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Improvement in Kidney Function after Ventricular Assist Device Implantation and Its Influence on Thromboembolism, Hemorrhage and Mortality

Brittney H. Davis, Pharm. D.[1,*], **Amelia K. Boehme, PhD MSPH**[2,*], **Salpy V. Pamboukian, MD MSPH**[3], **Michael Allon, MD**[4], **James F. George, PhD**[5], **Chrisly Dillon, MD MHA**[1], **James K. Kirklin, MD**[5], **Jose Tallaj, MD**[3], **Emily B. Levitan, ScD**[6], **Russell Griffin, PhD**[6], **Gerald McGwin Jr, MS PhD**[6], **T. Mark Beasley, PhD**[7], **Nita A. Limdi, Pharm. D, PhD, MSPH**[1,6]

[1]Department of Neurology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL

[2]Department of Neurology, Columbia University, New York, NY

[3]Division of Cardiovascular Diseases, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL

[4]Division of Nephrology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL

[5]Division of Cardiothoracic Surgery, Department of Surgery, University of Alabama at Birmingham, Birmingham, AL

[6]Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, AL

[7]Department of Biostatistics, School of Public Health, University of Alabama at Birmingham, Birmingham, AL

Abstract

Although heart transplantation remains the gold standard for management of heart failure, ventricular assist devices (VAD) have emerged as viable alternatives. VAD implantation improves kidney function. However, whether the improvement is sustained or associated with improved outcomes is unclear.

Herein we assess kidney function improvement, predictors of improvement, and associations with thromboembolism, hemorrhage, and mortality in VAD patients. Kidney function was defined using CKD stages: Stage 1 (glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73m^2), Stage 2 (eGFR 60–90 mL/min/1.73m^2), Stage 3a (eGFR 45–59 mL/min/1.73m^2), Stage 3b (eGFR 30–44 mL/min/1.73m^2), Stage 4 (eGFR 15–30 mL/min/1.73m^2), and Stage 5 (eGFR<15 mL/min/1.73m^2). Improvement in kidney function was defined as an improvement in eGFR that resulted in a CKD stage change to one of lesser severity.

Corresponding Author: Brittney H. Davis, Pharm. D., Department of Neurology, Jefferson Tower 1235, 619 19th Street South, Birmingham, AL 35294-0022, Phone: 205-934-3962, Fax: 205-996-9912, brittneydavis@uabmc.edu.
*Authors contributed equally

Kidney function improved post implant, and was maintained over 1 year for all patients, except those with baseline Stage-5 CKD. Younger age at implantation (OR 0.93, 95% CI 0.90–0.96, p<0.0001) was associated with sustained improvement in kidney function.

Poor kidney function was associated increased mortality but not with thromboembolism or hemorrhage. Compared to patients with baseline eGFR>45 mL/min/1.73m^2; patients with eGFR<45 mL/min/1.73m^2 had a higher mortality risk (HR 3.32, 95%CI 1.10–9.98, p=0.03 for Stage 3b; HR 4.07, 95%CI 1.27–13.1, p=0.02 for Stage 4; and HR 4.01, 95%CI 1.17–13.7, p=0.03 for Stage5 CKD).

Kidney function was not associated with thromboembolism or hemorrhage, and sustained improvement was not associated with lower risk of death. However, poor kidney function at implantation was associated with an increased risk of mortality.

Keywords

Ventricular assist device; kidney function; advanced heart failure; mechanical circulatory support

Introduction

The prevalence of chronic kidney disease (CKD) is increasing[1] especially in patients with cardiovascular disease. Thirty to forty percent of patients with heart failure (HF) have CKD, [2] and the prevalence increases further (up to 63%) among advanced HF patients.[3,4] In approximately 25% of advanced HF patients, chronic cardiac dysfunction is responsible for progressive CKD.[5,6] CKD is shown to be a stronger predictor of mortality among HF patients compared to cardiac function.[7–10]

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.[11,12] Among patients with end-stage HF, VAD implantation is increasingly used as a bridge to transplant (BTT), or as destination therapy (DT).

