PREDICTORS OF OUTCOMES IN PATIENTS ON VENTRICULAR ASSIST DEVICES

by

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EPIDEMIOLOGY

ABSTRACT

Ventricular assist devices (VAD) are used as a bridge to transplant and to increase the quality of life in advanced heart failure patients. The use of the VAD is not without risks itself, with an increased risk of thromboembolism, hemorrhage and death. Therefore, we aimed to (1) evaluate predictors of thromboembolism; (2) design a score to predict hemorrhages in VAD patients; and (3) evaluate the change in kidney function post-VAD implant and to investigate the relationship between kidney function and mortality in VAD patients using data collected from the University of Alabama at Birmingham Mechanical Circulatory Support Clinic.

Over the 51.3 person-years of follow-up for the 115 participants, a total of 23 first thromboembolic events were encountered (Incidence Rate (IR) 4.5 events /10 patient years, 95% CI 29.1-66.2). There was an increased risk of thromboembolism with Early lactate dehydrogenase elevation, and estimated glomerular filtration rate <30 prior to VAD implantation while there was a decreased risk with good anticoagulation control.

Out of 115 patients, total of 36 patients experienced a hemorrhage during the first year (Incidence Rate 70 per 100 person years (95%CI 50-96). Patients with a VAD bleeding risk score ≥3 have the highest risk of hemorrhage compared to the 3 fold increased risk of hemorrhage for patients with a HAS-BLED score of ≥ 3 and the 2.5 fold increased risk with an extended HAS-BLED score of ≥3.
In the 228 patients, kidney function improves post implant with improvement in kidney function maintained over 1 year for all patients except those with CKD Stage 5 at baseline. Age at implant was the only statistically significant predictor of sustained improvement in kidney function. Regardless of baseline CKD stage, most patients experience an improvement in CKD stage after VAD implantation. Despite improvement in kidney function post VAD implant, patients with CKD stage 3b, 4 or 5 prior to VAD are at an increased risk of mortality post-VAD implantation.

In conclusion, this study identifies predictors of thromboembolism, creates a VAD specific bleeding risk score and highlights how pre-VAD kidney function is an important risk factor for mortality post-VAD.

**Keywords:** Ventricular assist device, mechanical circulatory support, thromboembolism, hemorrhage, kidney function
DEDICATION

To Nate
ACKNOWLEDGEMENTS

I would like to take this opportunity to thank all of my colleagues, mentors, family and friends for their support over the past four years. I am not able to mention each of you individually, but rest assured, your support and kind words were greatly appreciated.

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INTRODUCTION

Advanced Heart Failure

Heart failure is one of the leading causes of morbidity and mortality in the US with approximately 5.7 million Americans currently living with heart failure.\(^1, 2\) Treatment of HF ranges and is used to decrease symptom and disease progression as well as increase patient survival.\(^3, 4\) The best treatment options for end stage heart failure are a heart transplant or ventricular assist device (VAD).\(^4, 5\) VADs are mechanical pumps, either pulsatile or continuous flow, that aide in ventricular function and assist in circulation.\(^6\) Older device designs were based on pulsatile flow, in which the pump filled and emptied, with newer devices based on continuous flow principles, where blood is constantly being propelled into the circulation.\(^3\) The VAD was originally developed in the 1960s as a bridge to recovery. The use of the VAD increased when the strategy for device implantation expanded to include use as a temporary bridge to transplantation. The expanded indication for VAD use increased the survival rates of advanced heart failure patients and improved the outcomes of patients post transplantation.\(^6, 18\) While heart transplantation is the gold standard in treating end stage HF, there are fewer than 3000 donor organs available per year. This facilitated the evolvement of VAD therapy to include destination therapy, which is a permanent treatment and alternative to cardiac transplantation as a long-term solution for treating heart failure.\(^3\) The use of VADs as a destination therapy increases the quality of life for end stage heart failure patients not eligible for transplantation.\(^6, 19-24\) VAD technology has been rapidly evolving over
the last few years with improvements in device durability; with these improvements increasing the duration that patients with end-stage systolic heart failure can be supported on VADs. This coupled with the increasing prevalence of end stage heart failure means that VAD populations will increase, thereby increasing the survival rates of end stage heart failure patients.

Mortality in VAD Patients

Despite the increased survival rates and increase in quality of life, there is still a considerable amount of morbidity and mortality associated with VAD use. VAD use has increased the functional outcomes in advance heart failure patients, however there is still an increased risk of mortality. Previous studies have estimated approximately 50% of destination therapy VAD patients survive their first year, reducing the risk of mortality by 48% compared to patients who are only on medication management. Furthermore, approximately 23% of destination therapy VAD patients survive to two years. The current literature has focused on comparing VAD mortality rates between VAD patients and medical management patients. Previous studies have not been powered for sub-analysis, but have shown that younger people with VADs placed are less likely to experience a mortality event than older people.

Risk of Thromboembolism in VAD Patients

The increasing improvement in survival of VAD patients has led to recognition of complications associated with VADs with approximately 5-11% of VAD patients experiencing a thromboembolic event. Thromboembolism is associated with all VADs due to blood flowing over a non-biologic surface causing an increase in platelet activation, thereby requiring combination antiplatelet/anticoagulant therapy to
reduce this risk.(3) Despite this intense antithrombotic regimen, VAD patients remain at high risk for thromboembolic events such as pump thrombosis, venous thromboembolism and stroke.(36) Risk factors for thromboembolism in VAD patients include impaired renal function, increased BMI, pre-operative atrial fibrillation, and international normalized ratio (INR) measurements below 1.5.(37, 38)(39) In addition to these risk factors, VAD patients are at risk for hemolysis due to their device. Hemolysis is an early warning sign for pump thrombosis, with elevated markers of hemolysis, associated with increased risk of pump thrombosis.(40) One such marker, lactate dehydrogenase (LDH), when elevated has been recently identified as a risk factor for pump thrombosis.(40, 41)

Risk of Hemorrhage in VAD Patients

In addition to thromboembolism, VAD patients are at increased risk of hemorrhagic events with 15-60% of VAD patients experiencing a hemorrhagic event.(20, 27, 29-35). The combination antiplatelet/anticoagulant therapy predisposes a patient to higher risks of hemorrhagic neurological complications.(42-47) Gastrointestinal hemorrhagic events are problematic as well not only from the AC therapy, but also from hypoperfusion of the bowel wall due to the continuous flow of blood created by the VAD.(42, 48, 49) The risk for hemorrhagic events due to antiplatelet/anticoagulant therapy and acquired von Willebrand disease are an increasing issue.(3, 45, 47, 50) Previous studies have shown that after VAD implantation platelet activation is increased. Institution of combination antiplatelet/anticoagulant therapy contributes to platelet function restoration and clot mechanics restoration in patients with VADs. Additionally acquired von Willebrand disease may ensue due shear stress from the device unfolding large von Willebrand factor (v-WF) multimers and causing enzymatic activation,
resulting in breakdown of the multimer. (51-54) The levels of platelet inhibition (measured by PFTs) and the level of anticoagulation (measured by INR and PTTR) have not been well studied in VAD populations. Generally, device manufacturers recommend INR ranges, with clinical decision-making at the discretion of the treating physicians. There are not well-established algorithms for initiation and monitoring of antiplatelet/anticoagulant therapy. Because of the ongoing risks associated with platelet dysfunction there is a great need for the determination of the ideal regimen of thrombosis prophylaxis. (52)

**Kidney Function in VAD Patients**

While chronic hemodialysis is a contraindication to VAD implantation, decreased cardiac output induced renal insufficiency is not a contraindication with these patients experiencing improved renal function post VAD placement. (6) This contributes to patients experiencing decreased kidney function prior to VAD placement due to the progression of heart failure with improvement in renal function after VAD implantation. (3, 55) (56, 57) (58) Additionally, in order to be transplant eligible patients must have a creatinine clearance of at least 50 ml/min. (58) Patients with VAD implants demonstrate an improvement in kidney function following implantation. (55) However, the bulk of the evidence is based on assessment of kidney function in the early (7-30 days) post-implant period. Smaller, previous studies have determined that the presence of renal comorbidities prior to VAD placement have an impact on outcomes post VAD placement, but the risk of subsequent redevelopment of renal dysfunction after VAD placement is not well documented. (55, 59) Once the VAD is placed renal function begins
to improve, but pre-implant renal function remains a primary predictor of post implant renal failure in addition to adverse events.(56, 57)

**Implications for current research**

The trade-off of decreased mortality rates for increased adverse events is acceptable given the nature of end stage HF, but the frequency of adverse events experienced by VAD patients creates an imminent need to understand and further improve patient care to decrease these events. The influence of clinical factors and changing end-organ function on outcomes in VAD patients needs to be addressed.

The research presented in this dissertation represents important contributions to the literature on the topic of risk of thromboembolism, risk of hemorrhage and the influence of kidney function on mortality post-VAD.

In the first manuscript we evaluate the association between traditional risk factors, biomarkers of hemolysis and previously developed thromboembolism risk scores with risk of thromboembolism in VAD patients. We assessed the traditional risk factors kidney function prior to VAD implantation and level of anticoagulation control. Prior studies investigated the relationship between the hemolysis biomarker LDH and pump thrombosis. We investigated the relationship between LDH and risk of any type of thromboembolism while accounting for the relationship between anticoagulation control and kidney function. Finally, we investigated whether previously developed risk scores, both continuous and categorized, were associated with thromboembolism in this high-risk population.

In the second manuscript we evaluate the association between traditional risk factors and previously developed hemorrhage risk scores with the risk of hemorrhage in
VAD patients. We assessed traditional risk factors including, but not limited to, age at implant, history of gastrointestinal bleed prior to implant, history of atrial fibrillation prior to implant and history of hyperlipidemia prior to implant. In addition to the investigation into the association between previously developed risk scores, we developed a VAD specific risk score for predicting hemorrhage post-implant.

Finally, in the third manuscript we assess change in kidney function over time post-VAD implant, predictors of kidney function improvement post-implant, and the association between kidney function prior to VAD and thromboembolism, hemorrhage and mortality. Change in kidney function over time was assessed as a continuous change in function as well as a categorical change in kidney disease.
PREDICTORS OF THROMBOEMBOLIC EVENTS IN VENTRICULAR ASSIST DEVICE PATIENTS

by

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In preparation for Circulation: Heart Failure

Format adapted for dissertation
**Background:** Ventricular assist device patients (VAD) are at increased risk for thromboembolism. Biomarkers of hemolysis, such as lactate dehydrogenase (LDH), and poorly controlled INR values have been identified as predictors of thromboembolism.

**Methods and Results:** Patients aged 19 years and older who had a continuous flow VAD placed from 2006-2012 were included in this study (N=115). We assessed LDH elevation (≥ 600 IU/L) on the day of VAD implant prior to the implant, and early LDH elevation defined LDH elevation at VAD implantation, 14 days post implantation or 1 month post implantation; LDH measurements after a thromboembolism were excluded. Over the 51.3 person-years of follow-up, a total of 23 first thromboembolic events were encountered (Incidence Rate (IR) 4.5 events /10 patient years, 95% CI 29.1-66.2).

Patients with elevated LDH at VAD implantation had an increased risk for thromboembolism (HR 4.72, 95% CI 1.44-15.4, p=0.0103). In a multivariable model there was an increased risk of thromboembolism with Early LDH elevation (HR 4.95, 95%CI 1.69-14.4, p=0.003), and estimated glomerular filtration rate <30 prior to VAD implantation (HR 4.74, 95%CI 1.12-20.1, p=0.0346) while there was a decreased risk with good anticoagulation control, more than 60% of their time post VAD in the target INR range of 1.8-3.2 (HR 0.30, 95%CI 0.10-0.86, p=0.0247).

**Conclusion:** Our study is the first to highlight the association between pre-VAD LDH and post VAD thromboembolism. Furthermore, this study details the increased risk of thromboembolism due to early LDH elevation after accounting for additional risk factors in VAD patients.

**Key Words:** Ventricular assist device, thromboembolism, lactate dehydrogenase, mechanical circulatory support
**Introduction**

Heart failure (HF) affects approximately 5.7 million Americans and is one of the leading causes of morbidity and mortality in the US. (1-3) Although medical management is the mainstay of therapy, heart transplantation or ventricular assist device (VAD) implantation are increasingly used among patients with end stage HF. (4, 5) While VAD implantation improves survival among those with end-stage HF, approximately 5-11% of VAD patients experience a thromboembolic event within the first year of implantation, with reports as high as 30-50%, despite advances in device technology. (3, 6-11). To mitigate the increased risk of thromboembolism, VAD patients are usually treated with dual antithrombotic therapy of an anticoagulant (warfarin) and an antiplatelet (aspirin, dipyridimole, or clopidogrel or a combination). (3) Despite this intense antithrombotic regimen, VAD patients remain at high risk for thromboembolic events such as pump thrombosis, venous thromboembolism and stroke. (12) These factors all contribute to the morbidity and mortality recognized in VAD patients. The increasing incidence of thromboembolism, particularly pump thrombosis, has been highlighted in recent reports. (13, 14)

Consistent with other at-risk populations, risk factors for thromboembolism in VAD patients include impaired renal function, increased BMI, pre-operative atrial fibrillation, and international normalized ratio (INR) measurements below 1.5. (14, 15) (16) In populations at high risk for thromboembolism, such as patients with atrial fibrillation, the CHADS$_2$ and CHA$_2$DS$_2$-VASc scores have been used to identify those at greatest risk of thromboembolism. (17, 18) While these risk factors and scores are informative in other populations requiring chronic anticoagulation, additional risk factors...
need to be considered in VAD patients. As hemolysis frequently precedes pump thrombosis, biomarkers associated with hemolysis can serve as an early warning for impending pump thrombosis. Elevated lactate dehydrogenase (LDH), a sensitive marker for hemolysis, has been evaluated to assess the increased risk of pump thrombosis. However, previous investigations have been limited to cross-sectional assessments.

At our institution, the routine measurement of LDH facilitates our presentation of the change in LDH over a 1 year follow-up and enables evaluation of its association with thromboembolic events.

**Methods**

*Study Setting and Inclusion and Exclusion*

This study was conducted at the University of Alabama at Birmingham (UAB) under the approval of the Institutional Review Board. Patients aged 19 years and older who had a continuous flow VAD (HeartMate II (Thoratec Corporation, Pleasanton, CA) or HeartWare (HeartWare Inc, Framingham, MA) device) placed at UAB from 2006-2012 were included in this study. Patients were followed for 1-year post VAD implantation to assess outcomes. Loss to follow up is minimal since both inpatient and outpatient care occurs at UAB with routine clinic visits at least monthly.

