Impact of Continuous Flow Left Ventricular Assist Device Therapy on Chronic Kidney Disease: A Longitudinal Multicenter Study

YUNUS C. YALCIN, BSc,[1,2] RAHATULLAH MUSLEM, MD, PhD,[1,2] KEVIN M. VEEN, BSc,[2] OSAMA I. SOLIMAN, MD, PhD,[1] DENNIS A. HESSELINK, MD, PhD,[3] ALINA A. CONSTANTINESCU, MD, PhD,[1] JASPER J. BRUGTS, MD, PhD,[1] OLIVIER C. MANINTVELD, MD, PhD,[1] MARAT FUDIM, MD, PhD,[4] STUART D. RUSSELL, MD,[4] BRETT TOMASHITIS, MD,[5] BRIAN A. HOUSTON, MD,[5] STEVEN HSU, MD,[6] RYAN J. TEDFORD, MD,[5] AD J.J.C. BOGERS, MD, PhD,[2] AND KADIR CALISKAN, MD, PhD FESC[1]

Rotterdam, the Netherlands, Durham, Charleston, and Baltimore, USA

ABSTRACT

Background: Many patients undergoing durable left ventricular assist device (LVAD) implantation suffer from chronic kidney disease (CKD). Therefore, we investigated the effect of LVAD support on CKD.

Methods: A retrospective multicenter cohort study, including all patients undergoing LVAD (HeartMate II (n = 330), HeartMate 3 (n = 22) and HeartWare (n = 48) implantation. In total, 227 (56.8%) patients were implanted as bridge-to-transplantation; 154 (38.5%) as destination therapy; and 19 (4.7%) as bridge-to-decision. Serum creatinine measurements were collected over a 2-year follow-up period. Patients were stratified based on CKD stage.

Results: Overall, 400 patients (mean age 53 ± 14 years, 75% male) were included: 186 (46.5%) patients had CKD stage 1 or 2; 93 (23.3%) had CKD stage 3a; 82 (20.5%) had CKD stage 3b; and 39 (9.8%) had CKD stage 4 or 5 prior to LVAD implantation. During a median follow-up of 179 days (IQR 28−627), 32,629 creatinine measurements were available. Improvement of kidney function was noticed in every preoperative CKD-stage group. Following this improvement, estimated glomerular filtration rates regressed to baseline values for all CKD stages. Patients showing early renal function improvement were younger and in worse preoperative condition. Moreover, survival rates were higher in patients showing early improvement (69% vs 56%, log-rank $P = 0$ .013).

Conclusions: Renal function following LVAD implantation is characterized by improvement, steady state and subsequent deterioration. Patients who showed early renal function improvement were in worse preoperative condition, however, and had higher survival rates at 2 years of follow-up. (*J Cardiac Fail 2020;26:333−341*)

Key Words: Left ventricular assist device, chronic kidney disease, end-stage heart failure, renal improvement.

Introduction

Left ventricular assist devices (LVADs) have become an accepted treatment modality for patients with end-stage heart failure (HF).[1] Patients with end-stage HF commonly suffer from end-organ dysfunction, including chronic kidney disease (CKD), which is often attributed to the cardiorenal syndrome.[2] Cardiorenal syndrome type 2, renal dysfunction caused by a number of factors, including high central venous pressures and insufficient cardiac output, frequently hampers the quality of life of these patients.[3] They are at risk of developing end-stage renal disease and have higher rates of mortality following LVAD implantation.[4-6]

Several studies have reported that after LVAD implantation, mean renal function improves within the first month.[2,7] However, this mean increase seems to be largely of a transient nature because mean renal function deteriorates subsequent to the improvement. This was largely confirmed by

From the [1]Thoraxcenter, Unit Heart Failure, Transplantation and Mechanical Circulatory Support, Department of Cardiology, University Medical Center Rotterdam, Rotterdam, the Netherlands; [2]Department of Cardiothoracic Surgery, University Medical Center Rotterdam, Rotterdam, the Netherlands; [3]Division of Nephrology and Renal Transplantation, Department of Internal Medicine, Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands; [4]Duke Clinical Research Institute, Division of Cardiology, Duke University, Durham, North Carolina, USA; [5]Department of Cardiology, Medical University of South Carolina, Charleston, South Carolina, USA and [6]Department of Cardiology, Johns Hopkins Heart and Vascular Institute, Baltimore, Maryland, USA.

Manuscript received September 10, 2019; revised manuscript received December 4, 2019; revised manuscript accepted January 17, 2020.

Reprint requests: Kadir Caliskan, MD, PhD, Thoraxcenter, Room RG 431, Erasmus MC, University Medical Center, Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands E-mail: k.caliskan@erasmusmc.nl

See page 340 for disclosure information.

1071-9164/$ - see front matter

© 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license.
(http://creativecommons.org/licenses/by-nc-nd/4.0/)

https://doi.org/10.1016/j.cardfail.2020.01.010

Brisco et al when they analyzed the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS).[2] They noticed a marked improvement of mean renal function following LVAD implantation and a subsequent deterioration of renal function. The mechanisms of why and how some patients' renal functions improve and why most patients' subsequently deteriorate has yet to be elucidated. Subsequently, it was hypothesized that perhaps intrinsic renal injury, continuous-flow physiology, hemolysis, and neurohormonal activity could be the reasons for this deterioration. Importantly, however, their methodology of depicting renal function is limited by the use of means at set points in time and their restricted follow-up period. This methodology favors the renal function of survivors and, therefore, may not depict accurately the evolution of renal function. There is a great demand for longitudinal assessment of renal function following LVAD implantation. Therefore, the aim of this study was to investigate the impact of prolonged LVAD support on changes in renal function and to identify patient-related factors associated with renal function improvement following LVAD implantation.