Patients with VAD implants demonstrate an improvement in kidney function, as measured by any increase in glomerular filtration rate (GFR) following implantation.[13] However, the bulk of the evidence supports improvement in the early (7–30 days) post-implant period. Recent studies with longer follow-up also suggest an early improvement in kidney function, but whether this improvement is sustained is unclear. Moreover, these studies defined improvement in kidney function as any increase in GFR, grouped patients using different GFR thresholds (GFR ≥60 vs. <60[14,15]; GFR ≥40 vs. <40[16]) or restricted analysis to subgroups, such as those with end-stage renal disease[17] or those who survived >3 years post-implantation.[18]

Herein, we include VAD patients across the kidney function spectrum, use baseline GFR to categorize patients into CKD stages as recommended by the Kidney Disease Outcomes Quality Initiative and define improvement in kidney function as an increase in GFR that results in a CKD stage change to one of lesser severity. Using this framework, 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 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. All patients were on standard antithrombotic therapy with warfarin (dose adjusted to maintain an international normalized ratioINR goal of 2–3) and aspirin (81 or 325mg / day). 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.[19]

Definition of Exposure

Kidney function was assessed based on estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI)[20] 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/1.73m^2), Stage 2 (eGFR 60–90 ml/min/1.73m^2), Stage 3a (eGFR 45–59 ml/min/1.73m^2), Stage 3b (eGFR 30–44 ml/min/1.73m^2), Stage 4 (eGFR 15–30 ml/min/1.73m^2) and Stage 5 (eGFR<15 ml/min/1.73m^2).[21]

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 χ^2 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/1.73m^2), 23% had Stage 3a CKD (eGFR 45–59 ml/min/1.73m^2), 23% had Stage 3b CKD (eGFR 30–44 ml/min/1.73m^2), 13% had Stage 4 CKD (eGFR 15–29 ml/min/1.73m^2) and 5% had Stage 5 CKD (eGFR <15 ml/min/1.73m^2). No patients were on dialysis prior to VAD implantation. 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. In patients with baseline GFR≥15, kidney function improved post-VAD implantation with maximal improvement attained at 3 months. 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 74 deaths occurred over a follow-up time of 153.6 person-years with an incidence rate of 4.8 per 10 person-years (95% CI 3.8–6.0). The primary etiology of death was multi-organ failure (85%; 63 of 74 deaths). The risk of death was higher amongst patients with compromised kidney function at baseline (Table 2). 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 2). 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 1- year for most patients. However, improvement in kidney function did not influence the risk of thromboembolism, hemorrhage or mortality. Although patients with Stage 5 CKD (baseline GFR<15) showed improvement in kidney function over the first 3 months, the improvement was not sustained. 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 clinically significant improvement and duration of improvement has not been well characterized. 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. 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). 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.[15,20–23] However, both of these studies assessed kidney function over time as continuous measures. Presenting changes in kidney function as a continuous measure (eGFR) and categorical measure (CKD stage) in Figure 1 provides another facet and timeline of changing kidney function post VAD implantation. Our findings confirm

previous observations that kidney function improves after VAD implantation and demonstrates that the improvements are clinically meaningful and sustained. However, among patients with Stage 5 CKD at baseline, the improvements are only temporal and not as sustained as previously hypothesized.

The greatest improvements in kidney function are realized early, in the first 14 days post implant, as organ perfusion is increased. Although improvements 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.[24] 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.[25] Therefore our results, wherein 55.8% of VAD patients demonstrated improvement in kidney function are of particular importance for two reasons. First, 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. However as we did not have assessment of right heart function, we cannot determine whether the improvement in kidney function is due to better renal perfusion or due to reduced pressure in the venous return. Second, 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 VAD[14] and non-VAD patient populations that have demonstrated that kidney function improvement is associated with a decrease in risk of thromboembolism and hemorrhage.[23,26–28] 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 prior to VAD implant was associated with higher mortality consistent with recent reports.[14,29] 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 by 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.[14,22,29] We investigated 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.[30] 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. Moreover, only four patients transferred care out-of-state. Therefore, we could not ascertain their status for this analysis. 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 also recognize our findings from this retrospective and single center study may not be generalizable to larger VAD populations. Using CKD staging to characterize baseline kidney dysfunction may misclassify patients as having kidney disease when the kidney dysfunction could be due to acute kidney injury instead of chronic kidney disease. We did not assess whether there is an association between right ventricular dysfunction or infections and kidney dysfunction. 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 ay 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.