*Data collection*
For all patients, a detailed baseline (pre-VAD) clinical phenotype including demographics (e.g. gender, race, ethnicity etc.), medical history before VAD (e.g. history of medical conditions, surgeries prior to VAD implant etc.), medications (e.g. antithrombotic medications and medications that influence thromboembolic events), and laboratory assessments (e.g. coagulation factors, liver function tests, kidney function tests etc.) was documented by a research assistant through retrospective medical record review. Post-VAD documentation included medications, laboratory assessments and outcomes. These were collected through medical records using definitions established by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Registry.(21)

**LDH Monitoring and Assay**

Lactate dehydrogenase was measured in VAD patients on the day of VAD implantation prior to the implant, and then 2 weeks ± 2 days, 1 month ± 2 days, 3 months ± 7 days, 6 months ± 7 days, 9 months ± 7 days and 12 months ± 7 days after VAD implantation. All samples were collected from a peripheral blood draw with special attention to specimen handling to avoid hemolysis. LDH levels were assessed by an enzymatic rate method, (22) that measures the change in absorbance at 340 nanometers (Beckman Coulter DCX 800 pro with SYNCHRON system, Beckman Coulter, Inc., Brea, CA) which is directly proportional to the activity of LDH in the sample. For adults, the reference range at UAB hospital laboratories is 120-240 IU/L for LDH. Based on the sensitivity and specificity of LDH as a predictor of thromboembolism, we defined
elevated LDH as $\geq 600$ IU/L, which is consistent with prior research on LDH levels in VAD populations.\(^{(20, 23)}\)

*Additional Risk Factors for Thromboembolism*

We also evaluated the influence of diabetes, atrial fibrillation, anticoagulation control, decreased kidney function, and thromboembolism risk scores on risk of thromboembolism. Factors with p-values $<$0.2 were included in multivariable analysis.\(^{(24)}\)

Among patients on warfarin, the proportion of time spent in target INR range (PTTR) is used as a measure of anticoagulation control. Poor anticoagulation control (low PTTR) is a risk factor for thromboembolism and hemorrhage. For patients on warfarin, the PTTR was estimated for each patient using the Rosendaal linear interpolation method.\(^{(25)}\) This method, which assumes a linear relationship exists between two consecutively measured INR values, allows one to allocate a specific INR value to each day for each patient. Time in target range for each patient was assessed by the percentage of interpolated INR values within the target range of 2.0–3.0 after attainment of first INR in target range. We also assessed proportion of time spent in extended target range (PTTRe; INR1.8-3.2) since deviations beyond this range usually trigger dose adjustments to minimize the increased risk of thrombosis and hemorrhage. PTTRe was categorized into Good control >60%, Moderate control $\geq 50 < 60\%$ and Poor control $< 50\%$.

Kidney function was assessed through the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-
EPI)(26) which incorporates gender, race, age, and serum creatinine (Scr; mg/dL). Kidney function was characterized with eGFR $\geq 60$ ml/min/1.73 m$^2$ considered to be no/mild kidney disease (CKD stage 1, 2); those with eGFR =30-59 ml/min/1.73 m$^2$ (CKD stage 3) considered to be moderate kidney disease and those with eGFR<30 ml/min/1.73 m$^2$ (or on dialysis) considered to be severe kidney disease (CKD stage 4, 5).(27, 28)

The thromboembolism risk scores, CHADS$_2$ and CHA$_2$DS$_2$-VASc, were assessed. The CHADS$_2$ risk score is a clinical prediction score ranging from 0- 6 for estimating the risk of thromboembolism in patients with atrial fibrillation. The score consists of 1 point for congestive heart failure, 1 point for hypertension, 1 point for age $\geq 75$, 1 point for diabetes and 2 points for prior history of stroke, transient ischemic attack or thromboembolism. The CHA$_2$DS$_2$-VASc risk score is an updated version of the CHADS$_2$ score to include additional stroke risk factors in the clinical prediction score. This updated scoring mechanism ranges from 0-10 and consists of 1 point for congestive heart failure, 1 point for hypertension, 2 points for age $\geq 75$, 1 point for diabetes, 2 points for prior history of stroke/transient ischemic attack/thromboembolism, 1 point for vascular disease, 1 point for age 65-74, and 1 point for female sex. The CHADS$_2$ and CHA$_2$DS$_2$-VASc score were evaluated as continuous variables and categorized into dichotomous risk groups.(17, 18) The CHADS$_2$ score was categorized into moderate risk (CHADS$_2$ $\geq$ 1) compared to high risk (CHADS$_2$ $\geq$ 2). The CHA$_2$DS$_2$-VASc score was categorized as moderate risk (CHA$_2$DS$_2$-VASc $\leq$3) compared to severe risk (CHA$_2$DS$_2$-VASc $\geq$4).

*Definition of Outcome*
The primary outcome of interest was any thromboembolic event defined as pump thrombosis requiring hospitalization, pulmonary embolus, deep vein thrombosis and ischemic stroke. Pump thrombosis was defined as a clinically documented pump thrombosis that required hospitalization for either medical management or pump exchange. Ischemic stroke was defined as a clinically documented ischemic stroke event diagnosed by a neurologist. DVT and pulmonary embolism were defined as a clinically documented DVT or PE event. As patients may experience multiple events within the 1-year follow-up period, only the first event was included in the analysis because the risk factors for a second event are heavily influenced by the first event. A sub analysis was conducted assessing early thromboembolism and late thromboembolism. An early thromboembolic event was defined as thromboembolism occurring within the first 30 days post-VAD implant. A late thromboembolic event was defined as defined as thromboembolism occurring after 30 days post-VAD implant.

Statistical Analysis

The $\chi^2$ test of independence was used to assess group differences for baseline demographic categorical variables and Wilcoxon Rank Sum for continuous variables. We evaluated whether elevated LDH at VAD-implantation was associated with risk of thromboembolism and early thromboembolism; and whether elevated LDH at 1-month was associated with risk of late thromboembolism. As early elevation of LDH (within the first month) is considered a risk factor for pump thrombosis, patients exhibiting elevation
at VAD implantation, 14 days post implantation or 1 month post implantation were categorized as Early LDH Elevation.\textsuperscript{14} Only LDH measurements prior to early thromboembolic events were included. Patients without this measurement were excluded from the analyses (N=18).

Repeated measures ANOVA was used to assess change in LDH over time among patients who experienced vs. did not experience thromboembolism. Kaplan-Meier curves with log rank tests were used to assess the influence of LDH on time to the thromboembolic event. Cox-proportional hazard modeling was conducted to evaluate the influence of LDH on risk of thromboembolism after adjustment for other factors. Log-log survival plots were used to assess the proportional hazards assumption. Patients were censored at the time of the first hemorrhage event, explantation (due to death, recovery or transplant) or at 1 year after VAD implantation. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC) at a non-directional alpha of 0.05.

**Results**

Of the sample of 127 patients with continuous flow VAD implants at treated at UAB between 2006 and 2012, a total of 115 patient the HeartMate II device (Thoratec Corporation, Pleasanton, CA) or the HeartWare (HeartWare Inc, Framingham, MA) were included in this study (Figure 1). Twelve patients implanted outside UAB were excluded as early data on anticoagulant controls and warfarin dosing was not available.. The mean age at implant was 52 years (±14.6), and the majority of patients were male (78.3%), white (67.8%) and implanted as a bridge to transplant (56.6%; Table 1).
Of the 115 patients in this study, 23 (20%) experienced a thromboembolism during the first year. A total of 11 thromboembolisms occurred within the first 30 days post-VAD implant with 12 thromboembolisms occurring more than 30 days post-VAD implant. Seven (30%) of the 23 experienced a second thromboembolic event and 7 (30%) of the 23 experienced a hemorrhage after the thromboembolic event within the first year. Patients experiencing thromboembolic events within the first year had a lower frequency of diabetes (21.7% vs 43.5%, p=0.031), atrial fibrillation (17.4% vs 42.4%, p=0.016) and a higher frequency of decreased kidney function (eGFR <30 ml/min/1.73m²) at VAD implantation (19.1% vs 6.7%, p=0.0136).

The 115 patients contributed 624.5 months (51.3 person years) of follow-up time. Patients were seen at least once a month, with an average of 1.4 (± 0.96) visits per patient per month (Table 2). Patients with a thromboembolism were seen more frequently each month compared to those who did not have a thromboembolism (2.7 times vs 1.8 times, p<0.0001) in the pre-thromboembolism time period. Anticoagulation control, measured as percent time in target range, was similar between patients with and without thromboembolism regardless of whether the standard INR range was used or the extended INR range. At the time of thromboembolic event, the average INR was 2.4 (SD 0.91). INR was sub-therapeutic among 4 patients at the time of the event.

A total of 56 patients had LDH measured at VAD implantation, and 7 (12.5%) of these patients had elevated LDH. There were 97 patients who had an Early LDH measurement, within the first month of VAD implantation, with 17 (17.5%) of these
patients having an elevated LDH measurement. As illustrated in Figure 2, the mean LDH increases over the first 14 days. Patients who experienced a thromboembolism in the first year post implant continue to have increased mean LDH levels at 1 month, compared to patients without a thromboembolic event. Patients with a thromboembolic event continued to have a higher mean LDH than those without a thromboembolic event, and this pattern remains throughout the follow-up after the thromboembolic event (p=0.0028).

**Association of LDH and Thromboembolism**

Over the 51.3 person-years of follow-up (Table 3), a total of 23 first thromboembolic events were encountered (Incidence Rate (IR) 4.5 events /10 patient years, 95% CI 29.1-66.2). Patients with elevated LDH at VAD implantation experienced a shorter time to thromboembolism (p=0.0046; Figure 3a), and an almost 5 fold increase in risk for thromboembolism (Hazard Ratio (HR) 4.72, 95% Confidence Interval (CI) 1.44-15.4, p=0.0103). Furthermore, elevated LDH at VAD implantation was associated with an increased risk of early thromboembolism (HR 5.55, 95%CI 1.32-23.3, p=0.0193). There was an association with elevated LDH at VAD implantation and late thromboembolism however this association was not statistically significant (HR 3.37, 95%CI 0.37-30.3, p=0.28). The small sample of LDH measurements at VAD implantation limited our ability to adjust for additional relationships.

Patients with Early LDH Elevation experienced a shorter time to thromboembolic events (Figure 3b; p=0.0198). There was an increased risk of thromboembolism
associated with Early LDH Elevation, with this association remaining after adjusting for kidney function at baseline and percent time in target INR range 1.8-3.2 post implant (HR 4.95, 95%CI 1.69-14.4, p=0.003; Table 4). Early LDH Elevation was associated with late thromboembolisms (HR 6.38, 95%CI 1.32-30.8, p=0.0211).

Additional Risk Factors for Thromboembolism

Significant differences in baseline kidney function, percent time spent in target INR range of 1.8-3.2, history of atrial fibrillation, and history of diabetes between those with and without thromboembolism were further evaluated.

Patients with an eGFR <30 prior to VAD implantation had an increased risk for thromboembolism after adjusting for Early LDH Elevation and PTTRe (HR 4.74, 95%CI 1.12-20.1, p=0.0346; Table 4). Patients who have moderate anticoagulation control, PTTRe 50-60%, had a reduced risk of thromboembolism, even after adjusting for Early LDH Elevation and kidney function at baseline (HR 0.09, 95%CI 0.01-0.86, p=0.0363; Table 4). Additionally, patients who have good anticoagulation control, PTTRe ≥60%, had a reduced risk of thromboembolism after adjusting for Early LDH Elevation and kidney function at baseline (HR 0.30, 95%CI 0.10-0.86, p=0.0247; Table 4).

Neither diabetes (HR 0.44, 95%CI 0.16-1.19, p=0.11), nor atrial fibrillation (HR 0.36, 95%CI 0.12-1.05, p=0.06) were significantly associated with thromboembolism. CHADS₂ as a continuous variable was not significantly associated with thromboembolism (HR 0.82, 95%CI 0.50-1.34, p=0.42); a CHADS₂ score ≥2 was not associated with the risk of thromboembolism (HR 0.70, 95%CI 0.29-1.71, p=0.44).
CHA$_2$DS$_2$-VASc as a continuous variable was not a statistically significant risk factor for thromboembolism (HR 0.91, 95%CI 0.63-1.31, p=0.61); the categorized CHA$_2$DS$_2$-VASc score $\geq 4$ was not associated with the risk of thromboembolism (HR 0.89, 95%CI 0.39-2.02, p=0.78).

*Secondary analysis of LDH as a Predictor of Ischemic Stroke and Pump Thrombosis*

During the 51.3 years of follow-up the average time to first ischemic stroke was 118 days among the 6 patients with ischemic stroke (IR 11.7 events/100 patient years, 95% CI 4.7-24.3). Patients with LDH elevation at time of VAD implant were at an increased risk of ischemic stroke (HR 19.8, 95%CI 1.79-218, p=0.0148). Patients with Early LDH Elevation were at an increased risk of ischemic stroke (HR 6.6, 95%CI 1.37-32.8, p=0.0211). There were 6 pump thrombosis events during the 51.3 years of follow-up (IR 11.7 events/100 patient years; 95% CI 4.7-24.3) with an average time to a first pump thrombosis 64 days. Patients with LDH elevation at time of VAD implant had an increased risk of pump thrombosis (HR 18.7, 95%CI 1.68-208, p=0.0172). Moreover, patients with Early LDH Elevation were at an increased risk of pump thrombosis (HR 9.6, 95%CI 1.6-57.5, p=0.0134). However, because so few events occurred, no adjustments to these models were possible.

**Discussion**
The concerning increase in the rate of thromboembolism in VAD patients with newer devices illustrates the need for clinical factors that can identify patients at high risk of a thromboembolic event.\(^\text{14}\) The ability to detect a subgroup at high risk could enable clinicians to more stringently monitor and potentially prevent thromboembolism in these patients. The current study demonstrates that early LDH elevation is associated with an increased risk of thromboembolism, ischemic stroke and pump thrombosis. Our study is the first to highlight the association between pre-VAD LDH and post VAD thromboembolism, indicating non-VAD related LDH elevation may identify a high risk subgroup.