Methods

Study Design

We retrospectively reviewed all patients who received an LVAD between October 2004 and April 2017 in the Erasmus MC, University Medical Center Rotterdam, the Netherlands; Johns Hopkins Hospital, Baltimore, USA; and the Medical University Hospital, Charleston, South Carolina, USA. Patients with missing data regarding preoperative and/or postoperative serum creatinine were not included in the analysis (N = 34). The study was approved by the institutional review boards of all participating centers. Patients were classified into 4 groups based on their preoperative CKD stages. Stages 1 and 2 and stages 4 and 5 were combined into 1 group (see Supplementary Table 1 for the Kidney Disease Improving Global Outcomes CKD stages).[8]

The primary study outcome was 1) quantification of the evolution of the kidney function and 2) the factors associated with (sustained) renal function improvement during the first 2 years following LVAD implantation by using longitudinal data. The secondary outcomes included all-cause mortality and the association between renal improvement and mortality. Patients were censored at the time of death, heart transplantation or explantation of the LVAD.

Data collection

All data were obtained from patients' electronic records. Baseline laboratory values were collected preoperatively for all patients. Devices included were HeartMate II, Heartmate 3 (Abbott, Chicago, IL, USA) and HeartWare (HeartWare International, Miami Lakes, FL, USA). Kidney function was defined as the estimated glomerular filtration rate (eGFR), which was measured regularly during outpatient clinic visits. Samples of serum creatinine were collected over a 2-year period to calculate eGFRs. To validate the calculated eGFRs, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used.[9] This formula is GFR = 141 * min(Scr/κ,1)α * max(Scr/κ, 1)-1.209 * 0.993Age * 1.018 (if female) * 1.159 (if black). Renal replacement therapy after LVAD implantation was defined as the start of either continuous veno-venous hemofiltration or intermittent hemodialysis. Patients were not excluded if they had received continuous veno-venous hemofiltration or hemodialysis before or at the time of LVAD implantation. Early ($\leq$ 70 days) renal function improvement was defined by either an increase of $\geq$ 10 mL/min/1.73m^2 of eGFR or as a $\geq$ 50% increase of baseline eGFR within 3 months following implantation. Sustained renal function was defined by maintaining the early improvement following LVAD implantation beyond 12 months.

Statistical Analysis

Continuous parameters are expressed as mean and standard deviation or median interquartile range (IQR) according to distribution and are compared with 1-way ANOVA, the Student *t* test or the Mann-Whitney U test. Continuous parameters were tested for normal distribution with the Shapiro-Wilk test. Categorical parameters are expressed as number and percentage and compared by the χ^2 test or the Fisher exact test. Kaplan-Meier curves stratified by preoperative CKD stage were constructed for the evaluation of mortality in the first 2 years postimplantation. Differences pooled over strata were compared by the log-rank test

Continuous repeated measurement data were analyzed using mixed models. Flexibility over time was established using natural splines. In total, 3 internal knots seemed sufficient upon graphic analyses (Supplementary Fig. 1) (Visualization of subject-specific prediction of 9 randomly chosen patients of a model containing time with a spline function using 4 knots (red line) and a model containing 3 knots (blue line)). Included random effects were intercepts for patients with random slopes for time. Two models were developed: the first contained only time since implant; the second contained time since implant and CKD stage, with their interaction term. The *t* tests were used to compare point estimates of CKD stage, as derived from the model. The models were visualized by effect plots. Mixed modeling analyses were done in R, version 3.3.3, with packages lme4 and emmeans (R Foundation for Statistical Computing, Vienna, Austria).[10]

Results

Baseline characteristics

In total, 400 patients were included (75% male, mean age 53 $\pm$ 14 years); 84 (21%) patients from the Erasmus MC University Medical Center, 224 (56%) patients from Johns Hopkins Hospital, and 92 (23%) patients from the Medical University of South Carolina. The Heartmate II device was the most frequently implanted: 330 (82%); followed by the HeartWare device: 48 (12%); and 22 (6%) patients received a HeartMate 3 device. The baseline characteristics of the 4 groups are

Table 1. Baseline Characteristics of Patients With Preoperative CKD Undergoing LVAD Implantation

Variables	All patients (N = 400)	CKD stage 1 and 2 (n = 186)	CKD stage 3a (n = 93)	CKDstage 3b (n = 82)	CKD stages 4 and 5 (n = 39)	*P* value
Age						**<0.001**
< 45	99 (25)	69 (37)	18 (19)	8 (10)	4 (10)	
45−54	84 (21)	44 (24)	17 (18)	19 (23)	4 (10)	
55−64	147 (37)	57 (30)	40 (43)	33 (40)	17 (44)	
≥ 65	70 (17)	16 (9)	18 (19)	22 (27)	14 (36)	
Male gender	298 (75)	125 (67)	74 (80)	68 (83)	31 (80)	**0.02**
BMI	26 (23−31)	26 (22−31)	26 (23−32)	26 (20−33)	28 (25−33)	0.51
Ischemic cardiomyopathy	139 (35)	51 (27)	35 (38)	36 (44)	17 (44)	**0.03**
Diabetes mellitus	157 (39)	73 (39)	31 (33)	31 (39)	22 (56)	0.1
Hypertension	186 (47)	78 (42)	50 (54)	39 (48)	19 (47)	0.3
ICD/PM	326 (82)	139 (75)	81 (87)	69 (84)	37 (95)	0.01
TIA or CVA	66 (17)	32 (17)	14 (15)	13 (16)	7 (18)	0.97
Destination therapy	154 (39)	58 (31)	35 (38)	39 (48)	22 (56)	0.14
IABP	133 (33)	63 (34)	24 (26)	33 (40)	13 (33)	0.25
ECMO	20 (5)	13 (7)	3 (3)	4 (5)	0	0.24
Inotropic support	323 (81)	156 (84)	71 (76)	67 (83)	29 (78)	0.45
INTERMACS (n = 384)						0.67
Profile 1	67 (17)	38 (20)	11 (13)	13 (17)	5 (14)	
Profile 2	120 (30)	53 (29)	27 (30)	27 (36)	13 (37)	
Profile 3	135 (34)	66 (36)	35 (39)	24 (32)	10 (29)	
Profile ≥ 4	62 (16)	28 (15)	16 (18)	11 (15)	7 (20)	
Device type	0.02					
HM 2	330 (82)	162 (87)	74 (80)	61 (74)	33 (85)	
HM 3	22 (6)	3 (2)	6 (6)	9 (11)	4 (10)	
HW	48 (12)	21 (11)	13 (14)	12 (15)	2 (5)	
Laboratory values						
eGFR mL/min/1.73 m^2	57 (42−79)	81 (69−97)	52 (48−56)	39 (33−42)	24 (21−27)	< 0.001
Creatinine mg/dL	1.40 (1.09−1.79)	1.09 (0.9−1.19)	1.50 (1.40−1.65)	1.95 (1.70−2.10)	2.70 (2.39−3.09)	< 0.001
Blood urea nitrogen mg/dL	28 (19−42)	22 (16−30)	30 (24−42)	35 (28−50)	48 (36−63)	< 0.001
Sodium mmol/L	136 (132−139)	135 (131−138)	136 (132−139)	136 (133−140)	136 (132−138)	0.56
Bilirubin mg/dL	1,1 (0,7−1,8)	1,1 (0,6−1,6)	1,1 (0,8−2,5)	1,1 (0,7−1,7)	1,2 (0,8−1,7)	0.12