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Conflicts of Interest and Sources of Funding

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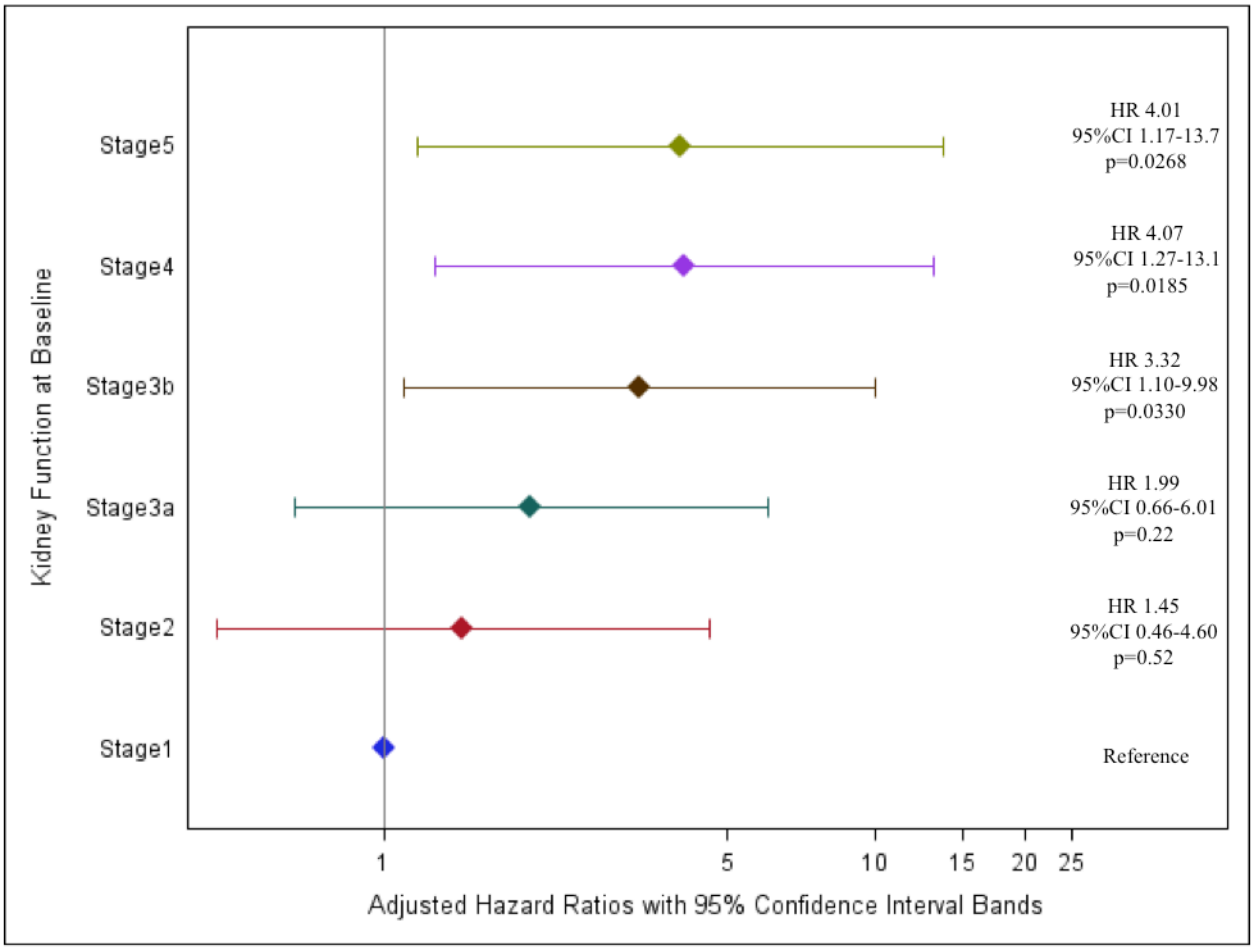