There is a dynamic hemostatic environment post VAD implant with considerable variability in coagulation and fibrinolysis markers.\(^\text{29}\) Despite this, the biomarker LDH has been identified as a sensitive predictor of hemolysis, an indicator of pump thrombosis.\(^\text{20, 23}\) Furthermore, elevations of LDH in and of itself have been shown to be associated with increased embolic events in VAD patients.\(^\text{20}\) Our study is the first to assess LDH prior to VAD implant as well as early LDH elevation as a primary predictor of thromboembolism, ischemic stroke and pump thrombosis. We illustrate that early LDH elevation is a predictor of not only pump thrombosis, but also all thromboembolic events including ischemic stroke. The mean LDH remains higher over time for patients with a thromboembolic event than for patients without a thromboembolic event, even after the event occurred. This finding suggests that some patients may have a higher risk of hemolysis and subsequent thromboembolism due to cell and platelet injury from other conditions in addition to the VAD itself. The association between elevated LDH at VAD implant and early thromboembolism as well as thromboembolism at any time suggests
that elevated LDH could be a marker of tissue breakdown and fibrin clots affecting platelets prior to VAD implantation. This phenomenon, when combined with the VAD could contribute to increased hemolysis thereby increasing the risk of thromboembolism. Furthermore, consistent with previous studies, elevated LDH at 1-month post implant is associated with late thromboembolic events.

Inadequate anticoagulation has been identified as a primary risk factor for thromboembolism, with the risk of thrombotic events increasing with INR values below 1.5. However, the findings from the current study indicate that some of these thromboembolic events are occurring when the patients are adequately anticoagulated based on current guidelines. Our study found that only 4 people had an INR below 1.5 leading up to and at the time of thromboembolic event, with 2 of these patients experiencing their thromboembolic event within 2 days after VAD implant while being treated with heparin. There is no difference in percent time below INR target range, percent time in target INR range or percent time above target INR range leading up to their thromboembolic event between patients who have a thromboembolism and patients who do not have a thromboembolism. However, patients who spend more percent time in the target INR range of 1.8-3.2 have a reduced risk of thromboembolism. Clinically non-significant fibrin deposits on the pump can occur during periods of poor anticoagulation and remain even once anticoagulation control has been achieved. These minor deposits could dislodge at a later time regardless of if a patient achieved anticoagulation control leading to a thromboembolic event. This suggests that more emphasis should be place on early good anticoagulation control to prevent the buildup of these fibrin deposits, thereby reducing the risk of thromboembolism.
The current study highlights that in addition to LDH and anticoagulation control, kidney function is a strong predictor of thromboembolism. Kidney function is a known risk factor for thromboembolism in other patient populations, with an increased risk of thromboembolism for patients with an eGFR < 30. (31) Chronic kidney disease is associated with an increased procoagulant profile, with these patients having higher levels of fibrinogen, Factor VIII and vWF. (32) Patients who have a VAD placed typically regain kidney function after implantation due to reversal of the cardiorenal syndrome; however, the damage from the decreased kidney function in addition to the increased procoagulant profile, could contribute to the increasing the risk of thromboembolism.

Other risk factors for thromboembolism in VAD patients include history of diabetes, increased BMI and a history of atrial fibrillation; (14, 16) however, these factors are not statistically significantly associated with thromboembolism in this study. Furthermore, we assessed the CHADS2 and CHA2DS2-VASc scores as possible predictors of thromboembolism in this high-risk patient population. (17, 18) These scores are clinical prediction scores used in estimating the risk of stroke in patients with atrial fibrillation. There was no relationship between these scores and risk of thromboembolism in VAD patients despite these patients having high CHADS2 and CHA2DS2-VASc scores. In this population, the increased risk of thromboembolism from traditional risk factors may be overwhelmed by the hypercoagulable state induced by the device.

Our study was not without limitations. We only included patients with HeartMate II and HeartWare devices to reduce patient heterogeneity and increase the relevance to
current clinical practice. Although the UAB clinic treats a large number of HeartMate II/HeartWare patients for a single center, the number of thromboembolic events was low, thereby decreasing statistical power. We did not have enough information on serum free hemoglobin over time to cross-reference serum free hemoglobin with LDH as an exposure. Since this was a retrospective study we were limited by the data in the medical records. LDH was not routinely collected as part of standard of medical care until recently, thus many patients in the sample were missing LDH measurements at various time points.

Our study is the first to highlight the association between pre-VAD LDH and post VAD thromboembolism. Furthermore, we show that early LDH elevation, in addition to kidney function prior to VAD implantation and post-VAD anticoagulation control, are significant risk factors for thromboembolism. We found that the risk for thromboembolism was 5 fold higher for patients with early LDH elevation, 5 fold higher for patients with an eGFR <30 prior to VAD implantation and decreased for patients with adequate anticoagulation control. Prospective studies are needed to further evaluate these associations in larger VAD populations.
Reference List


Table 1. Demographic and Clinical Characteristics for the Entire Cohort Stratified by Thromboembolism

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N=115)</th>
<th>No Thromboembolism (N=92)</th>
<th>Thromboembolism (N=23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at Implant</strong></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>52±15</td>
<td>53 ±14</td>
<td>49±15</td>
<td></td>
</tr>
<tr>
<td><strong>Body Mass Index at Implant</strong></td>
<td>28 ± 8</td>
<td>29±7</td>
<td>29±7</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>N (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>90 (78.3%)</td>
<td>74 (80.4%)</td>
<td>16 (69.6%)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Black Race</strong></td>
<td>37 (32.2%)</td>
<td>29 (31.5%)</td>
<td>8 (34.8%)</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>Status in the first year</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased</td>
<td>19 (16.5%)</td>
<td>13 (14.1%)</td>
<td>6 (26.1%)</td>
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<tr>
<td>Transplanted</td>
<td>23 (20.0%)</td>
<td>20 (21.7%)</td>
<td>3 (13.0%)</td>
<td></td>
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<tr>
<td>Recovered</td>
<td>4 (3.5%)</td>
<td>3 (3.3%)</td>
<td>1 (4.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Etiology of Heart Failure</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ischemic</td>
<td>60 (53.1%)</td>
<td>50 (55.5%)</td>
<td>10 (43.5%)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>45 (39.8%)</td>
<td>35 (38.8%)</td>
<td>10 (43.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Indication for VAD</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>Bridge to transplant</td>
<td>64 (56.6%)</td>
<td>49 (54.5%)</td>
<td>15 (65.2%)</td>
<td></td>
</tr>
<tr>
<td>Bridge to candidacy</td>
<td>2 (1.8%)</td>
<td>2 (2.2%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bridge to recovery</td>
<td>1 (0.9%)</td>
<td>0</td>
<td>1 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>Destination</td>
<td>46 (40.7%)</td>
<td>39 (43.3%)</td>
<td>7 (30.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Comorbid Conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>45 (39.1%)</td>
<td>40 (43.5%)</td>
<td>5 (21.7%)</td>
<td>0.031</td>
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<tr>
<td>Right Ventricular Dysfunction</td>
<td>28 (24.4%)</td>
<td>21 (22.8%)</td>
<td>7 (30.4%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>46 (40.0%)</td>
<td>37 (40.2%)</td>
<td>9 (39.1%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>23 (20.0%)</td>
<td>19 (20.7%)</td>
<td>4 (17.4%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Hypertension</td>
<td>71 (61.7%)</td>
<td>59 (64.1%)</td>
<td>12 (52.2%)</td>
<td>0.29</td>
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<tr>
<td>Hyperlipidemia</td>
<td>43 (37.4%)</td>
<td>44 (47.8%)</td>
<td>8 (34.8%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>26 (22.6%)</td>
<td>39 (42.4%)</td>
<td>4 (17.4%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Ventricular Tachycardia</td>
<td>19 (16.5%)</td>
<td>45 (48.9%)</td>
<td>10 (43.5%)</td>
<td>0.64</td>
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<td>Concurrent Meds at VAD Implantation</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Warfarin</td>
<td>115 (100%)</td>
<td>92 (100%)</td>
<td>23 (100%)</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>113 (98.2%)</td>
<td>90 (97.8%)</td>
<td>23 (100%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Plavix</td>
<td>67 (58.3%)</td>
<td>53 (57.6%)</td>
<td>14 (60.9%)</td>
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<tr>
<td>Colchicine</td>
<td>6 (5.2%)</td>
<td>5 (5.4%)</td>
<td>1 (4.3%)</td>
<td>0.84</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>70 (60.9%)</td>
<td>54 (58.7%)</td>
<td>16 (69.6%)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Estimated Glomerular Filtration rate (eGFR ml/min/1.73m²) prior to VAD implantation</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.014</td>
</tr>
<tr>
<td>eGFR ≥60</td>
<td>47 (42.3%)</td>
<td>40 (44.4%)</td>
<td>7 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>eGFR 30 to 59</td>
<td>54 (48.7%)</td>
<td>44 (48.9%)</td>
<td>10 (47.6%)</td>
<td></td>
</tr>
<tr>
<td>eGFR &lt; 30</td>
<td>10 (9.0%)</td>
<td>6 (6.7%)</td>
<td>4 (19.1%)</td>
<td></td>
</tr>
</tbody>
</table>
Estimated glomerular filtration rate (eGFR ml/min/1.73m2) was calculated using the Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI).

Continuous variables were tested using Wilcoxon Rank Sum test and categorical variables were tested using a Chi-squared test.
### Table 2. Anticoagulation Control for the Entire Cohort and Stratified by Thromboembolic Events using an INR range of 2-3 and an INR range of 1.8-3.2

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>No Thromboembolism</th>
<th>Thromboembolism</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Patients</strong></td>
<td>115</td>
<td>92</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td><strong>Number of Visits</strong></td>
<td>4902</td>
<td>4311</td>
<td>591</td>
<td>0.003</td>
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<tr>
<td><strong>Total Follow Up (months)</strong></td>
<td>624.5</td>
<td>569.6</td>
<td>54.9</td>
<td>&lt;0.0001</td>
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<tr>
<td><strong>Follow Up Months/patient</strong></td>
<td>5.4 ± 4.8</td>
<td>8.4 ±4.5</td>
<td>2.4 ±2.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Number of Visits/patient/month</strong></td>
<td>2.1 ± 1.2</td>
<td>1.8 ±0.91</td>
<td>2.7 ± 1.4</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Anticoagulation control for INR Range of 2-3

- **Percent Time Below Range**: 41.6 ± 28.4 vs 41.8±25.9 vs 42.7±36.7 (0.46)
- **Percent Time In Range**: 42.9 ± 22.5 vs 43.6 ±20.4 vs 42.2±28.9 (0.95)
- **Percent Time Above Range**: 15.8 ± 13.9 vs 15.1±12.1 vs 18.5±19.4 (0.93)

Anticoagulation Control for INR Range of 1.8-3.2

- **Percent Time Below Range**: 30.3 ± 28.5 vs 29.1 ±26.9 vs 35.5 ±34.5 (0.77)
- **Percent Time In Range**: 59.2 ± 26.4 vs 61.1±24.1 vs 54.6±32.2 (0.61)
- **Percent Time Above Range**: 11.1 ± 11.5 vs 10.5±9.7 vs 13.8±16.9 (0.92)

*Follow-up is calculated as time from VAD to first event, or in the circumstance of no event the end of study period (1 year), explantation, transplantation or death

Continuous variables were tested using Wilcoxon Rank Sum test
Table 3. Incidence of Thromboembolic Events in the First Year after Implantation

<table>
<thead>
<tr>
<th>N</th>
<th>Follow-up*</th>
<th>Incidence Rate (IR) (95% Confidence Interval (CI)) per 10 person years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause TE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entire Sample (N=115)</td>
<td>23</td>
<td>51.3 years</td>
</tr>
<tr>
<td>TE Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic Stroke 6</td>
<td>6</td>
<td>51.3 years</td>
</tr>
<tr>
<td>Pump Thrombosis 6</td>
<td>6</td>
<td>51.3 years</td>
</tr>
<tr>
<td>DVT 5</td>
<td>5</td>
<td>51.3 years</td>
</tr>
<tr>
<td>TIA 2</td>
<td>2</td>
<td>51.3 years</td>
</tr>
<tr>
<td>PE 2</td>
<td>2</td>
<td>51.3 years</td>
</tr>
<tr>
<td>Mediastinal Clot 2</td>
<td>2</td>
<td>51.3 years</td>
</tr>
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</table>

*Follow-up is calculated as time from VAD to first event, or in the circumstance of no event the end of study period (1 year), explantation, transplantation or death
Table 4. Association of Elevated LDH within the first month post VAD implantation and Risk (Hazard ratio (HR) and 95% Confidence interval (95%CI)) of Thromboembolism

<table>
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<th>Crude Analyses</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
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</thead>
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<tr>
<td>No Early LDH Elevation (&lt;600 IU/L)</td>
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<td>ref</td>
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<tr>
<td>Early LDH Elevation(≥600 IU/L)</td>
<td>2.99</td>
<td>1.14-7.88</td>
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</table>

Estimated Glomerular Filtration rate (eGFR ml/min/1.73m²) prior to VAD implantation

<table>
<thead>
<tr>
<th>Anticoagulation Control</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Poor Control</td>
<td>ref</td>
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<tr>
<td>Moderate Control</td>
<td>0.15</td>
<td>0.02-1.20</td>
<td>0.07</td>
</tr>
<tr>
<td>Good Control</td>
<td>0.37</td>
<td>0.16-0.87</td>
<td>0.0231</td>
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</table>

Adjusted Analyses*

<table>
<thead>
<tr>
<th>Adjusted Analyses*</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Early LDH Elevation (&lt;600 IU/L)</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>Early LDH Elevation(≥600 IU/L)</td>
<td>4.95</td>
<td>1.69-14.4</td>
</tr>
</tbody>
</table>

Estimated Glomerular Filtration rate (eGFR ml/min/1.73m²) prior to VAD implantation

<table>
<thead>
<tr>
<th>Anticoagulation Control</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor Control</td>
<td>ref</td>
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<tr>
<td>Moderate Control</td>
<td>0.09</td>
<td>0.01-0.86</td>
<td>0.0363</td>
</tr>
<tr>
<td>Good Control</td>
<td>0.30</td>
<td>0.10-0.86</td>
<td>0.0247</td>
</tr>
</tbody>
</table>

Patients exhibiting elevation at VAD implantation, 14 days post implantation or 1 month post implantation were categorized as Early LDH Elevation. No LDH measurements that occurred after a thromboembolic event were included in the categorization of elevated
LDH within the first month post-VAD implant. The proportion of time spent in target INR range of 1.8-3.2 (PTTRe) was used as a measure of anticoagulation control. PTTRe was categorized into Good control>60%, Moderate control ≥50<60% and Poor control <50%.