HR denotes hazard ratio.

CI, confidence interval; CKD, chronic kidney disease; CVA, cerebrovascular accident; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; HM II, Heartmate II; HM 3, Heartmate 3; HW, HeartWare; IABP, intra-aortic balloon pump; ICD, implantable cardioverter defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; PM, pace maker; TIA, transient ischemic attack.

presented in Table 1. Stratified according to preoperative CKD stages, 186 (46.5%) patients had CKD stages 1 or 2; 93 (23.3%) patients had CKD stage 3a; 82 (20.5%) patients had CKD stage 3b; and 39 (9.8%) patients had CKD stage 4 or 5. Patients with preoperative CKD stages of 1 or 2 were younger ($P < 0.001$), more commonly had nonischemic etiologies of their cardiomyopathy ($P = 0.03$) and had lower rates of implantable cardioverter-defibrillators or pacemakers ($P = 0.02$).

Evolution of eGFR

During the 2 years following LVAD implantation, 32,629 measurements of eGFR were collected: CKD stage 1 or 2 group: 15,760 (48.3%); CKD stage 3a group: 7202 (22%); CKD stage 3b group: 6854 (21%); CKD stage 4 or 5 group: 2813 (8.6%). The mean number of serum creatinine measurements per patient was 82 ± 43. The general evolution of eGFR for all patients is plotted in Fig. 1a. Model summary is presented in Supplementary Table 2a (Supplement: Model summary depicting the individual time points used to determine the *p*-values (compared to time = 0, and in table 2b, compared to CKD stages 1 and 2) of the of the mixed model Figs. 1 and 2). The greatest improvement in kidney function was noted at 90 days post LVAD implantation. In addition, kidney function did not differ from baseline at day 210, and the nadir was noted at day 455, after which kidney function plateaued.

Fig. 1b depicts the evolution of eGFR stratified by preoperative CKD stage. Model summary is presented in Supplementary Table 2b (Supplement: Model summary depicting the individual time points used to determine the *p*-values (compared to time = 0, and in table 2b, compared to CKD stages 1 and 2) of the of the mixed model Figs 1 and 2). The mean improvement of eGFR at 70 days is 14% in CKD stages 1 and 2, 25% in CKD stage 3a, 29% in CKD stage 3b, and 83% in CKD stages 4 and 5. This improvement remained significant up to day 150 following LVAD implantation for CKD stages 3a, 3b, 4, and 5. Following the first 150 days, all CKD stages regressed toward their respective baselines. None of the preoperative CKD stages remained significantly improved compared to baselines. After 1 year of follow-up, the kidney function reached a plateau comparable to that of the baseline kidney function. Following the 1-year follow-up mark, no significant changes (ie, improvement or deterioration) were noticed compared to baseline.