Figure 1. Change in Kidney Function over 1 year follow-up from VAD Implantation

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/1.73m^2), Stage 3a (eGRF 45-59 ml/min/1.73m^2), Stage 3b (eGFR 30-44 ml/min/1.73m^2), Stage 4 (eGFR 15-30 ml/min/1.73m^2) and Stage 5 (eGFR<15 ml/min/1.73m^2)

*At 14 days, 200 patients were included and 28 patients were excluded (2 patients received transplants, 1 patient recovered and was explanted, and 25 patients died).

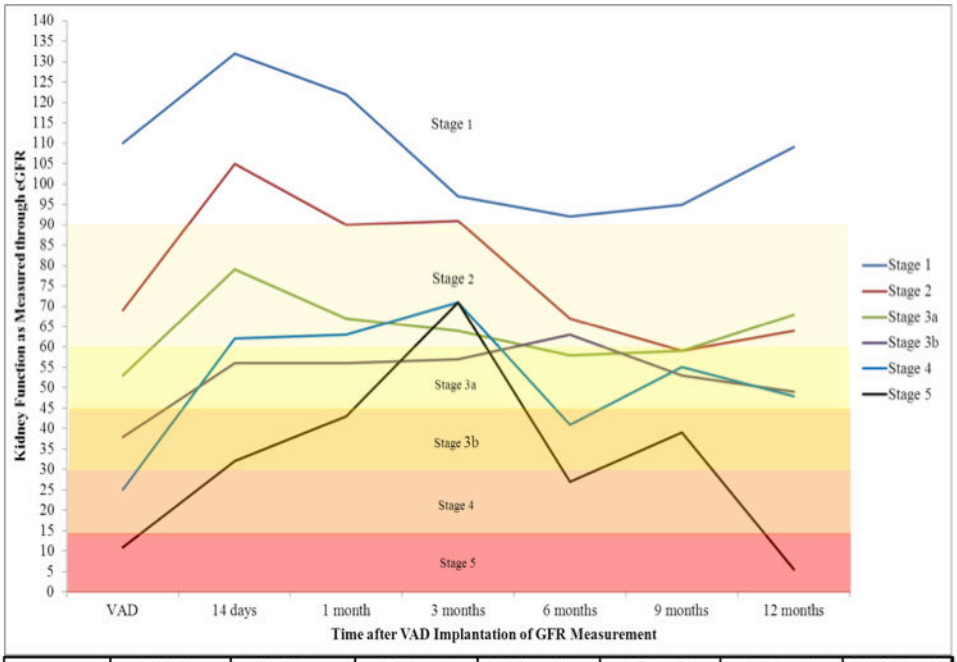
** At 30 days, 188 patients were included and.12 patients were excluded (12 patients died).

§ At 3 months, 158 patients were included and 30 patients were excluded (4 patient withdrawals, 2 patients recovered, 11 patients had a transplant and 13 patients died)

† At 6 months, 136 patients were included and 22 patients were excluded (1 withdrawal, 11 patients received transplants and 10 patients died)

‡At 9 months, 121 patients were included and 15 patients were excluded (10 patients received transplants and 5 patients died)

¥ At 12 months, 104 patients were included and 17 patients were excluded (8 patients received transplants and 9 patients died)



	VAD (N=228)		14 Days (N=200)*		1 Month (N=188)**		3 Months (N=158)§		6 Months (N=136)†		9 Months (N=121)‡		12 Months (N=104)¥	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Stage 1	32	14	93	46	72	38	54	34	31	23	24	20	22	21
Stage 2	49	21	40	20	51	27	49	31	44	32	36	30	31	30
Stage 3a	53	23	32	16	30	16	24	15	22	16	30	25	25	24
Stage 3b	53	23	23	11	21	11	25	16	25	18	23	19	15	14
Stage 4	30	13	11	5	12	6	5	3	11	8	6	5	10	10
Stage 5	11	5	1	1	2	1	1	1	3	2	2	2	1	1