*The full model includes Early LDH Elevation, eGFR at VAD implantation and anticoagulation control

Cox Proportional Hazards Models were used to assess the relative risk of thromboembolism. The proportional hazards assumptions were met.
Figure 1. Inclusion and Exclusion Criteria Used to Establish the Cohort

127 HeartMate II/HeartWare patients implanted from 2006-2012

115 patients with anticoagulation medications and lab values available for enrollment in this study

23 patients experienced a primary thromboembolic event

7 patients go on to have a second thromboembolism within the first year

7 patients go on to have a hemorrhage as their second event within the first year

9 patients do not have a second event within the first year

12 patients who were implanted at different facilities were excluded due to missing information on anticoagulation at the time of VAD implant

92 patients did not have a primary thromboembolic event
Figure 2. Change in LDH Over Time for the Entire Cohort and Stratified by Thromboembolism

Differences in changes in LDH over time stratified by thromboembolism were assessed using repeated measures ANOVA

\[ p = 0.0028 \]
Figure 3a. Kaplan Meier Curve Illustrating Time to Thromboembolism Stratified by Elevated LDH at VAD Implantation

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p=0.005
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Legend:
- LDH less than 600 at VAD Implantation
- LDH greater than 600 at VAD Implantation
Figure 3b. Kaplan Meier Curve Illustrating Time to Thromboembolism Stratified by Early LDH Elevation

\[ p = 0.020 \]
PREDICTORS OF HEMORRHAGE IN VENTRICULAR ASSIST DEVICE PATIENTS

by

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ABSTRACT

Background: Ventricular assist device (VAD) patients are at increased risk for hemorrhagic events due to intensive antithrombotic therapies and device-induced platelet shearing.

Methods: Patients aged 19 years and older who have had a continuous flow device placed at UAB from 2006-2012 were included in this study. This study developed a VAD Bleeding risk score and compared it with the HAS-BLED hemorrhagic risk score.

Results: A total of 36 patients experienced a hemorrhage during the first year (Incidence Rate 70 per 100 person years (95%CI 50-96). The VAD Bleeding Risk score ranges from 0-5 and included age greater than 65 (1 point), history of gastrointestinal bleed prior to VAD implantation (1 point), ischemic etiology of heart failure (1 point), history of hyperlipidemia prior to implantation (1 point), and eGFR <30 prior to VAD implantation (1 point), with a Harrell’s adjusted c-statistic of 0.789. The VAD Bleeding risk score has a better c-statistic than the HAS-BLED score, 0.789 compared to 0.661. Patients with a VAD bleeding risk score ≥3 have the highest risk of hemorrhage (HR 4.61, 95%CI 2.37-8.99, p<0.0001) compared to the 3-fold increased risk of hemorrhage for patients with a HAS-BLED score of ≥ 3 (HR 3.18, 95%CI 0.96-10.5, p=0.06).

Conclusion: Our study is the first to create a VAD-specific bleeding risk score. We found that the simple, newly developed VAD Bleeding risk score can identify patients at risk for developing a hemorrhage.

Key Words: Ventricular assist device, hemorrhage, mechanical circulatory support
Introduction

Approximately 5.7 million Americans are living with heart failure (HF), a leading cause of morbidity and mortality, with the prevalence continuing to increase in the US. (1-3) The best treatment options for end-stage advanced HF is heart transplantation or placement of a ventricular assist device (VAD), (4, 5) with the use of VAD therapy increasing as a long-term solution for treating end-stage HF. (6-12) The design of VADs has changed through the years; newer devices (HeartMate II and HeartWare) maintain continuous flow, with blood constantly being propelled into the circulation, while older devices produce pulsatile flow. (3)

VAD implantation improves the life expectancy and quality of life for advanced HF patients; however, this treatment option has an increased risk of both thromboembolism and hemorrhage. To mitigate the risk of thromboembolism, VAD patients are treated with dual antithrombotic therapy, including an anticoagulant (warfarin) and an antiplatelet medication (aspirin, dipyridomole, clopidogrel, or a combination agent). (3) Dual antithrombotic therapy predisposes these patients to even higher risks of hemorrhagic complications. (13-18) Further complicating the coagulation abnormalities of these complex patients, continuous-flow devices have been found to result in an acquired form of von Willebrand syndrome, resulting in a higher risk for hemorrhage. (19) Due to the increase in the number of VAD implants, the risk for hemorrhagic events due to antithrombotic therapy and acquired von Willebrand disease is becoming an increasingly pressing issue. (3, 16, 18, 20)
The risk of bleeding while on chronic anticoagulant therapy has been well studied in other populations. The development of the novel bleeding risk score HAS-BLED offers clinicians a method to establish the bleeding risk of patients with atrial fibrillation on chronic anticoagulation. Specific components in the HAS-BLED score, such as age, have also been identified as risk factors for post-implantation bleeding in the VAD population. The HAS-BLED score, however, has not been validated in this high risk population on chronic anticoagulation. Prior research has shown that risk factors for hemorrhagic events in VAD patients, such as gender and etiology of heart failure, are not included in the HAS-BLED score.

We present data on predictors of hemorrhagic events in continuous flow VADs for 115 patients implanted with HeartMate II and HeartWare devices. This study evaluates risk factors for hemorrhagic events and the utility of the HAS-BLED score in this high risk population. Furthermore, we developed a simple hemorrhagic risk score to identify patients at highest risk for a hemorrhagic event while implanted with a VAD.

**Methods**

*Study Setting and Inclusion and Exclusion*

This study was conducted at the University of Alabama at Birmingham (UAB) under the approval of the Institutional Review Board. Patients aged 19 years and older who had a continuous flow VAD (HeartMate II (Thoratec Corporation, Pleasanton, CA) or HeartWare (HeartWare Inc, Framingham, MA) device) placed at UAB from 2006-2012 were included in this study. Patients were followed for 1-year post VAD
implantation to assess outcomes. Loss to follow up is minimal since patients receive both inpatient care and routine monthly outpatient clinic visits at UAB.

Data collection

For all patients, a detailed baseline (pre-VAD) clinical phenotype was documented by a research assistant through retrospective medical record review. These data included demographics (e.g. gender, race, ethnicity etc.), medical history before VAD (e.g. history of medical comorbidities, surgeries prior to VAD implant etc.), medications (e.g. antithrombotic medications and medications that influence thromboembolic events), and laboratory assessments (e.g. coagulation factors, liver function tests, kidney function tests etc.). Post-VAD documentation included medications, laboratory assessments and outcomes. These were collected through medical records using definitions established by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Registry. (23)

Definition of Exposures

We evaluated the influence pre-existing history of hypertension, atrial fibrillation, and decreased kidney function as well as type of post-VAD anticoagulation control on risk of hemorrhage. Factors with p-values <0.2 were included in the multivariable analysis. (24)

Oral anticoagulation is a risk factor for a hemorrhagic event in VAD patients. (22) To explore this, anticoagulation control was assessed through the proportion of time spent within target International Normalized Ratio (INR) range, which is referred to as proportion of time in target range (PTTR). PTTR was estimated for each patient using
the Rosendaal linear interpolation method,(25) which assumes a linear relationship exists between two consecutively measured INR values. This allows a specific INR value to be allocated each day for every patient. Time in target range for each patient was assessed by the percentage of interpolated INR values within the target range of 2.0–3.0 after attainment of first INR in target range. We also assessed proportion of time spent in extended target range (PTTRe; INR1.8-3.2) since deviations below or above this range usually trigger dose adjustments to minimize risk of thrombosis and hemorrhage, respectively. PTTRe was categorized into “good” control (>60%), “moderate” control (≥50, but <60%), and “poor” control (<50%).

Kidney function was assessed through the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI)(26) which incorporates gender, race, age, and serum creatinine (Scr; mg/dL). Kidney function was characterized with eGFR ≥60 ml/min/1.73 m² considered to be no/mild kidney disease (Stage 1, 2), those with eGFR =30-59 ml/min/1.73 m² considered to be moderate kidney disease (Stage 3), and those with eGFR<30 ml/min/1.73 m² (or on dialysis) considered to be severe kidney disease (Stage 4, 5).(27, 28) Patients with kidney dysfunction are known to experience additional platelet dysfunction, making this measure germane to this study.

In addition to these individual-level risk factors, the hemorrhage risk score, HAS-BLED, was assessed as both a continuous variable and categorized into a dichotomous risk group (low risk HAS-BLED<3 vs. HAS-BLED ≥3).(21) The score was calculated with giving one point each for the following components: age at implant >65, pre-VAD kidney function of CKD stage 4 or 5, impaired pre-VAD liver function (cirrhosis or AST
>3 times the upper limit normal), history of hypertension, major bleeding event prior to VAD implantation, alcohol abuse, illicit drug use, history of stroke prior to VAD implant, antithrombotic use, and percent time in target INR range post-VAD. The only components of the score that use post-VAD information were antithrombotic treatments and percent time in target range <60%. We evaluated the traditional HAS-BLED score with the post-VAD INR range of 2.0-3.0 as well as an extended HAS-BLED (eHAS-BLED) score, where percent time in range post-VAD was calculated on the INR range of 1.8-3.2.

Definition of Outcomes

All hemorrhagic events were documented during the one-year follow-up. Since patient with VADs only receive their care at UAB, the study ascertainment of complications was robust. Hemorrhagic events included intracranial hemorrhage, gastrointestinal (GI) bleeding, mediastinal bleeding requiring surgical intervention, or an episode requiring transfusion of greater than four units of packed red blood cells (pRBCs). As patients may experience multiple events within the 1-year follow-up period, only the first event was included in the analysis. For patients who did not experience a hemorrhagic event, follow-up time was censored at end of the study (1 year) or explantation/transplantation/death (if earlier than 1 year).

Considering the risk of bleeding due to the surgery for the implantation of the VAD itself, a secondary analysis was done assessing predictors of late hemorrhages, defined as a hemorrhagic event occurring greater than 30 days post-VAD implant.
The \( \chi^2 \) test of independence or Wilcoxon Rank Sum test was used to assess baseline group differences for categorical variables and continuous variables, respectively. Univariable logistic regression and Cox Proportional Hazards models were used to assess the association between baseline characteristics and risk of hemorrhage to establish which variables (\( p \leq 0.2 \)) should be considered for development of a VAD specific bleeding risk score. All variables that met the \( p \leq 0.2 \) were evaluated for the final prediction model using logistic regression models. Model performance was assessed using the c-statistic, corrected for optimism. (29) To correct for optimism, reduce bias and internally validate the model we calculated the estimated decrease in the c-statistic that would be expected in an independent dataset using the 0.632 bootstrap method. (30) This option was chosen over the traditional split-sample modeling because the bootstrap resampling technique has been shown to reduce bias and produce a stable and efficient estimate of predictive accuracy when compared to other methods. (30) For this study we created 100 datasets through bootstrap sampling with replacement. The models were fit in each dataset and the average difference in the c-statistic between the bootstrap dataset (the derivation dataset) and the original dataset (the validation dataset). This value represents the expected optimism in the c-statistic calculated in this study. The points assigned to the variables in the score were assigned based on the beta coefficients from the logistic regression models. A cut point of the VAD bleeding risk score was established based on sensitivity and specificity of the dichotomized score in predicting hemorrhage.
The Cox-proportional hazard model was used to determine the influence of HAS-BLED, the extended HAS-BLED and the newly developed VAD bleeding risk score on the risk of first hemorrhagic event. Log-log survival plots were used to assess the proportional hazards assumption. A sub-analysis was done using Cox-proportional hazards models to assess the newly developed VAD bleeding risk score on the risk of late hemorrhage. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC) at a non-directional alpha of 0.05.

Results

A total of 115 patients who were implanted with HeartMate II device (Thoratec Corporation, Pleasanton, CA) or HeartWare (HeartWare Inc, Framingham, MA) devices at UAB between 2006 and 2012 were included in this study (Figure 1). The mean age at implant was 52(±14.6 years, and the majority of patients were male (78.3%), white (67.8%) and implanted as a bridge to transplant (56.6%) (Table 1).

A total of 36 patients experienced a hemorrhage during the first year (Incidence Rate 70 per 100 person years (95%CI 50-96). Of these, 12 (33.3%) experienced a second hemorrhage and 7 (19.4%) had a thromboembolism after the primary hemorrhage. There were 3 (8.3%) with intracranial hemorrhage, 25 (69.4%) with GI bleeding, 6 (16.7%) with mediastinal bleeding, and 2 (5.6%) required greater than 4 units of pRBCs. Patients who had a hemorrhage within the first year had a higher percentage of ischemic HF etiology (75% vs 41.8%, p=0.0124), hyperlipidemia (69.4% vs. 34.2%, p=0.0004), atrial fibrillation (52.8% vs 30.4%, p=0.0213) and a higher age (60.9±10.1 vs. 50.3±14.8 years,
Patients with a hemorrhage also had a higher frequency of moderate kidney function (CKD Stage 3, eGFR 30-59; 60% vs 43.4%, p=0.0135) prior to VAD implantation.

The 115 participants contributed 624.5 months (51.3 person years) of follow-up time, an average 5.4 (± 4.8) months per patient. Patients were seen at least once a month, an average of 1.4± 0.96 visits per patient per month (Table 2). The mean time to first hemorrhage was 2.8± 3.1 months. Patients with a hemorrhage were seen more frequently per month compared to those who did not have a hemorrhage (2.8±1.2 times vs 1.7±0.9 times, p<0.0001). Anticoagulation control, measured as percent time in target range, was similar between patients with and without hemorrhage regardless of which INR range is used.