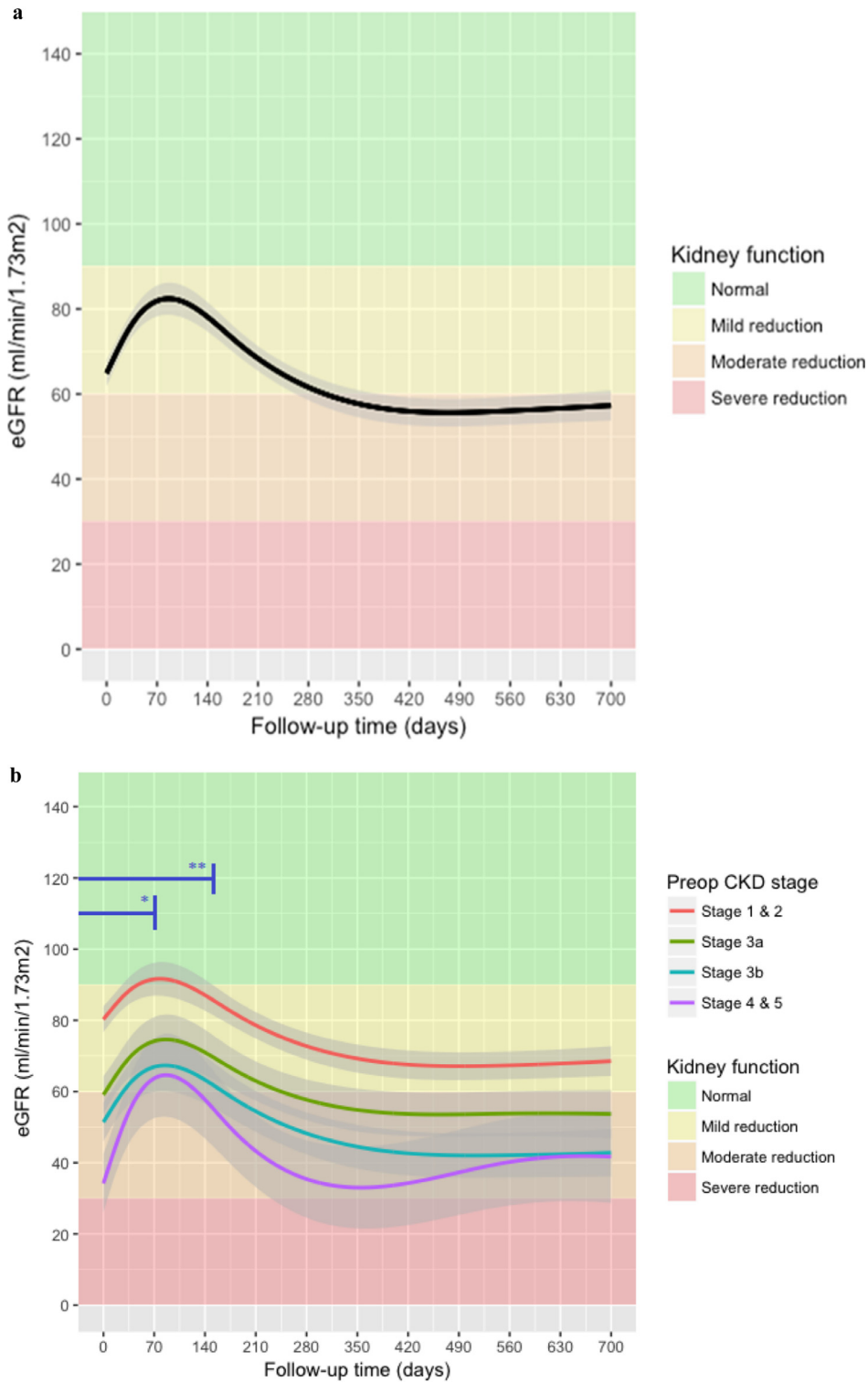

Fig. 1. a, Advanced mixed modeling illustrating the evolution of overall eGFR over 2 years of follow-up (central illustration). b, Advanced mixed modeling illustrating the evolution of eGFR over 2 years of follow-up, stratified by preoperative CKD stage. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Early renal improvement

Early renal function improvement was experienced by 230 (57%) of the patients, whereas 160 (40%) experienced no early renal improvement or early renal deterioration, and 10 (3%) patients had missing follow-up until day 70. The patients showing early renal improvement were divided as follows: 96 (53.3%) patients were in CKD stages 1 or 2; 56 (61.5%) patients were in CKD stage 3a; 48 (58.5%) were in CKD stage 3b; and 30 (81.1%) were in CKD stage 4 or 5 (P = 0.018). Patients who experienced early renal function

improvement were younger in age, had lower mean baseline eGFRs and were more often implanted as bridge-to-transplant than as destination therapy. Additionally, patients showing early renal function improvement had higher needs for intra-aortic balloon pump support and had overall lower INTERMACS scores (ie, profile 1 or 2) prior to LVAD implantation. The need for extracorporeal membrane oxygenation and the need for inotropic support had no effect on renal function improvement. All baseline characteristic differences are noted in Table 2.

Sustained renal function improvement was observed in 53 (13.2%) patients. Differences in patients with sustained renal function improvement were younger in age (47 ± 14 vs 53 ± 13, $P = 0.001$), had higher eGFRs (65 ± 27 vs 55 ± 24, $P = 0.02$) and had less preoperative diabetes (22.6% vs 41.2%, $P = 0.01$).

Thereafter, a subset of the cohort was analyzed with preoperative (maximum of 30 days prior to implantation) right heart catheterization (RHC) measurements (n = 300) (Table 3a and 3b). No significant differences in preoperative RHC measurements between the preoperative CKD stages were observed. Comparing patients who experienced early renal function improvement to those who did not experience improvement resulted in the following differences: patients who experienced early renal function improvement had lower preoperative cardiac indexes, higher mean right arterial pressures, higher right ventricular diastolic pressures, higher pulmonary artery diastolic pressures, and higher pulmonary capillary wedge pressures.

Table 2. Differences in Baseline Characteristics in Patients who Experienced Renal Function Improvement or not After LVAD Implantation

Variables	Improvement (n = 230)	No improvement (n = 160)	*P* value
Age			0.02
< 45	65 (28)	29 (18)	
45−54	43 (19)	41 (26)	
55−64	89 (39)	55 (34)	
≥ 65	33 (14)	35 (22)	
Male gender	166 (72)	123 (77)	0.3
BMI	26 (23-31)	27 (23-32)	0.23
Ischemic Cardiomyopathy	76 (33)	62 (39)	0.25
Diabetes mellitus	85 (37)	70 (44)	0.18
Hypertension	107 (47)	76 (48)	0.85
ICD/PM	190 (83)	132 (83)	0.98
TIA or CVA	39 (17)	27 (17)	0.99
Destination therapy	78 (34)	72 (45)	0.03
IABP	89 (39)	40 (25)	0.005
ECMO	8 (4)	10 (6)	0.2
Inotropic support	184 (80)	131 (82)	0.68
INTERMACS			0.003
Profile 1	32 (15)	31 (20)	
Profile 2	81 (37)	36 (23)	
Profile 3	68 (31)	66 (42)	
Profile ≥ 4	36 (17)	25 (15)	
Device type			0.08
HM II	186 (81)	135 (84)	
HM 3	26 (11)	21 (13)	
HW	18 (8)	4 (3)	
Laboratory values			
eGFR, mL/min/1.73m^2	53 (41−72)	65 (44−87)	< 0.001
Creatinine mg/dL	1.47 (1.19−1.94)	1.30 (0.99−1.67)	0.005
Bilirubin mg/dL	1.2 (0.7−1.8)	1.1 (0.6−1.8)	0.73

HR denotes hazard ratio.