Figure 2. Adjusted Relative Risk Estimates for Mortality Stratified by baseline CKD Stage

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/1.73m^2), Stage 3a (eGRF 45-59 ml/min/1.73m^2), Stage 3b (eGFR 30-44 ml/min/1.73m^2), Stage 4 (eGFR 15-30 ml/min/1.73m^2) and Stage 5 (eGFR<15 ml/min/1.73m^2)

Cox proportional hazards models were used to assess the adjusted risk of death. The proportional hazards assumption was met.

Table 1.

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

	Stage 1 eGFR ≥90 (N=32)	**Stage 2 eGFR 60-89 (N=49)**	**Stage 3A eGFR 45-59 (N=53)**	**Stage 3B eGFR 30-44 (N=53)**	**Stage 4 eGFR 15-30 (N=30)**	**Stage 5 eGFR <15 (N=11)**	**p-value**
				Mean (SD)			
Age	43.2 ±15.9	51.1 ±15.6	51.7 ±13.4	56.2±14	56.8±11.4	52.6±12.6	**0.002**
Body Mass Index	30.9 ±7.7	27.6±8.8	27.1±7.8	26.7±5.8	30.3±8.2	25.4±4.6	0.11
				N (%)			
Male	25 (78)	39 (80)	35 (66)	41 (77)	20 (67)	7 (64)	0.49
Black Race	14 (44)	16 (33)	16 (30)	10 (19)	6 (20)	2 (18)	0.14
Status within the First Year							0.06
Deceased	4 (12)	11 (22)	17 (32)	19 (36)	14 (47)	8 (73)	
Transplanted	10 (31)	12 (25)	8 (15)	4 (8)	7 (23)	2 (18)	
Recovered	0 (0)	1 (2)	2 (4)	0 (0)	0	0	
Device Type							**0.001**
Pulsatile Flow	11 (34)	18 (37)	25 (47)	23 (43)	19 (63)	11 (100)	
Continuous Flow	21 (66)	31 (63)	28 (53)	30 (57)	11 (37)	0	
Etiology of Heart Failure							0.17
Ischemic	8 (25)	28 (57)	25 (47)	32 (60)	17 (57)	6 (55)	
Idiopathic	16 (50)	14 (28)	23 (44)	13 (25)	10 (33)	3 (27)	
Other	8 (25)	7 (14)	5 (9)	8 (15)	3 (10)	2 (18)	
Indication for VAD							0.07
Bridge to transplant	23 (72)	31 (66)	31 (58)	25 (48)	13 (43)	8 (73)	
Bridge to candidacy	1 (3)	3 (6)	3 (6)	3 (6)	5 (17)	2 (18)	
Bridge to recovery	0	0	0	2 (4)	1 (3)	1 (9)	
Destination	8 (25)	13 (28)	19 (36)	22 (42)	11 (37)	0	
Comorbid Conditions							
Diabetes	9 (28)	11 (22)	24 (45)	27 (51)	13 (43)	2 (18)	**0.019**
Chronic Obstructive Pulmonary Disease	2 (6)	1 (2)	2 (4)	5 (9)	1 (3)	0	0.51
Congestive Heart Failure	27 (84)	44 (90)	43 (81)	44 (83)	24 (80)	6 (55)	0.15