Individual Predictors of Hemorrhage

Ischemic etiology of heart failure prior to VAD implantation had a higher risk of hemorrhage (Hazard Ratio (HR) 2.77, 95%CI 1.30-5.89, p=0.0082). Patients with a history of hyperlipidemia (HR 2.93, 95%CI 1.44-5.97, p=0.0030), atrial fibrillation (HR 1.91, 95%CI 0.99-3.69, p=0.05), age older than 65 at time of VAD implant (HR 2.51, 95%CI 1.28-1.85, p=0.0003) and history of a GI bleed prior to VAD (HR 3.81, 95%CI 1.66-8.75, p=0.0016) had a significantly higher risk of hemorrhage. Moderate decrease in kidney function prior to VAD (CKD Stage 3, eGFR 30-59) increased the risk of hemorrhage (HR 1.96, 95%CI 0.97-4.00, p=0.06); however, this association was not statistically significant. There was no association between severely decreased kidney
function prior to VAD (eGFR < 30) and risk of hemorrhage (HR 1.08, 95%CI 0.24-4.84, p=0.92).

Risk of Hemorrhage by Bleeding Risk Scores

Of the variables included in the development of the VAD bleeding risk score, the variables that were selected for use in the final scoring system using Harrell’s optimism bootstrapping method included age greater than 65 (1 point), history of GI bleed prior to VAD implantation (1 point), ischemic etiology of HF (1 point), history of hyperlipidemia prior to implantation (1 point), and eGFR <30 prior to VAD implantation (1 point). The VAD bleeding risk score ranged from 0-5. This score had the lowest Akaike Information Criterion (118.6) with a Harrell’s adjusted c-statistic of 0.789. The sensitivity and specificity of the dichotomized VAD Bleeding Risk Score <3 compared to VAD Bleeding Risk Score ≥3 for predicting hemorrhage was 45.7% and 93.4%, respectively. The positive predictive value and the negative predictive value of the dichotomized VAD Bleeding Risk Score <3 compared to VAD Bleeding Risk Score ≥3 for predicting hemorrhage was 76.2% and 78.9%.

The HAS-BLED, eHAS-BLED, and newly developed VAD Bleeding risk score all predicted hemorrhagic complications. However, the VAD score predicted hemorrhage better in VAD patients than the HAS-BLED or eHAS-BLED score (Figure 2) with an AUC of 0.789 ( vs. 0.661 and 0.655, respectively) (Table 3). The proportional hazards assumption was met for each dichotomous score. Patients with a VAD bleeding risk score ≥3 had the highest risk of hemorrhage (HR 4.61, 95%CI 2.37-8.99, p<0.0001) compared to the 3 fold increased risk of hemorrhage for patients with a HAS-BLED score
\[ \geq 3 \] (HR 3.18, 95%CI 0.96-10.5, \( p = 0.06 \)) and the 2.5 fold increased risk with an extended HAS-BLED score \( \geq 3 \) (HR 2.52, 95%CI 1.11-5.74, \( p = 0.0275 \).

The newly developed VAD Bleeding risk score predicted hemorrhage better in VAD patients than the HAS-BLED or extended HAS-BLED score (Figure 2) with an AUC of 0.789. A higher bleeding risk score placed VAD patients at a higher risk of hemorrhage (Table 3). The proportional hazards assumption was met for each dichotomous score. The sensitivity and specificity of the VAD Bleeding risk score is 45.7% and 93.4% with a PPV of 76.2% and an NPV of 78.9%. The sensitivity and specificity of the HAS-BLED score was 89.3% and 30.2% with a PPV of 36.2% and an NPV of 86.4%. The sensitivity and specificity of the eHAS-BLED score was 71.4% and 50.8% with a PPV of 39.2% and an NPV of 80.0%.

Sub analysis of Late Hemorrhage

There were 23 (63.9%) hemorrhages that occurred 30 days post-VAD implant. The newly developed VAD Bleeding Risk score as a continuous variable was predictive of hemorrhages occurring 30 days post-VAD implant (HR 1.66, 95%CI 1.21-2.27, \( p = 0.0015 \)). Patients with a VAD Bleeding Risk score \( \geq 3 \) had an almost 5-fold increase in risk of a hemorrhage that occurred 30 days post-VAD (HR 4.64, 95%CI 2.03-10.6, \( p = 0.0003 \)) compared to those with a VAD Bleeding Risk score <3.

Discussion

Hemorrhage remains one of the most frequently reported complications post VAD, and prevalence estimates range from 15-60%. (8, 9, 31-38) The ability to predict which patients are at greatest risk for a hemorrhagic event can enable clinicians to
identify a high risk subgroup and alter anticoagulation therapy accordingly. To our knowledge, this is the first study to develop a VAD-specific bleeding risk score and assess the HAS-BLED score in a VAD population.

The VAD bleeding risk score is a simple and easy to use metric that can provide clinicians information on risk of developing a hemorrhage post-VAD. This score ranges from 0-5 and is predictive of hemorrhage in patients with a c-statistic of 0.789. When dichotomized, a score of 3 or greater has a sensitivity and specificity of 45.7% and 93.4%, respectively, and a positive predictive value of 76.2% and an negative predictive value of 78.9%. We acknowledge that by setting the VAD bleeding risk score threshold relatively high, some patients with low VAD bleeding risk scores will be missed. Other factors not included in the VAD bleeding risk score can contribute to patients with a low risk score going on to have a hemorrhage. The VAD bleeding risk score is similar to the HAS-BLED and extended HAS-BLED score, but it includes simple components that are more VAD-specific in the calculation. Each component of the VAD bleeding risk score is itself a risk factor for hemorrhagic events in this population. In testing the predictability of the score, not all risk factors that place patients at risk for a hemorrhage were included in the risk score due to their low predictive capabilities when included. The VAD bleeding risk score is consistent with prior work that has shown risk factors for hemorrhage in VAD patients include age, ischemic cardiomyopathy, and history of gastrointestinal bleeding as pre-VAD risk factors implicated in post-VAD bleeding. (22, 39-42) Regardless of the population, advanced age is a significant factor in hemorrhage in patients on chronic anticoagulation therapies. (41, 43) (44) Prior studies have assessed predictors of hemorrhage, and age has consistently been shown to be the most important
determinant of whether a patient will experience GI bleeding.(41) Of interest, while in
the univariable analysis of risk factors moderate kidney dysfunction prior to VAD was a
significant risk factor for hemorrhage, however, the Harrell optimism score found that
severe kidney dysfunction prior to VAD was better in the overall score for predicting
hemorrhage. Other risk factors that were not included in the VAD bleeding risk score,
such as hypertension or increased BMI, could explain why some patients with a lower
VAD bleeding risk score experienced a hemorrhagic complication.

The bleeding rate in this population is higher than what has been reported in other
VAD populations (70 per 100 person years compared to 63 per 100 person years) and
even higher than other chronic anticoagulated populations (5.7 per 100 patient-years).(45,
46) A HAS-BLED score ≥3 and an extended HAS-BLED score ≥3 place patients at 3
and 2.5 times, respectively, the risk of hemorrhage compared to patients with lower
scores. The HAS-BLED score uses established risk factors in other populations on
chronic warfarin therapy to predict patients at highest risk for bleeding while on
antithrombotic therapy with a c-statistic of 0.91.(21) However, the propensity for
hemorrhagic complications in VAD patients cannot be attributed to anticoagulation alone
since they experience a higher rate of hemorrhagic complications compared to patients on
anticoagulation for other indications.(40) The components of the VAD bleeding risk
score emphasize the importance of pre-implant risk factors on the risk of hemorrhage
post-implant. Furthermore, the score is predictive of hemorrhages that occur 30 days
post-VAD. Hemorrhages are more likely to be ascribed to the device or the
antithrombotic regimen rather than complications of surgical implantation of the VAD.
When compared to non-VAD patients on anti-thrombotic therapy, VAD patients are at a higher risk for hemorrhage. (22, 46, 47) The increased risk for gastrointestinal bleeding in VAD patients is multifactorial and could be due to antithrombotic therapies, development of arteriovenous malformations (AVMs), Heyde syndrome, or mucosal ischemia. (45) VAD devices may predispose patients to develop AVMs by decreasing intraluminal pressure due to the continuous flow VADs, thereby increasing the sympathetic tone and dilating the mucosal veins, leading to the formation of AVMs. (40, 48, 49) These AVMs are predisposed to bleeding due to anticoagulation and device-induced stress. (49) Another potential reason for the increased risk of hemorrhage is that continuous-flow devices have been found to result in acquired von Willebrand syndrome, which further complicate the coagulation profiles of these patients. (19) The increased risk of thromboembolism necessitates the use of antithrombotic therapies that increase the risk of hemorrhagic complications. (50)

Our study was not without limitations. We only included patients with a HeartMate II and HeartWare devices to reduce bias and increase generalizability to the newer devices currently being implanted. While this is a large number of HeartMate II/HeartWare patients at a single center, the numbers of events are low and decrease the statistical power. We were not able to assess specific types of hemorrhagic events. Since this was a retrospective study, we were limited by the data available in the medical records. The VAD bleeding risk score is limited to first events and was not designed to predict a hemorrhage in patients who had a thromboembolism prior to their hemorrhage. We did not have an independent population to validate our risk score, although we did correct for the expected overestimate of the c-statistic that results from testing its
properties in the population in which it was developed. Prospective, multicenter studies are needed to validate the VAD bleeding risk score.

This complex patient population is at very high risk of hemorrhagic events due to the device itself as well as the therapies needed to prevent thromboembolism. Our study is the first to develop a VAD specific bleeding risk score and to compare it to the HAS-BLED score, which was designed to assess risk of bleeding in patients on chronic oral anticoagulation. We found that patients with a VAD bleeding risk score of \( \geq 3 \) are at 4 times the risk of hemorrhage than patients with a lower VAD bleeding risk score. Further studies are needed to validate this score in other VAD populations.
Reference List


32. Frazier OH, Rose EA, Oz MC, Dembitsky W, McCarthy P, Radovancevic B, et al. Multicenter clinical evaluation of the HeartMate vented electric left ventricular


Table 1. Baseline Characteristics of VAD Patients with and without a Hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N=115)</th>
<th>No Hemorrhage (N=79)</th>
<th>Hemorrhage (N=36)</th>
<th>p-value</th>
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<tbody>
<tr>
<td><strong>Age at Implant</strong></td>
<td>52 (14.6)</td>
<td>50.3 (14.8)</td>
<td>60.9 (10.1)</td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>BMI at VAD Implantation</strong></td>
<td>28 (7.6)</td>
<td>29.4 (6.6)</td>
<td>28.2 (5.5)</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>90 (78.3%)</td>
<td>59 (74.6%)</td>
<td>31 (86.1%)</td>
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<td><strong>Black Race</strong></td>
<td>37 (32.2%)</td>
<td>27 (34.2%)</td>
<td>10 (27.8%)</td>
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</tr>
<tr>
<td><strong>Etiology of Heart Failure</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ischemic</td>
<td>60 (53.1%)</td>
<td>33 (41.8%)</td>
<td>27 (75%)</td>
<td></td>
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<tr>
<td>Idiopathic</td>
<td>45 (39.8%)</td>
<td>38 (48.1%)</td>
<td>7 (19.4%)</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Indication for VAD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bridge to transplant</td>
<td>64 (56.6%)</td>
<td>47 (59.5%)</td>
<td>17 (47.2%)</td>
<td></td>
</tr>
<tr>
<td>Bridge to candidacy</td>
<td>2 (1.8%)</td>
<td>1 (1.3%)</td>
<td>1 (2.8%)</td>
<td></td>
</tr>
<tr>
<td>Bridge to recovery</td>
<td>1 (0.9%)</td>
<td>1 (1.3%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Destination</td>
<td>46 (40.7%)</td>
<td>29 (36.7%)</td>
<td>17 (47.2%)</td>
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<tr>
<td><strong>Comorbid Conditions</strong></td>
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<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>45 (39.1%)</td>
<td>27 (34.2%)</td>
<td>18 (50%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Right Ventricular Dysfunction</td>
<td>28 (24.4%)</td>
<td>21 (26.7%)</td>
<td>7 (19.4%)</td>
<td>0.41</td>
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<tr>
<td>Coronary Artery Disease</td>
<td>46 (40.0%)</td>
<td>30 (37.9%)</td>
<td>16 (44.4%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>23 (20.0%)</td>
<td>12 (15.2%)</td>
<td>11 (30.6%)</td>
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<td>Hypertension</td>
<td>71 (61.7%)</td>
<td>45 (56.9%)</td>
<td>26 (72.2%)</td>
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<td>Hyperlipidemia</td>
<td>52 (45.2%)</td>
<td>27 (34.2%)</td>
<td>25 (69.4%)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>43 (37.4%)</td>
<td>24 (30.4%)</td>
<td>19 (52.8%)</td>
<td>0.021</td>
</tr>
<tr>
<td>Ventricular Tachycardia</td>
<td>55 (47.8%)</td>
<td>38 (48.1%)</td>
<td>17 (47.2%)</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Concurrent Meds at VAD Implantation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>115 (100%)</td>
<td>79 (100%)</td>
<td>36 (100%)</td>
<td>-</td>
</tr>
<tr>
<td>Aspirin</td>
<td>113 (98.2%)</td>
<td>79 (100%)</td>
<td>34 (94.4%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>67 (58.3%)</td>
<td>42 (53.2%)</td>
<td>25 (69.4%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Colchicine</td>
<td>6 (5.2%)</td>
<td>3 (3.8%)</td>
<td>3 (8.3%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>70 (60.9%)</td>
<td>49 (62.0%)</td>
<td>21 (58.3%)</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Estimated Glomerular Filtration rate (eGFR ml/min/1.73m²) prior to VAD Implantation</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.014</td>
</tr>
<tr>
<td>eGFR ≥60</td>
<td>47 (42.3%)</td>
<td>35 (46.1%)</td>
<td>12 (34.3%)</td>
<td></td>
</tr>
<tr>
<td>eGFR 30 to 59</td>
<td>54 (48.7%)</td>
<td>33 (43.4%)</td>
<td>21 (60%)</td>
<td></td>
</tr>
<tr>
<td>eGFR &lt; 30</td>
<td>10 (9.0%)</td>
<td>8 (10.5%)</td>
<td>2 (5.7%)</td>
<td></td>
</tr>
</tbody>
</table>

Estimated glomerular filtration rate (eGFR ml/min/1.73m²) was calculated using the Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI). Continuous variables were tested using Wilcoxon Rank Sum test and categorical variables were tested using a Chi-squared test.
## Table 2. Anticoagulation Control for the Entire Cohort