BMI, body mass index; CI, Confidence interval; CKD, chronic kidney disease; CVA, cerebrovascular accident; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; HM II, Heartmate II; HM 3, Heartmate 3; HW, HeartWare; ICD, implantable cardioverter defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; PM, pace maker; TIA, transient ischemic attack.

Clinical course

Overall, 175 patients (44%) died during the first 2 years of follow-up. Stratified by CKD stage, the median follow-up time was 244 (34−710) days for CKD stages 1 and 2; 121 (24−481) days for CKD stage 3a; 141 (204−593) days for CKD stage 3b; and 103 (24−409) days for CKD stages 4 and 5. The 2-year overall survival rate (Fig. 2) in these respective groups was 58.1% vs 54.8% vs 58.5% vs 46.2% (log-rank: $P < 0.001$). The Kaplan-Meier curves of 5-year survival are provided in Supplementary Fig. 2 (Kaplan Meier Curve based on pre-operative CKD stage, illustrating the differences in 5-year survival stratified by preoperative CKD stages). Furthermore, patients with higher CKD stages required renal replacement therapy more commonly following LVAD implantation: 12% in CKD stages 1 and 2; 22%, 22% and 39% in CKD stages 3a, 3b, 4, and 5 (log-rank: $P < 0.001$), respectively. Fig. 3 compares the 2-year survival rates of patients who did (69; 5%) and did not (56; 2%) experience early renal function improvement (log-rank: $P = 0.013$), respectively. Finally, patients with sustained renal function improvement were identified (n = 53). Patients with sustained renal function improvement were younger in age ($P = 0.01$), had lower rates of diabetes mellitus ($P = 0.01$), had higher baseline eGFRs ($P = 0.01$), and had higher mean diastolic pulmonary pressures ($P = 0.02$).

Discussion

The current study evaluated the impact of prolonged LVAD therapy on kidney function. Our principal findings are as follows. 1) Following LVAD therapy, all patient groups (in all preoperative CKD stages) experienced significant early mean renal function improvement and subsequent regression to baseline. At 1 year of follow-up, all patient groups had mean renal function similar to their respective mean baseline eGFRs. 2) Patients who experienced early renal function improvement were younger, had higher preoperative CKD stages, lower INTERMACS scores and worse hemodynamic profiles. 3) Patients who experienced early renal function improvement had higher 2-year survival rates than patients who did not experience improvement. These results underline the transient nature of renal function improvement in all preoperative CKD stages. However, despite the observed transient nature, early renal function improvement is associated with higher survival rates at 2 years of follow-up.

The next step in personalized medicine is considering and examining all available data. The appropriate methodology to

Table 3a. Baseline Right Heart Catheterization Measurements (n = 300) for Each of the Preoperative CKD Stages

Variables	All patients (N = 300)	CKD stages 1 and 2 (n = 141)	CKD stage 3a (n = 68)	CKD stage 3b (n = 61)	CKD stages 4 and 5 (n = 30)	*P* value
Cardiac output (thermodilution L/min)	3.6 ± 1.1	3.6 ± 1.2	3.4 ± 1.1	3.6 ± 1	3.5 ± 1.2	0.71
Cardiac index (L/min/m^2)	2.7 ± 1.6	2.7 ± 1.5	2.7 ± 1.7	3 ± 1.9	2.1 ± 1.2	0.14
Right atrial pressure (mmHg)	13.1 ± 6.9	13.0 ± 7.0	12.8 ± 6.4	12.6 ± 6.0	15.6 ± 9	0.23
Right ventricular systolic pressure (mmHg)	53 ± 14.8	51.0 ± 14.5	52.5 ± 15.6	56.6 ± 13.8	56.3 ± 15.8	0.09
Right ventricular diastolic pressure (mmHg)	12.7 ± 6.8	12.8 ± 7.4	12.6 ± 6.3	12.3 ± 5.6	13.3 ± 7.4	0.93
Pulmonary artery pressure (mmHg)	37 ± 10.3	36.1 ± 11.1	37.7 ± 10.3	37.2 ± 8.5	39.0 ± 9.7	0.22
Pulmonary artery systolic pressure (mmHg)	53.8 ± 14.9	52.0 ± 15.4	54.2 ± 15.0	55.9 ± 13.7	56.7 ± 14.4	0.89
Pulmonary artery diastolic pressure (mmHg)	28.0 ± 8.8	27.7 ± 9.6	28.4 ± 8.4	27.7 ± 7.5	28.9 ± 8.5	0.48
Pulmonary capillary wedge pressure (mmHg)	25.9 ± 8.8	25.8 ± 9.9	26.4 ± 8.5	25.2 ± 6.4	26.7 ± 8.5	0.85

CKD, chronic kidney disease.

depict changes accurately takes all individual measurements into consideration. This allows for the use of mixed-modeling analyses depicting more accurate evolutions. This novel approach adjusts both the correlation among patients and the correlation among measurements in the same patient. Moreover, it adjusts, to a certain degree, for missing data and mortality. This methodology yields the most accurate depiction of renal function evolution following LVAD implantation.