	Stage 1 eGFR ≥90 (N=32)	Stage 2 eGFR 60-89 (N=49)	Stage 3A eGFR 45-59 (N=53)	Stage 3B eGFR 30-44 (N=53)	Stage 4 eGFR 15-30 (N=30)	Stage 5 eGFR <15 (N=11)	p-value
				Mean (SD)			
Peripheral Vascular Disease	2 (6)	2 (4)	2 (4)	1 (2)	1 (3)	0	0.90
Gout	3 (9)	9 (18)	5 (9)	4 (8)	5 (17)	2 (18)	0.50
Right Ventricular Dysfunction	6 (19)	14 (29)	8 (15)	14 (26)	5 (17)	3 (27)	0.52
Coronary Artery Disease	8 (25)	13 (26)	22 (41)	17 (32)	14 (47)	2 (18)	0.21
History of Myocardial Infarction	5 (16)	8 (16)	11 (21)	14 (26)	8 (27)	2 (18)	0.74
Hypertension	15 (47)	28 (57)	38 (72)	27 (51)	10 (33)	4 (36)	**0.014**
Pulmonary Hypertension	12 (37)	7 (14)	13 (24)	10 (19)	6 (20)	1 (9)	0.16
Hyperlipidemia	8 (25)	19 (39)	22 (41)	20 (38)	15 (50)	1 (9)	0.14
Atrial Fibrillation	10 (31)	16 (33)	19 (36)	18 (34)	10 (33)	0	0.34
Ventricular Tachycardia	11 (34)	19 (39)	28 (53)	16 (30)	16 (53)	3 (27)	0.11

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/1.73m^2), Stage 3a (eGRF 45-59 ml/min/1.73m^2), Stage 3b (eGFR 30-44 ml/min/1.73m^2), Stage 4 (eGFR 15-30 ml/min/1.73m^2) and Stage 5 (eGFR<15 ml/min/1.73m^2)

Continuous variables were tested using Wilcoxon Rank Sum test and categorical variables were tested using a Chi-squared test

Table 2.

Influence of Baseline Kidney Function on Risk (Hazard Ratio (HR) and 95% Confidence Interval (CI)) of Thromboembolism and Hemorrhage

	Hazard Ratio	95 % Confidence Interval	p-value
Thromboembolic Events			
Stage of Kidney Disease at Baseline			
Stage 1 (eGFR≥90)	ref	Ref	ref
Stage 2 (eGFR 60-89)	0.82	0.23-2.94	0.77
Stage 3a (eGFR 45-59)	1.47	0.47-4.62	0.51
Stage 3b (eGFR 30-44)	1.75	0.55-5.58	0.35
Stage 4 (eGFR 15-29)	1.52	0.41-5.68	0.53
Stage 5 (eGFR <15)	0.94	0.10-8.38	0.95
Hemorrhagic Events			
Stage of Kidney Disease at Baseline			
Stage 1 (eGFR≥90)	ref	ref	ref
Stage 2 (eGFR 60-89)	1.55	0.56-4.32	0.40
Stage 3a (eGFR 45-59)	1.71	0.63-4.67	0.29
Stage 3b (eGFR 30-44)	2.04	0.73-5.67	0.17
Stage 4 (eGFR 15-29)	0.99	0.26-3.70	0.99
Stage 5 (eGFR <15)	n/a	n/a	n/a
Death			
Stage of Kidney Disease at Baseline			
Stage 1 (eGFR≥90)	ref	ref	ref
Stage 2 (eGFR 60-89)	1.52	0.48-4.77	0.47
Stage 3a (eGFR 45-59)	2.21	0.74-6.57	0.15
Stage 3b (eGFR 30-44)	3.12	1.16-9.17	0.039
Stage 4 (eGFR 15-29)	3.94	1.29-12.0	0.02
Stage 5 (eGFR <15)	7.24	2.18-24.1	0.0012

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/1.73m^2), Stage 3a (eGRF 45-59 ml/min/1.73m^2), Stage 3b (eGFR 30-44 ml/min/1.73m^2), Stage 4 (eGFR 15-30 ml/min/1.73m^2) and Stage 5 (eGFR<15 ml/min/1.73m^2)

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, and death. The proportional hazards assumption was met.

Table III.