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N=115)</th>
<th>No Hemorrhage (N=79) Mean(SD)</th>
<th>Hemorrhage (N=36)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>115</td>
<td>79</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Number of Visits</td>
<td>4902</td>
<td>3612</td>
<td>1298</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total Follow Up (months)*</td>
<td>624.5</td>
<td>523.5</td>
<td>100.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Follow Up Months/patient</td>
<td>5.4 ± 4.8</td>
<td>6.6 ± 4.9</td>
<td>2.8 ± 3.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Number of Visits/patient/month</td>
<td>2.1 ± 1.2</td>
<td>1.7±0.9</td>
<td>2.8 ± 2.6</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Anticoagulation control for INR Range of 2-3**

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N=115)</th>
<th>No Hemorrhage (N=79) Mean(SD)</th>
<th>Hemorrhage (N=36)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent Time Below Range</td>
<td>41.6 ± 28.4</td>
<td>40.8±26.5</td>
<td>44.7±31.9</td>
<td>0.74</td>
</tr>
<tr>
<td>Percent Time In Range</td>
<td>42.9 ± 22.5</td>
<td>44.9±21.1</td>
<td>39.9±24.7</td>
<td>0.35</td>
</tr>
<tr>
<td>Percent Time Above Range</td>
<td>15.8 ± 13.9</td>
<td>16.5±13.6</td>
<td>14.2±14.6</td>
<td>0.21</td>
</tr>
</tbody>
</table>

**Anticoagulation Control for INR Range of 1.8-3.2**

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N=115)</th>
<th>No Hemorrhage (N=79) Mean(SD)</th>
<th>Hemorrhage (N=36)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent Time Below Range</td>
<td>30.3 ± 28.5</td>
<td>29.2±25.5</td>
<td>32.9±34.8</td>
<td>0.84</td>
</tr>
<tr>
<td>Percent Time In Range</td>
<td>59.2 ± 26.4</td>
<td>61.2±23.2</td>
<td>56.6±31.3</td>
<td>0.81</td>
</tr>
<tr>
<td>Percent Time Above Range</td>
<td>11.1 ± 11.5</td>
<td>11.9±11.8</td>
<td>9.3±10.8</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*Follow up time is designated as time to thromboembolism, hemorrhage, death, transplant, withdrawal or end of study (1-year)

Continuous variables were tested using Wilcoxon Rank Sum test
Table 3. Association of Bleeding Risk Scores with Risk (Hazard Ratio (HR) and 95% Confidence Interval (95%CI)) of Hemorrhage

<table>
<thead>
<tr>
<th>Scores Assessed as Continuous Variables</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HASBLED</td>
<td>1.62</td>
<td>1.13-2.33</td>
<td>0.0088</td>
</tr>
<tr>
<td>eHASBLED</td>
<td>1.73</td>
<td>1.21-2.49</td>
<td>0.0028</td>
</tr>
<tr>
<td>VAD Bleeding Risk Score</td>
<td>1.66</td>
<td>1.29-2.15</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scores Assessed as Dichotomous Variables</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HASBLED ≥3</td>
<td>3.18</td>
<td>0.96-10.5</td>
<td>0.06</td>
</tr>
<tr>
<td>eHASBLED ≥3</td>
<td>2.52</td>
<td>1.11-5.74</td>
<td>0.0275</td>
</tr>
<tr>
<td>VAD Bleeding Risk Score ≥ 3</td>
<td>4.61</td>
<td>2.37-8.99</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Hazard Ratios were generated through Cox Proportional Hazards Models. The proportionality assumption was met for the dichotomized score. The proportional hazards assumption was met for the assessment of the dichotomized score variable.
Figure 1. Inclusion and Exclusion Criteria Used to Establish the Cohort

- 241 VAD patients enrolled in the Cohort from 2002-2012
- Excluded 114 patients with Pulsatile devices
- 127 HeartMate II/HeartWare patients
- 115 patients with Anticoagulation medications and lab values available for enrollment in this study
  - 92 patients met the inclusion/exclusion criteria
    - 36 patients experienced a primary hemorrhage
      - 2 of these patients go on to have a second thromboembolism
      - 12 of these patients go on to have a hemorrhage as a secondary event
    - 79 of these patients did not have a thromboembolic or hemorrhagic event
      - 12 of these patients go on to have a hemorrhage as a secondary event
  - 23 of these patients experienced a thromboembolism, changing their INR range to 2.5-3.5 were excluded
  - 12 patients who were implanted at different facilities were excluded due to no detailed information on anticoagulation at the time of VAD implant
  - 79 of these patients did not have a thromboembolic or hemorrhagic event
    - 8 patients go on to have a second hemorrhage
      - 7 patients go on to have a thromboembolism
Figure 2. Comparing HAS-BLED to the Extended HAS-BLED to the VAD Bleeding Risk Score in the Entire VAD Population
ROC curves were generated through logistic regression analyses using the Harrell Optimism prediction method.
IMPROVEMENT IN KIDNEY FUNCTION AFTER VENTRICULAR ASSIST DEVICE IMPLANTATION AND ITS INFLUENCE ON THROMBOEMBOLISM, HEMORRHAGE, AND MORTALITY

by

AMELIA K BOEHME, SALPY V PAMBOUKIAN, JAMES F GEORGE, CHRISLY DILLON, JAMES K KIRKLIN, JOSE TALLAJ, EMILY B LEVITAN, RUSSELL GRIFFIN, GERALD McGWIN, MICHAEL ALLON, NITA A LIMDI

In Preparation for the Clinical Journal of American Society of Nephrology

Format adapted for dissertation

64
ABSTRACT

**Background and Objectives:** To examine improvement in kidney function post-implant of a Ventricular Assist Device (VAD), identify predictors of kidney function improvement, and examine the whether kidney function improvement is associated with thromboembolism, hemorrhage, and mortality.

**Design, Setting, Participants and Measurements:** Patients (aged 19 or older) with either a continuous or pulsatile flow VAD placed from 2002-2012 at a single center were included (N=228). Kidney function was defined using chronic kidney disease (CKD) stages: Stage 1 (glomerular filtration rate (eGFR) ≥ 90 ml/min/1.73m²), Stage 2 (eGFR 60-90 ml/min/1.73m²), Stage 3a (eGFR 45-59 ml/min/1.73m²), Stage 3b (eGFR 30-44 ml/min/1.73m²), Stage 4 (eGFR 15-30 ml/min/1.73m²) and Stage 5 (eGFR<15 ml/min/1.73m²). We assessed change in kidney function at: pre-implantation, 14 days, 1, 3, 6, 9 and 12 months post-implantation. Improvement in kidney function was defined as an improvement that resulted in a CKD stage change to one of lesser severity. Baseline kidney function and improvement in kidney function were assessed as risk factors for thromboembolism, hemorrhage and mortality.

**Results:** Kidney function improves post implant with improvement in kidney function maintained over 1 year for all patients except those with CKD stage 5 at baseline. Age at implant was the only predictor of sustained improvement in kidney function (OR 0.93, 95% CI 0.90-0.96, p<0.0001). The adjusted risk of death was 3 times higher for patients with baseline CKD stage 3b (HR 3.32, 95%CI 1.10-9.98, p=0.03), and 4 times higher for baseline CKD stage 4 (HR 4.07, 95%CI 1.27-13.1, p=0.02) and stage 5 (HR 4.01, 95%CI...
1.17-13.7, p=0.03). Sustained improvement in kidney function was not associated with a lower risk of death.

**Conclusions:** Most patients experience an improvement in CKD stage after VAD implantation. However, despite these improvements in kidney function post-VAD implant, it was renal function at the time of VAD implantation that was associated with mortality.
Introduction

The prevalence of chronic kidney disease (CKD) is increasing, especially in patients with cardiovascular disease. Thirty to forty percent of patients with heart failure (HF) have CKD, and the prevalence increases further (up to 63%) among advanced HF patients. In approximately 25% of advanced HF patients, chronic cardiac dysfunction is responsible for progressive CKD. CKD is shown to be a stronger predictor of mortality among HF patients compared to cardiac function.

Treatment strategies for HF range from lifestyle changes and medical management to heart transplant or ventricular assist device (VAD) depending on the severity of HF. Among patients with end-stage HF, VAD implantation is increasingly used as a bridge to recovery, bridge to transplant, or as destination therapy. Patients with VAD implants demonstrate an improvement in kidney function following implantation. However, the bulk of the evidence is based on assessment of kidney function in the early (7-30 days) post-implant period. In a recent report of eighty-three VAD recipients, kidney function, assessed by glomerular filtration rate (eGFR), improved post-implant and this improvement was sustained at 180 days. Additionally, Kirklin et al illustrated sustained improvement in blood urea nitrogen (BUN) and creatinine concentrations up to 2 years after VAD implantation. However no studies have evaluated whether improvements in kidney function are associated with better clinical outcomes.

Herein we assess improvement in kidney function post-VAD implantation, whether the improvement in kidney function is sustained for a period of one year, identify predictors of kidney function improvement, and examine the whether kidney function
improvement is associated with a decrease in risk of thromboembolic events, hemorrhagic events, and all-cause mortality.

**Materials and Methods**

*Study Setting*

The study enrolled patients who received a ventricular assist device (VAD) from 2002-2012 at the University of Alabama at Birmingham under the approval of the Institutional Review Board.

*Inclusion and Exclusion Criteria*

Patients aged 19 years and older who had a VAD (continuous-flow or pulsatile flow) placed at UAB from 2002-2012 were included in this study. All patients received post-implant medical care at the implanting center. Most patients received inpatient care for 2-4 weeks post-implantation. After discharge, all patients received care as outpatients at monthly intervals.

Of the 241 VAD patients eligible, 13 patients were implanted at another institution and then received follow-up care at UAB. These individuals were excluded because their baseline kidney function assessment at time of implantation was not available. This resulted in 228 patients in our final study sample.

*Data collection*

For all patients, information including demographic variables (age at implant, self-reported race, ethnicity etc.), medical history prior to VAD (comorbid conditions, heart failure etiology etc.), and laboratory assessments were collected at baseline (pre-
VAD implantation). Clinical data, including medications and laboratory assessments, were collected from each post-VAD clinic visit or hospitalization period during the 1-year follow-up period. Patients were followed for 1-year post-VAD implantation or until explantation of the device, transplant or death prior to 1 year. All adverse events were defined using definitions from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Registry.(15)

**Definition of Exposure**

Kidney function was assessed based on estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI)(16) which incorporates gender, race, age, and serum creatinine (Scr; mg/dL). We assessed change in kidney function from VAD implantation at the following six time-points: pre-implantation, 14 ± 2 days, 1 month ± 2 days, 3 months ± 7 days, 6 months ± 7 days, 9 months ± 7 days and 12 months ± 7 days post-implantation.

We present CKD stages as recommended by the Kidney Disease Outcomes Quality Initiative guidelines: The groups were Stage 1 (eGFR≥90 ml/min/1.73m²), Stage 2 (eGFR 60-90 ml/min/1.73m²), Stage 3a (eGFR 45-59 ml/min/1.73m²), Stage 3b (eGFR 30-44 ml/min/1.73m²), Stage 4 (eGFR 15-30 ml/min/1.73m²) and Stage 5 (eGFR<15 ml/min/1.73m²). (17)

Improvement in kidney function was defined as an improvement in eGFR that resulted in a CKD stage change to one of lesser severity. For example, consider two patients with eGFR of 36 at baseline. One patient’s eGFR improves to 52ml/min while the second patient’s eGFR improves to 39ml/min. While eGFR improved in both
patients, in the first patient the improvement would reclassify the CKD stage from Stage 3b to Stage 3a.

We also assessed if improvements in eGFR were sustained over the 1-year follow-up period post implantation. Sustained improvement was defined as improvement in CKD stage over baseline and improvement in CKD stage that was sustained over the 1-year follow-up period. Patients with CKD Stage 1 or 2 at baseline who maintained kidney function within the pre-VAD CKD stage were included in the sustained improvement category as they did not have a decrease in kidney function post VAD.

Definition of Outcomes

Outcomes of interest included thromboembolic events, hemorrhagic events, and all-cause mortality. Outcomes were determined as a documented event through review of medical records. Thromboembolic events included ischemic stroke, transient ischemic attack, pulmonary embolus, deep vein thrombosis, pump thrombosis requiring hospitalization, and mediastinal clot requiring surgical removal. Hemorrhagic events included intracranial hemorrhage, pericardial bleeding, intraarticular bleeding, gastrointestinal bleed, greater than 2 units of packed red blood cells administered at one time, and mediastinal bleeding requiring surgical intervention. Mortality was defined as death from any cause.

Statistical Analysis
The χ² test of independence was used to assess group differences for categorical variables and ANOVA/Student’s t-test or Kruskal-Wallis/Wilcoxon Rank Sum where appropriate for continuous variables. Logistic regression models were used to assess predictors of sustained improvement. Cox proportional hazards models were used to evaluate the association between kidney function and thromboembolism, hemorrhage, and death. Log survival plots were used to assess the proportional hazards assumption. For mortality analysis, follow-up time was censored at time of transplant, explant (removal of the VAD device), or death. For analysis of thromboembolic or hemorrhagic event, the follow-up time was censored at the time of first event; repeated events were not considered. For patients who did not experience a thromboembolic or hemorrhagic event, follow-up time was censored at end of the study (1 year) or explantation (if earlier than 1 year). All tests were performed using SAS version 9.2 (SAS Institute, Cary, NC) at a non-directional alpha level of 0.05.

Results

Overall Population

Of the 241 VAD patients who were treated at UAB between 2002 and 2012, thirteen patients implanted at an outside hospital were excluded because baseline kidney function information was not available. Of the 228 patients (72% men, 71% White) included in the analysis, the mean age at implant was 52 years (14.6 SD), and the majority (57%) received VAD implants as a bridge to transplantation (57 %). At baseline, 35.5% participants had Stage 1 or 2 CKD (eGFR ≥ 60 ml/min/1.73m²), 23% had Stage 3a
CKD (eGFR 45-59 ml/min/1.73m²), 23% had Stage 3b CKD (eGFR 30-44 ml/min/1.73m²), 13% had Stage 4 CKD (eGFR 15-29 ml/min/1.73m²) and 5% had Stage 5 CKD (eGFR <15 ml/min/1.73m²). Baseline characteristics of the cohort, stratified by kidney function, are presented in Table 1. No significant differences were observed between CKD stages and comorbidities except patients with continuous flow devices who had less severe kidney dysfunction (p=0.001), and those with history of diabetes (p=0.02), and history of hypertension (p=0.01) who had more baseline kidney dysfunction.