The differing phases of renal function

We confirm that the evolution of renal function can be divided into 3 phases. The first phase is characterized by a marked improvement in renal function, which is proportionally greater in patients with higher CKD stages. This phase transpires in the first 70 days following LVAD implantation. Improvement of renal function is most likely driven by improved cardiac output and relief of venous congestion. In patients with HF, venous congestion is 1 of the major factors that drive worsening renal function.[11] Indeed, our results show that patients with higher preoperative right atrial pressures, which are closely linked to central venous pressures, were more likely to show early renal function improvement.

The second phase marks renal recovery. This phase starts after the renal improvement phase and concludes at approximately 150 days of follow-up. This phase represents an opportunity to maintain the regained function from the first phase for as long as possible, perhaps by adjusting the LVAD parameters to provide optimal output, by closely monitoring the fluid status, and by monitoring and optimizing right ventricle (RV) function.

Finally, the deterioration phase sets in. This phase is noticed in all baseline CKD stages, suggesting multifactorial determinants, and it could be inherent in contemporary LVAD therapy. Because it is the most poorly understood phase, various hypotheses have been proposed. One postulated mechanism for renal function deterioration is the worsening of RV function. Longitudinal studies have yielded mixed conclusions concerning this phenomenon, with some showing improvement in RV function over time and others the opposite.[12,13] Unfortunately, the effects of postoperative RV dysfunction or failure of kidney function in patients after LVAD remain poorly understood.[14] Other postulated mechanisms include dysregulation of the baroreceptors, local upregulation of the renin-angiotensin system and possible hyperfiltration.[15–17] Additionally, shear stress caused by the mechanical suction (inducing hemolysis) could cause chronic renal ischemia, nephrotoxicity and proapoptosis of renal tubular epithelial cells.[18] Last, the prolonged use of anticoagulation, in the form of warfarin, may be associated with the onset of anticoagulant-related nephropathy.[19] Prospective studies are necessary to elucidate the delicate mechanisms behind renal function deterioration.

Table 3b. Differences in Right Heart Catheterization Measurements (N = 300) Between Patients who Show Early Renal Function Improvement and Those who Do not Improve

Variables	Renal improvement at 70 days (n = 160)	No renal improvement at 70 days (n = 140)	*P* value
Cardiac output (thermodilution L/min)	3.5 ± 1.2	3.6 ± 1.1	0.97
Cardiac index (L/min/m^2)	2.5 ± 1.5	3.0 ± 1.8	0.02
Right atrial pressure (mmHg)	14.0 ± 7.2	12.0 ± 6.6	0.01
Right ventricular systolic pressure (mmHg)	52.2 ± 14.5	52.0 ± 15.3	0.25
Right ventricular diastolic pressure (mmHg)	13.6 ± 7.3	11.7 ± 6.2	0.02
Pulmonary artery pressure (mmHg)	38.0 ± 9.8	35.8 ± 10.8	0.06
Pulmonary artery systolic pressure (mmHg)	55.0 ± 14.6	52.6 ± 15.3	0.17
Pulmonary artery diastolic pressure (mmHg)	29.1 ± 8.4	26.7 ± 9.0	0.02
Pulmonary capillary wedge pressure (mmHg)	27.0 ± 8.9	24.5 ± 8.7	0.02

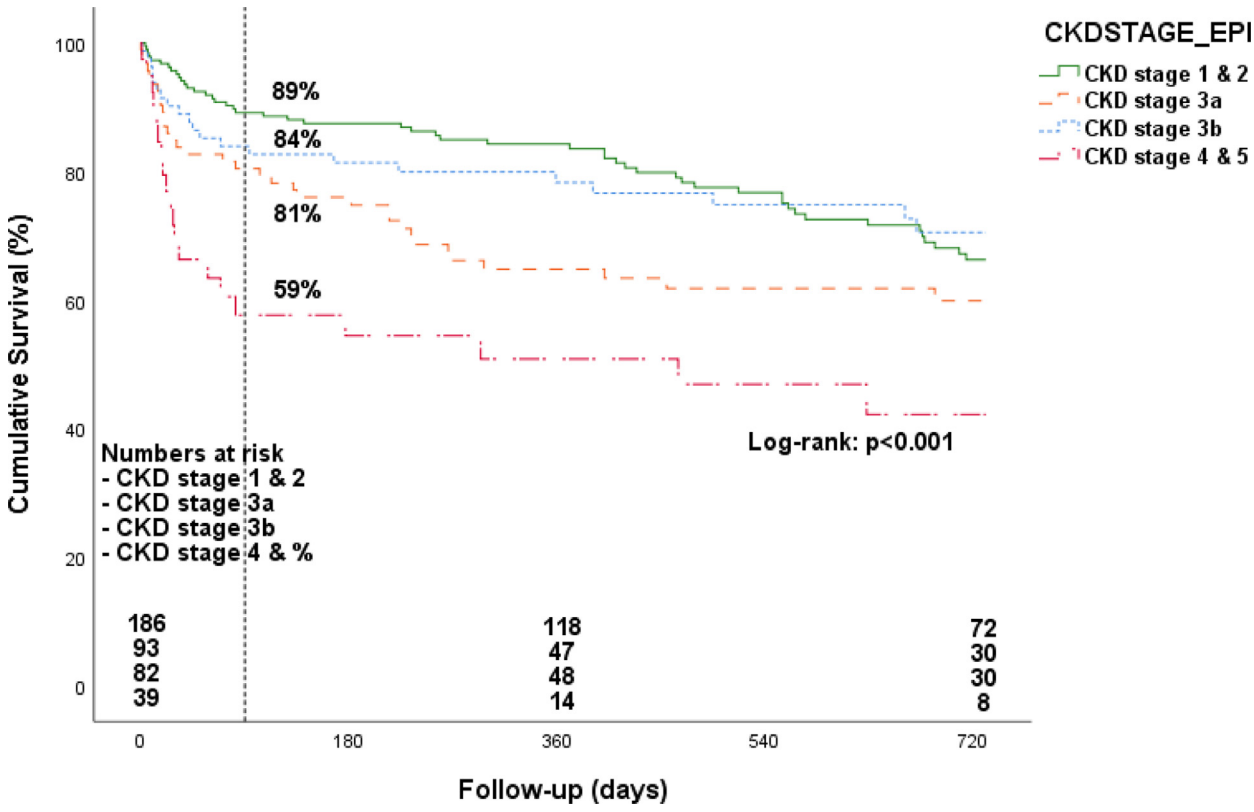

Fig. 2. Kaplan-Meier survival curve based on preoperative CKD stages, illustrating the differences in 2-year survival stratified by preoperative CKD stages. CKD, chronic kidney disease.