Prior VAD Studies that Investigate Kidney Function post VAD Implantation and the Relationship between Kidney Function and Mortality

Authors	Sample Size	Definition of Kidney Function	Assessment of Kidney Function	Outcome of Interest	Key Findings
Kirklin (2013)[22]	4,917	eGFR <30 for severe kidney disease and eGFR 30-60 for moderate kidney disease	Assessed at baseline, BUN and creatinine were assessed up to 4 years after implantation	Death, change in serum creatinine and BUN	Pre-implant renal dysfunction is related to higher mortality post VAD implant.
Borgi (2013)[31]	100	Acute Renal Failure (ARF)	Assessed at baseline and 7 days	Change in KF and its influence on 1-year mortality	Postoperative ARF is associated with mortality
Iwashima et al (2012)[32]	110	Change in estimated glomerular filtration rate (eGFR) from baseline to 2 weeks	Assessed at baseline and 2 weeks	Mortality at 2 years	Impaired renal function as well as renal function that does not improve with VAD placement are predictors of mortality
Hasin et al (2012)[33]	83	eGFR	Assessed before VAD, and 1,3 and 6 months after VAD	eGFR	Renal function improves after VAD implantation
Butler et al (2006)[34]	220	Renal function as defined by creatinine clearance	Assessed 1 month post VAD	All-cause mortality, and disease specific mortality at 1 year	Poor renal function at baseline is associated with worse outcomes. Patients with improving renal function after VAD placement experience improved outcomes
Genovese et al (2010)[35]	163	Acute Renal Failure (ARF)	Assessed 60 days post implantation	One year mortality	The presence of some adverse events increased the risk of mortality, namely renal events, respiratory events, bleeding events and reoperation
Ma et al (2008)[36]	28	Renal function as measured through creatinine	Assessed at baseline and 1 month post implant	Length of recovery	Pre-VAD renal function is predictive of post-VAD renal function and length of ICU stay
Russell et al (2009)[37]	309	Renal function as defined by BUN and creatinine	Assessed at baseline and 6 months post VAD	Renal function as defined by BUN and creatinine	Implantation of a VAD improves renal function
Sandner et al (2009)[38]	86	Pre-VAD eGFR	Assessed prior to VAD	Mortality post-VAD to 6 months	Patients with pre-VAD renal dysfunction have poorer outcomes than patients without pre-VAD renal dysfunction. Renal function improves regardless of pre-VAD renal status.
Sandner et al (2008)[39]	92	Renal function as defined by creatinine and eGFR	Assessed at baseline and 3 months	Renal function, and mortality at 3 months	There is no difference between continuous flow and pulsatile flow devices on renal function
Singh et al (2011)[40]	116	Creatinine clearance prior to VAD	Assessed prior to VAD	Creatinine clearance 1 month after VAD implant	VAD use improves renal function after implantation
Raichlin et al (2016)[16]	165	Baseline glomerular filtration rate (bGFR) ≤40 and bGFR >40	Assessed at baseline, 1, 3, 6, and 12 months after implantation	Length of hospitalization, death, dialysis, and time on dialysis at 1 year	GFR increased significantly at 1 month. At 1 year, patients with bGFR >40 had a return to pre-LVAD GFR, whereas those with bGFR ≤40 had a sustained increase in GFR.
Mohamedali et al (2017)[14]	213	Pre-implant GFR <60 (moderate/severely reduced renal function) or GFR ≥ 60 (normal/mildly	Assessed at baseline and at discharge	All-cause mortality and hospitalizations	Higher all-cause mortality in patients with pre-implant GFR<60. Those who do not improve GFR to ≥ 60 after implantation, have highest risk of

Authors	Sample Size	Definition of Kidney Function	Assessment of Kidney Function	Outcome of Interest	Key Findings
		impaired renal function)			cardiovascular morbidity and mortality.
Daimee et al (2017)[29]	184	GFR<45 (low renal function), GFR 45-59 (intermediate renal function), and GFR ≥ 60 (normal renal function)	Assessed at baseline, day 1, day 7, 1 month, 3 months, 6 months, 1 year, and 2 years post-LVAD	All-cause mortality, first hospital readmission due to any cause within 2 years	Those with pre-LVAD GFR<45 experienced sustained improvement in renal function after 2 years follow-up. Patients with no improvement in renal function after 1 month had increased risk of mortality and readmission.

* Bansal et al (2018)[17]: Not included due to primarily looking at patients with ESRD