Change in Kidney Function over Time

Within the first 14 days, a majority (56.7%; n=130) of VAD recipients demonstrated meaningful improvement in kidney function compared to baseline kidney function (Figure 1). Regardless of fluctuations in eGFR over time, early improvement in kidney function was sustained for a majority of patients (n=127) for the duration of the 1-year follow up, except those with Stage 5 CKD at baseline (n=11). Although patients with Stage 5 CKD showed improvement in kidney function over the first 3 months, the improvement was not sustained. There was no difference in improvement in CKD stage after implantation between continuous and pulsatile flow devices.

Increasing age at implantation was inversely associated with sustained improvement in kidney function. For each year increase in age at implant, the odds of having sustained improvement in kidney function decreased by 5% (OR 0.95, 95% CI 0.92-0.97, p<0.0001). This association remained after adjusting for baseline CKD stage,
gender, race, history of diabetes and history of hypertension (OR 0.93, 95% CI 0.90-0.96, p<0.0001). Patients who sustained kidney function improvement over time were more likely to receive a heart transplant than those who did not sustain kidney function over time (28% vs. 16%, p=0.05).

*Kidney Function and Thromboembolism*

There were 39 thromboembolic events over a follow-up time of 101 person-years with an incidence rate of 3.9 per 10 person years (95% CI 2.8-5.2). Neither baseline kidney function (*Table 2*), nor sustained improvement in kidney function at 1 year (data not shown; HR 0.98, 95% CI 0.54-1.78, p=0.95) were associated with the risk of thromboembolic events.

*Kidney Function and Hemorrhage*

There were 58 hemorrhagic events over a follow-up time of 101 person-years with an incidence rate of 5.7 per 10 person years (95% CI 4.4-7.4). There was no statistically significant association with baseline kidney function and risk of hemorrhagic events (*Table 2*). There was no significant reduction in the risk of hemorrhage for those who sustained kidney function improvement over the follow-up as compared to those who did not sustain improvement (HR 0.75, 95% CI 0.46-1.22, p=0.24).

*Kidney Function and Death*
A total of 80 deaths occurred over a follow-up time of 151 person-years with an incidence rate of 5.3 per 10 person-years (95% CI 4.2-6.6). The risk of death was higher amongst patients with compromised kidney function at baseline (Figure 2a). Patients with CKD stage 3b (HR 3.12, 95%CI 1.16-9.17, p=0.039), CKD stage 4(HR 3.94, 95%CI 1.29-12.0, p=0.02) and CKD stage 5 (HR 7.24, 95%CI 2.18-24.1, p=0.001) had a significantly higher risk of mortality compared to those with CKD stage 1. This association persisted, even after adjustment for device type, age at implant, history of diabetes, and history of hypertension (Figure 2b). The risk of death was 3 times higher for CKD stage 3b (HR 3.32, 95%CI 1.10-9.98, p=0.03), and 4 times higher for CKD stage 4 (HR 4.07, 95%CI 1.27-13.1, p=0.02) and Stage 5 (HR 4.01, 95%CI 1.17-13.7, p=0.03) compared to those with CKD stage 1. Improvement in kidney function that was sustained for 1-year was not associated with a lower risk of death (HR 1.03, 95%CI 0.58-1.84, p=0.91).

Discussion

Our study demonstrates that VAD implantation is associated with clinically meaningful improvement in kidney function that is sustained over a 1- year. However, improvement in kidney function did not influence the risk of thromboembolism, hemorrhage or mortality. We found that kidney function at the time of implantation increased the risk of mortality, with patients in the more advanced stages of kidney dysfunction having the highest risk of death.
Kidney function has been shown to improve after VAD implantation, but the extent and duration of improvement has not been well characterized. The limited follow-up in prior reports has enabled demonstration of short-term kidney function improvement. Only two studies have explored kidney function over a longer time period (Table 3). Our study fills this gap by investigating long-term kidney function with detailed information on the change in CKD stage and eGFR after VAD implantation. Hasin et al illustrated improvement in eGFR post implant to 6 months in 83 VAD patients, and Kirklin et al illustrated improvement in serum creatinine and BUN up to 2 years post implant in 4917 VAD patients. However, both of these studies assessed kidney function over time as continuous measures. Assessing changes in kidney function that reclassifies the CKD stage provides a clinically meaningful metric. Our findings confirm previous observations that renal function improves after VAD implantation and demonstrates that the improvements are clinically meaningful and sustained.

The greatest improvements in kidney function are realized early, in the first 14 days post implant, as organ perfusion is increased. Although improvement in kidney function are sustained, early gains in eGFR are attenuated after 14 days. Therefore gain in kidney function after 14 days may more closely represent the organ capacity that was previously masked due to poor kidney perfusion in these patients with poor cardiac function.

Decreased kidney function is the most common contraindication to heart transplantation. Previous studies have shown that among patients with HF receiving heart transplants, those maintained on VADs (vs. inotrope support) have better kidney
function at time of transplantation. (20) Therefore our results, wherein 55.8% of VAD patients demonstrating sustained improvement in kidney function are of particular importance for three reasons. First, it suggests the potential benefit of VAD implantation over inotrope support, a hypothesis being investigated in REVIVE-IT study. Second, kidney function improvement (or lack thereof) post-VAD implantation facilitates assessment of organ capacity that was previously masked due to poor kidney perfusion in these patients with poor cardiac function. Third, sustained improvement in kidney function improves the candidacy for receiving a heart transplant. The latter is supported by our findings wherein patients who demonstrated sustained kidney function improvement over time were more likely to than those who did not sustain kidney function over time.

In our study, neither baseline kidney function nor improvement in kidney function was associated with thromboembolism or hemorrhage. This is contrary to reports from non-VAD patient populations that have demonstrated that kidney function improvement is associated with a decrease in risk of thromboembolism and hemorrhage. (21-24) The lack of association in our study could be due to two reasons. First, patients who demonstrated sustained improved kidney function on VAD support were more likely to be transplanted, and therefore censored from further analysis. Second, unlike non-VAD patient populations, patients with VADs have a different risk profile for these events due to the complex nature of the device itself and its effects on the coagulation system and the vasculature. Given these considerations, along with the baseline risk in patients with cardiovascular disease in general, improvement in kidney function alone, even if sustained over a one year period, may not be enough to outweigh the risk associated with
the VAD device itself or mitigate the risk associated with longstanding cardiovascular
disease. Moreover, the one-year follow-up time may have limited our ability to detect
associations between kidney function and thromboembolism or hemorrhage.

Decreased kidney function at prior to VAD implant was associated with higher
mortality consistent with reports in advanced heart failure patients. Although
improvement in kidney function decreases mortality in non-VAD patients, our findings
did not demonstrate decrease in mortality among VAD recipients. This may be explained
the higher and long standing disease burden in patients with advanced heart failure.
Although VAD implantation improves kidney function and reverses the cardiorenal
syndrome, the improvements do not attenuate the risk of mortality.

While previous studies have illustrated the influence of pre-VAD kidney function
on post-VAD mortality, these studies have primarily assessed eGFR, creatinine and BUN
as continuous measures, and their subsequent association with mortality. Consistent with
previous studies, poor kidney function pre-VAD is associated with a higher mortality
rate. (18) This is the first study to investigate CKD stage pre-VAD implantation and the
association with mortality post-VAD implantation. Furthermore, we categorized CKD
stage 3 into stage 3a (eGFR 45-59 ml/min) and stage 3b (eGFR 30-44 ml/min) as Levey
et al have demonstrated clinically meaningful differences in mortality among the two
groups. (25) To our knowledge, this report is the first to report that VAD patients stage 3b
CKD have a higher mortality, compared to those with stage 3a CKD.

The study has several strengths including a large (n=228) sample size, a racially
diverse population, uniformity of care at a single institution, detailed clinical
documentation, and ascertainment of clinically relevant events with minimal loss (n=4;
patient transferred care out-of-state) to follow-up. Kidney function was assessed at multiple time points, and improvement in kidney function is defined using a clinically relevant rubric. However we recognize its limitations such as lack of ascertainment of biomarkers. We recognize that this is a single center study. Therefore independent validation of our findings in larger datasets is needed to confirm our findings.

Regardless of baseline kidney function, most patients experience an improvement in kidney function after VAD implantation. Regardless of the improvement in kidney function post VAD implant, risk of mortality is driven by baseline kidney function. Patients with CKD stage 3b, 4 or 5 prior to VAD are at an increased risk of mortality post-VAD implantation. This has important implications on patient selection during evaluation for VAD therapy. Further research is needed to establish whether patients with decreased kidney function due to advancing heart failure would benefit from earlier implantation of a VAD to reduce the mortality associated with advancing kidney dysfunction.
Reference List


Table 1. Demographic and Clinical Characteristics for the Entire Cohort Stratified by Kidney Function prior to VAD Implantation

<table>
<thead>
<tr>
<th></th>
<th>Stage 1 eGFR ≥90 (N=32)</th>
<th>Stage 2 eGFR 60-89 (N=49)</th>
<th>Stage 3A eGFR 45-59 (N=53)</th>
<th>Stage 3B eGFR 30-44 (N=53)</th>
<th>Stage 4 eGFR 15-30 (N=30)</th>
<th>Stage 5 eGFR &lt;15 (N=11)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD)</strong> Age</td>
<td>43.2 ±15.9</td>
<td>51.1 ±15.6</td>
<td>51.7 ±13.4</td>
<td>56.2±14</td>
<td>56.8±11.4</td>
<td>52.6±12.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>30.9 ±7.7</td>
<td>27.6±8.8</td>
<td>27.1±7.8</td>
<td>26.7±5.8</td>
<td>30.3±8.2</td>
<td>25.4±4.6</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>N (%)</strong> Male</td>
<td>25 (78)</td>
<td>39 (80)</td>
<td>35 (66)</td>
<td>41 (77)</td>
<td>20 (67)</td>
<td>7 (64)</td>
<td>0.49</td>
</tr>
<tr>
<td>Black Race</td>
<td>14 (44)</td>
<td>16 (33)</td>
<td>16 (30)</td>
<td>10 (19)</td>
<td>6 (20)</td>
<td>2 (18)</td>
<td>0.14</td>
</tr>
<tr>
<td>Status within the First Year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Deceased</td>
<td>4 (12)</td>
<td>11 (22)</td>
<td>17 (32)</td>
<td>19 (36)</td>
<td>14 (47)</td>
<td>8 (73)</td>
<td></td>
</tr>
<tr>
<td>Transplanted</td>
<td>10 (31)</td>
<td>12 (25)</td>
<td>8 (15)</td>
<td>4 (8)</td>
<td>7 (23)</td>
<td>2 (18)</td>
<td></td>
</tr>
<tr>
<td>Recovered</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td><strong>Device Type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Pulsatile Flow</td>
<td>11 (34)</td>
<td>18 (37)</td>
<td>25 (47)</td>
<td>23 (43)</td>
<td>19 (63)</td>
<td>11 (100)</td>
<td></td>
</tr>
<tr>
<td>Continuous Flow</td>
<td>21 (66)</td>
<td>31 (63)</td>
<td>28 (53)</td>
<td>30 (57)</td>
<td>11 (37)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Etiology of Heart Failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>Ischemic</td>
<td>8 (25)</td>
<td>28 (57)</td>
<td>25 (47)</td>
<td>32 (60)</td>
<td>17 (57)</td>
<td>6 (55)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>16 (50)</td>
<td>14 (28)</td>
<td>23 (44)</td>
<td>13 (25)</td>
<td>10 (33)</td>
<td>3 (27)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8 (25)</td>
<td>7 (14)</td>
<td>5 (9)</td>
<td>8 (15)</td>
<td>3 (10)</td>
<td>2 (18)</td>
<td></td>
</tr>
<tr>
<td><strong>Indication for VAD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>Bridge to transplant</td>
<td>23 (72)</td>
<td>31 (66)</td>
<td>31 (58)</td>
<td>25 (48)</td>
<td>13 (43)</td>
<td>8 (73)</td>
<td></td>
</tr>
<tr>
<td>Comorbid Conditions</td>
<td>Bridge to candidacy</td>
<td>Bridge to recovery</td>
<td>Destination</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>-------------------------------------</td>
<td>--------------------</td>
<td>--------------------</td>
<td>-------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (28)</td>
<td>11 (22)</td>
<td>24 (45)</td>
<td>27 (51)</td>
<td>13 (43)</td>
<td>2 (18)</td>
<td>0.019</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>2 (6)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>5 (9)</td>
<td>1 (3)</td>
<td>0</td>
<td>0.51</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>27 (84)</td>
<td>44 (90)</td>
<td>43 (81)</td>
<td>44 (83)</td>
<td>24 (80)</td>
<td>6 (55)</td>
<td>0.15</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>2 (6)</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td>0</td>
<td>0.90</td>
</tr>
<tr>
<td>Gout</td>
<td>3 (9)</td>
<td>9 (18)</td>
<td>5 (9)</td>
<td>4 (8)</td>
<td>5 (17)</td>
<td>2 (18)</td>
<td>0.50</td>
</tr>
<tr>
<td>Right Ventricular Dysfunction</td>
<td>6 (19)</td>
<td>14 (29)</td>
<td>8 (15)</td>
<td>14 (26)</td>
<td>5 (17)</td>
<td>3 (27)</td>
<td>0.52</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>8 (25)</td>
<td>13 (26)</td>
<td>22 (41)</td>
<td>17 (32)</td>
<td>14 (47)</td>
<td>2 (18)</td>
<td>0.21</td>
</tr>
<tr>
<td>History of Myocardial Infarction</td>
<td>5 (16)</td>
<td>8 (16)</td>
<td>11 (21)</td>
<td>14 (26)</td>
<td>8 (27)</td>
<td>2 (18)</td>
<td>0.74</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (47)</td>
<td>28 (57)</td>
<td>38 (72)</td>
<td>27 (51)</td>
<td>10 (33)</td>
<td>4 (36)</td>
<td>0.014</td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>12 (37)</td>
<td>7 (14)</td>
<td>13 (24)</td>
<td>10 (19)</td>
<td>6 (20)</td>
<td>1 (9)</td>
<td>0.16</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>8 (25)</td>
<td>19 (39)</td>
<td>22 (41)</td>
<td>20 (38)</td>
<td>15 (50)</td>
<td>1 (9)</td>
<td>0.14</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>10 (31)</td>
<td>16 (33)</td>
<td>19 (36)</td>
<td>18 (34)</td>
<td>10 (33)</td>
<td>0</td>
<td>0.34</td>
</tr>
<tr>
<td>Ventricular Tachycardia</td>
<td>11 (34)</td>
<td>19 (39)</td>
<td>28 (53)</td>
<td>16 (30)</td>
<td>16 (53)</td>
<td>3 (27)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Kidney function is presented as CKD stages as recommended by the Kidney Disease Outcomes Quality Initiative guidelines using estimated glomerular filtration rate (eGFR) from the Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI).
Table 2. Association of Kidney Function at Baseline with Risk (Hazard Ratio (HR) and 95% Confidence Interval(CI)) of Thromboembolism and Hemorrhage

