health counseling	
<u>H.O.P.E Mission - Honduras</u>	March 2012
Responsible for basic medical assessment of patients at a local parish clinic, aiding nurses in the administration of care and coordination of treatment; acted as lead provider for a visiting clinic held in the village of Las Canas.	

Abstracts

Turno, D., Huntsman, C., Interprofessional Oral Healthcare in the Homeless Population, *Boston University School of Medicine Physician Assistant Program*, Boston Massachusetts, October 2014 and *Massachusetts Association of Physician Assistants Fall CME Conference Student Presentations*, Cambridge Massachusetts, November 2014

Turno, D., Huntsman, C., Interventional Counseling for Tobacco Cessation and Nutrition in the Homeless Community, *Boston University School of Medicine Physician Assistant Program*, Boston Massachusetts, October 2014 and *Massachusetts Association of Physician Assistants Fall CME Conference Student Presentations*, Cambridge Massachusetts, November 2014

Presentations

Turno, D., End Stage Heart Failure and Palliative Care, VA Healthcare Brockton Community Living Center, Brockton Massachusetts, October 2015

Turno, D., Abdominal Compartment Syndrome, Roger Williams Medical Center, Providence Rhode Island, November 2016

Turno, D., Stroke in the Young, Boston University School of Medicine Physician Assistant Program, Boston Massachusetts, December 2015

Turno, D., When the Heart Won't Go On – Mechanical Circulatory Support, Boston University School of Medicine Physician Assistant Program, Boston Massachusetts, March 2016

Publications

- Fernandes SM, Khairy P, Fishman L, et al. Referral Patterns and Perceived Barriers to Adult Congenital Heart Disease Care. *J Am Coll Cardiol.* 2012;60(23):2411-2418. doi:10.1016/j.jacc.2012.09.015.

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Available upon request