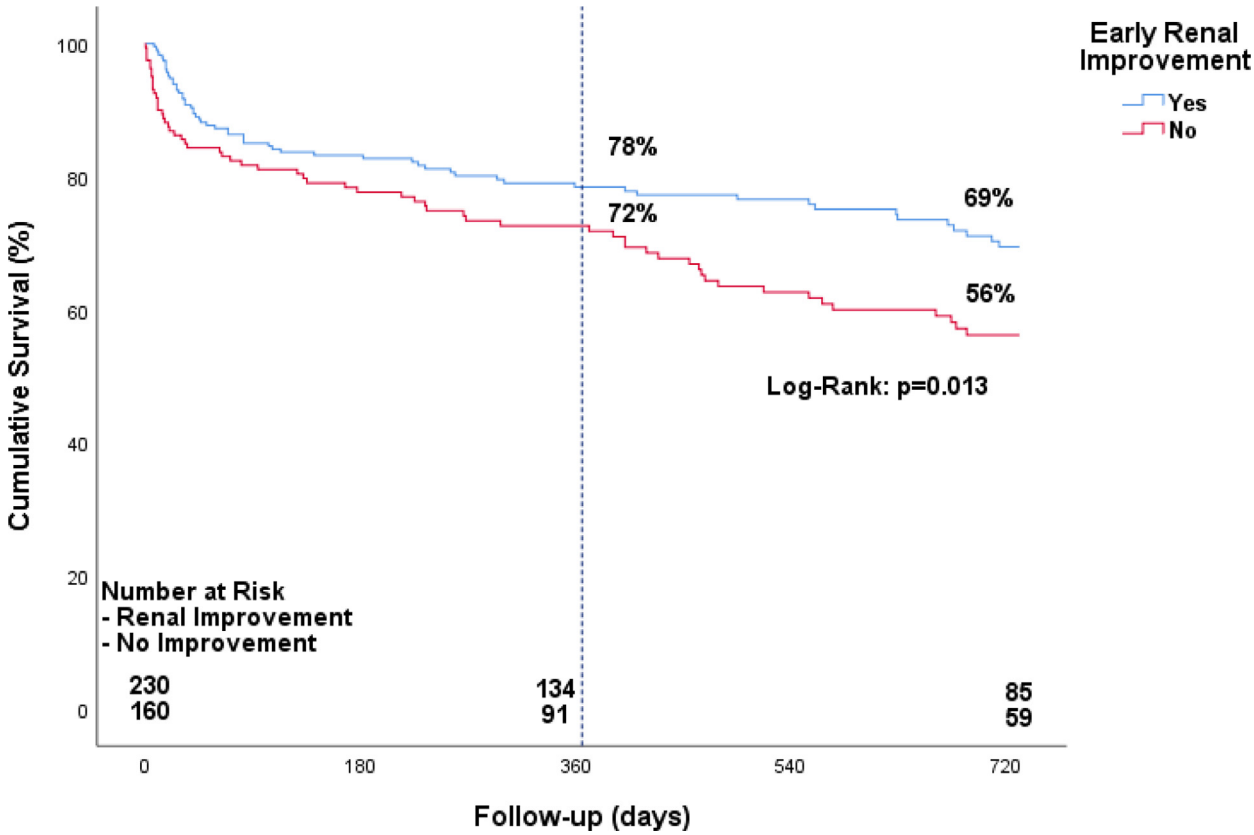

Fig. 3. Kaplan-Meier survival curve based on postoperative early renal function improvement, illustrating the differences in survival.

Survival

Unfortunately, not all individuals experience renal function improvement following LVAD implantation. We found early improvement present in 59% of patients. These patients were younger, were implanted under worse conditions (ie, needing intra-aortic balloon pump support, overall lower INTERMACS scores and worse hemodynamic profiles) and had worse preoperative renal function. The findings are consistent with a group of patients with type 2 cardiorenal syndrome.[3] Interestingly, subsequent survival rates were higher in patients experiencing early renal function improvement, despite its transient nature. Renal function improvement was linked with superior outcomes compared to those with no improvement, regardless of LVAD implantation indication (Supplementary Material 5) (Competing outcomes analysis). This distinction is of paramount importance because of the increasing number of candidates for LVAD who are implanted when they have acute renal dysfunction, cardiogenic shock and seemingly worse renal function. Last, sustained renal function improvement was observed in 13% of all implanted patients. Older patients with diabetes and worse preoperative renal function were more commonly associated with nonsustained renal function improvement. Evidently, earlier studies reported that preoperative proteinuria (often seen in patients with diabetes) is independently associated with an increase in renal replacement therapy and worse survival rates.[5,6] This finding alludes to intrinsic preoperative renal damage, most likely caused by diabetic nephropathy. More research is needed to further elucidate factors associated with sustained renal function following LVAD implantation.