<table>
<thead>
<tr>
<th>Thromboembolic Events</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage of Kidney Disease at Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1 (eGFR≥90)</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>Stage 2 (eGFR 60-89)</td>
<td>0.82</td>
<td>0.23-2.94</td>
<td>0.77</td>
</tr>
<tr>
<td>Stage 3a (eGFR 45-59)</td>
<td>1.47</td>
<td>0.47-4.62</td>
<td>0.51</td>
</tr>
<tr>
<td>Stage 3b (eGFR 30-44)</td>
<td>1.75</td>
<td>0.55-5.58</td>
<td>0.35</td>
</tr>
<tr>
<td>Stage 4 (eGFR 15-29)</td>
<td>1.52</td>
<td>0.41-5.68</td>
<td>0.53</td>
</tr>
<tr>
<td>Stage 5 (eGFR &lt;15)</td>
<td>0.94</td>
<td>0.10-8.38</td>
<td>0.95</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemorrhagic Events</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage of Kidney Disease at Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1 (eGFR≥90)</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>Stage 2 (eGFR 60-89)</td>
<td>1.55</td>
<td>0.56-4.32</td>
<td>0.40</td>
</tr>
<tr>
<td>Stage 3a (eGFR 45-59)</td>
<td>1.71</td>
<td>0.63-4.67</td>
<td>0.29</td>
</tr>
<tr>
<td>Stage 3b (eGFR 30-44)</td>
<td>2.04</td>
<td>0.73-5.67</td>
<td>0.17</td>
</tr>
<tr>
<td>Stage 4 (eGFR 15-29)</td>
<td>0.99</td>
<td>0.26-3.70</td>
<td>0.99</td>
</tr>
<tr>
<td>Stage 5 (eGFR &lt;15)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Kidney function is presented as CKD stages as recommended by the Kidney Disease Outcomes Quality Initiative guidelines using estimated glomerular filtration rate (eGFR) from the Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI). The groups are Stage 1 (eGFR≥90 ml/min/1.73m²), Stage 2 (eGFR 60-90 ml/min/1.73m²), Stage 3a (eGFR 45-59 ml/min/1.73m²), Stage 3b (eGFR 30-44 ml/min/1.73m²), Stage 4 (eGFR 15-30 ml/min/1.73m²) and Stage 5 (eGFR<15 ml/min/1.73m²). Follow-up is calculated as time from VAD to first event or end of study period (1 year or time until explantation/transplantation) for thromboembolic events and hemorrhagic events. Follow-up time for incidence of death is calculated as time to death or end of study period (1 year or explantation/transplantation. Cox proportional hazards models were used to assess the risk of thromboembolism and hemorrhage. The proportional hazards assumption was met.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample Size</th>
<th>Definition of Kidney Function</th>
<th>Assessment of Kidney Function</th>
<th>Outcome of Interest</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kirklin (2013)(^{18})</td>
<td>4,917</td>
<td>eGFR &lt;30 for severe kidney disease and eGFR 30-60 for moderate kidney disease</td>
<td>Assessed at baseline, BUN and creatinine were assessed up to 4 years after implantation</td>
<td>Death, change in serum creatinine and BUN</td>
<td>Pre-implant renal dysfunction is related to higher mortality post VAD implant.</td>
</tr>
<tr>
<td>Borgi (2013)(^{26})</td>
<td>100</td>
<td>Acute Renal Failure (ARF)</td>
<td>Assessed at baseline and 7 days</td>
<td>Change in KF and its influence on 1-year mortality</td>
<td>Postoperative ARF is associated with mortality</td>
</tr>
<tr>
<td>Iwashi ma et al (2012)(^{27})</td>
<td>110</td>
<td>Change in estimate glomerular filtration rate (eGFR) from baseline to 2 weeks</td>
<td>Assessed at baseline and 2 weeks</td>
<td>Mortality at 2 years</td>
<td>Impaired renal function as well as renal function that does not improve with VAD placement are predictors of mortality</td>
</tr>
<tr>
<td>Hasin et al (2012)(^{28})</td>
<td>83</td>
<td>eGFR</td>
<td>Assessed before VAD, and 1,3 and 6 months after VAD</td>
<td>eGFR</td>
<td>Renal function improves after VAD implantation</td>
</tr>
<tr>
<td>Butler et al (2006)(^{29})</td>
<td>220</td>
<td>Renal function as defined by creatinine clearance</td>
<td>Assessed 1 month post VAD</td>
<td>All-cause mortality, and disease specific mortality at 1 year</td>
<td>Poor renal function at baseline is associated with worse outcomes. Patients with improving renal function after VAD placement experience improved outcomes</td>
</tr>
<tr>
<td>Genovese et al (2010)(^{30})</td>
<td>163</td>
<td>Acute Renal Failure (ARF)</td>
<td>Assessed 60 days post implantation</td>
<td>One year mortality</td>
<td>The presence of some adverse events increased the risk of mortality, namely renal events, respiratory events, bleeding events and reoperation</td>
</tr>
<tr>
<td>Ma et al (2008)(^{31})</td>
<td>28</td>
<td>Renal function as measured through creatinine</td>
<td>Assessed at baseline and 1 month post implant</td>
<td>Length of recovery</td>
<td>Pre-VAD renal function is predictive of post-VAD renal function and length of stay in the ICU</td>
</tr>
<tr>
<td>Russell et al (2009)(^{32})</td>
<td>309</td>
<td>Renal function as defined by BUN and creatinine</td>
<td>Assessed at baseline and 6 months post VAD</td>
<td>Renal function as defined by BUN and creatinine</td>
<td>Implantation of a VAD improves renal function</td>
</tr>
<tr>
<td>Sandner et al (2009)(^{33})</td>
<td>86</td>
<td>Pre-VAD eGFR</td>
<td>Assessed prior to VAD</td>
<td>Mortality post-VAD to 6 months</td>
<td>Patients with pre-VAD renal dysfunction have poorer outcomes than patients without pre-VAD renal dysfunction. Regardless of pre-VAD renal status, renal function improves after VAD outcome</td>
</tr>
<tr>
<td>Sandner et al (2008)(^{34})</td>
<td>92</td>
<td>Renal function as defined by creatinine and eGFR</td>
<td>Assessed at baseline and 3 months</td>
<td>Renal function, and mortality at 3 months</td>
<td>There is no difference between continuous flow and pulsatile flow devices on renal function</td>
</tr>
<tr>
<td>Singh et al (2011)(^{35})</td>
<td>116</td>
<td>Creatinine clearance prior to VAD</td>
<td>Assessed prior to VAD</td>
<td>Creatinine clearance 1 month after VAD implant</td>
<td>VAD use improves renal function after implantation</td>
</tr>
</tbody>
</table>
Figure 1. Change in Kidney Function over 1 year follow-up from VAD Implantation

Kidney function is presented as CKD stages as recommended by the Kidney Disease Outcomes Quality Initiative guidelines using estimated glomerular filtration rate (eGFR) from the Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI). The groups are Stage 1 (eGFR ≥90 ml/min/1.73m²), Stage 2 (eGFR 60-90 ml/min/1.73m²), Stage 3a (eGFR 45-59 ml/min/1.73m²), Stage 3b (eGFR 30-44 ml/min/1.73m²), Stage 4 (eGFR 15-30 ml/min/1.73m²) and Stage 5 (eGFR<15 ml/min/1.73m²)
* A total of 28 patients was not included in this assessment due to 2 patients being transplanted, 1 patient recovered and 25 patients died

** An additional 12 patients were not included in this assessment due to patient death

§ An additional 30 patients were not included in this assessment due to 4 patient withdrawals, 2 patients recovered, 11 patients had a transplant and 13 patients died

† An additional 22 patients were not included in this assessment due to 10 patient deaths, 11 patients were transplanted and 1 patient withdrew

‡ An additional 15 patients were not included in this assessment due to 5 patient deaths and 10 transplants

§ An additional 17 patients were not included in this assessment due to 8 patient deaths and 9 transplants
Kidney function is presented as CKD stages as recommended by the Kidney Disease Outcomes Quality Initiative guidelines using estimated glomerular filtration rate (eGFR) from the Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI). The groups are Stage 1 (eGFR ≥ 90 ml/min/1.73m²), Stage 2 (eGFR 60-90 ml/min/1.73m²), Stage 3a (eGFR 45-59 ml/min/1.73m²), Stage 3b (eGFR 30-44 ml/min/1.73m²), Stage 4 (eGFR 15-30 ml/min/1.73m²) and Stage 5 (eGFR < 15 ml/min/1.73m²). Cox proportional hazards models were used to assess the risk of death. The proportional hazards assumption was not met, however Cox proportional hazards models are robust to moderate deviations in proportionality and the deviations in this model were minor.
Kidney function is presented as CKD stages as recommended by the Kidney Disease Outcomes Quality Initiative guidelines using estimated glomerular filtration rate (eGFR) from the Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI). The groups are Stage 1 (eGFR ≥ 90 ml/min/1.73m²), Stage 2 (eGFR 60-90 ml/min/1.73m²), Stage 3a (eGFR 45-59 ml/min/1.73m²), Stage 3b (eGFR 30-44 ml/min/1.73m²), Stage 4 (eGFR 15-30 ml/min/1.73m²) and Stage 5 (eGFR < 15 ml/min/1.73m²). Cox proportional hazards models were used to assess the adjusted risk of death. The proportional hazards assumption was met.
SUMMARY CONCLUSIONS

Heart failure is a major concern in the United States with the prevalence increasing. The treatment options for heart failure range with the degree of severity. Medication and lifestyle changes can aid in controlling symptoms and decrease disease progression for those with mild and moderate heart failure, however the gold standard treatment for advanced heart failure remains the heart transplant. The use of the ventricular assist device (VAD) as a treatment option for advanced heart failure patients is increasing. While the VAD has increased the survival rate and quality of life there is still a considerable amount of morbidity and mortality associated with VAD use. VAD patients are at increased risk for thromboembolism, hemorrhage and death.

A retrospective analysis of patients under the care of the Mechanical Circulatory Support Clinic at UAB was conducted to assess predictors of thromboembolism. We assessed traditional risk factors for thromboembolism, clinical factors and the biomarker lactate dehydrogenase (LDH). In this study we found an association between pre-VAD LDH and post-VAD thromboembolism. Furthermore, we show that early LDH elevation within the first month post-VAD implant, in addition to kidney function prior to VAD implantation and post-VAD anticoagulation control, are significant risk factors for thromboembolism. We found that the risk for thromboembolism was 5 fold higher for patients with early LDH elevation, 5 fold higher for patients with poor kidney function.
prior to VAD implantation and a decreased risk of thromboembolism for patients with adequate anticoagulation control.

A retrospective analysis of patients under the care of the Mechanical Circulatory Support Clinic at UAB was conducted to create a VAD specific bleeding risk score and compare it to the previously developed HAS-BLED risk score, a score designed to predict hemorrhage in other anticoagulated patients. We found that the HAS-BLED score is not as predictive in the VAD population as it is in other chronic anticoagulation populations. We found that patients with a VAD bleeding risk score of $\geq 3$ are at 4 times the risk of hemorrhage than patients with a lower VAD bleeding risk score. Further studies are needed to validate this score in other VAD populations.

A retrospective analysis of patients under the care of the Mechanical Circulatory Support Clinic at UAB was conducted to assess the change in kidney function over time post-VAD implant, and evaluate whether change in kidney function post-VAD is associated with thromboembolism, hemorrhage and death. Regardless of baseline CKD stage, most patients experience an improvement in CKD stage after VAD implantation. These results support the theories that while heart failure induced hypoperfusion of the kidneys may cause kidney dysfunction, the dysfunction can be partially reversed once perfusion of the kidneys is restored. Regardless of the improvement in kidney function post VAD implant, patients with CKD stage 3b, 4 or 5 prior to VAD are at an increased risk of mortality post-VAD implantation. Our study further illustrates the importance of kidney function in heart failure patients; and how baseline kidney function remains a strong predictor of mortality post-VAD regardless of improvements due to VAD implantation. Further research is needed to establish whether patients with decreased
kidney function due to advancing heart failure would benefit from earlier implantation of a VAD to reduce the mortality associated with advancing kidney dysfunction.

These studies identify risk factors for thromboembolism, hemorrhage and mortality in VAD patients. Identifying risk factors for these outcomes is paramount in this high risk patient population. The identification of subgroups with significant risk factors can be identified and managed more closely to possibly prevent thromboembolism and hemorrhage and reduce the mortality rate associated with VAD use. In conclusion, in these three studies, we established the biomarker LDH is associated with risk of thromboembolism, established a VAD Bleeding Risk score to identify VAD patients at greatest risk of hemorrhage, and identified pre-VAD kidney function as a strong risk factor for mortality post-VAD.
GENERAL LIST OF REFERENCES


APPENDIX A

INSTITUTIONAL REVIEW BOARD APPROVAL
Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The Assurance number is FWA00005960 and it expires on January 24, 2017. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56.

Principal Investigator: BOEHME, AMELIA K.
Co-Investigator(s): LIMDI, NITA A
                        PAMBOUKIAN, SALPY VERONICA
Protocol Number: X110524002
Protocol Title:  Predictors of Outcomes in Patients on Ventricular Assist Devices (Predictors of Thromboembolism and Hemorrhage in patients on Ventricular Assist Devices)

The IRB reviewed and approved the above named project on 12-12-13. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received EXPEDITED review.

IRB Approval Date: 12-12-13

Date IRB Approval Issued: 12-12-13

HIPAA Waiver Approved?: Yes

Marilyn Doss, M.A.
Vice Chair of the Institutional Review Board for Human Use (IRB)

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.