Clinical perspectives

The trend of eGFRs after LVAD implantation displays an initial improvement of overall mean eGFRs. However, subsequent to this improvement, a regression in overall mean eGFR to the baseline is noticed in all patient groups, regardless of eGFR function prior to LVAD implantation. Nonetheless, early renal function improvement is associated with better survival rates following LVAD implantation. Therefore, sole severe renal dysfunction (eGFR < 45) should not exclude candidacy for LVAD implantation. Selection criteria should include age, the primary presentation, the setting of LVAD implantation (emergent or elective), the baseline renal function, and concomitant hemodynamic profile (renal venous congestion and/or forward failure). Those with the most severe hemodynamic derangements are most likely to benefit. Additional research is warranted to identify which factors predict sustained renal function improvement post LVAD implantation and what the underlying mechanisms are.

Strengths and limitations

There are a number of limitations that should be taken into consideration when interpreting our findings. First, due to the retrospective study design, causality cannot be established. Second, the group with CKD stages 4 or 5 consisted of a relatively small number of patients, possibly affecting the outcome of the analysis by overestimating their survival. Third, this cohort consisted mostly of INTERMACS class 1 and 2 patients, which has resulted in a rather higher 2-year mortality rate. This may have affected the evolution of renal function. Fourth, not all patients had RHC data 30 days prior to LVAD implantation. To uphold the predictive value of the measurements, only the 300 patients with prior 30-day RHC data could be analyzed. This should be taken into consideration when reading the results. Fifth, clinicians were not blinded to changes in renal function and treated patients accordingly, thereby possibly altering the clinical outcomes. Sixth, the lack of postoperative hemodynamic measurements hindered our ability to associate late hemodynamic profile changes with renal function deterioration. Last, using serum creatinine-based GFR estimations in a population suffering from muscle wasting and subsequent gain of muscle after LVAD implantation can over- and/or underestimate the impact of changes in serum creatinine. Unfortunately, no other renal function estimation biomarkers, such as cystatin C or 24-hour urine creatinine clearance, were available. However, due to the longitudinal approach, instead of using means over set points in time, a more accurate evolution of renal function was possible. In addition, in our opinion, the inclusion of all available contemporary types of LVADs and multicenter, transatlantic patients strengthens the conclusions and generalizability of this study.

Conclusions

Renal function following LVAD implantation shows a triphasic pattern characterized by significant early improvement, a period of steady-state function and subsequent deterioration to baseline. Patients with early renal function improvement were younger and had worse preoperative conditions and CKD stages but had better survival rates at long-term follow-up.

Disclosures

D.A. Hesselink has received lecture and consulting fees from Astellas Pharma and Chiesi Farmaceutici SpA as well as grant support (paid to the Erasmus MC) from Astellas Pharma, Bristol Myers-Squibb and Chiesi Farmaceutici SpA.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2020.01.010.

References

1. Kormos RL, Cowger, Pagani FD, et al. The Society of Thoracic Surgeons Intermacs database annual report: evolving indications, outcomes, and scientific partnerships. J Heart Lung Transplant 2019;38:114–26.

2. Brisco MA, Kimmel SE, Coca SG, et al. Prevalence and prognostic importance of changes in renal function after mechanical circulatory support. Circ Heart Fail 2014;7:68–75.
3. Ronco C, Di Lullo L. Cardiorenal syndrome in Western countries: epidemiology, diagnosis and management approaches. Kidney Dis (Basel) 2017;2:151–63.
4. Muslem R, Caliskan K, Akin S, et al. Acute kidney injury and 1-year mortality after left ventricular assist device implantation. J Heart Lung Transplant 2018;37:116–23.
5. Muslem R, Caliskan K, Akin S, et al. Pre-operative proteinuria in left ventricular assist devices and clinical outcome. J Heart Lung Transplant 2018;37:124–30.
6. Topkara VK, Colombo PC. Proteinuria in left ventricular assist device candidates: an emerging risk factor for renal failure and mortality. J Heart Lung Transplant 2018;37:143–5.
7. Hasin T, Topilsky Y, Schirger JA, et al. Changes in renal function after implantation of continuous-flow left ventricular assist devices. J Am Coll Cardiol 2012;59:26–36.
8. Kidney Disease: Improving Global Outcomes CKDMBDUWG. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int 2017;7 (Suppl (2011)):1–59.
9. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150: 604–12.
10. Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. 2015;67:48.
11. Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 2009;53: 589–96.
12. Houston BA, Kalathiya RJ, Hsu S, et al. Right ventricular afterload sensitivity dramatically increases after left ventricular assist device implantation: a multi-center hemodynamic analysis. J Heart Lung Transplant 2016;35:868–76.
13. Rich JD, Gosev I, Patel CB, et al. The incidence, risk factors, and outcomes associated with late right-sided heart failure in patients supported with an axial-flow left ventricular assist device. J Heart Lung Transplant 2017;36:50–8.
14. Brisco MA, Testani JM, Cook JL. Renal dysfunction and chronic mechanical circulatory support: from patient selection to long-term management and prognosis. Curr Opin Cardiol 2016;31:277–86.
15. Cornwell WK. 3rd, Urey M, Drazner MH, Levine BD. Continuous-flow circulatory support: the Achilles heel of current-generation left ventricular assist devices? Circ Heart Fail 2015;8:850–2.
16. Fudim M, Rogers JG, Frazier-Mills C, Patel CB. Orthostatic hypotension in patients with left ventricular assist devices: acquired autonomic dysfunction. ASAIO J 2018;64:e40–2.
17. Markham DW, Fu Q, Palmer MD, et al. Sympathetic neural and hemodynamic responses to upright tilt in patients with pulsatile and nonpulsatile left ventricular assist devices. Circ Heart Fail 2013;6:293–9.
18. Rodrigues J, Alam A, Bernard C, Giannetti N, Podymow T. Secondary hemosiderosis on kidney biopsy in a patient with a left ventricular assist device. Am J Med Sci 2014;347:172–3.
19. Wheeler DS, Giugliano RP, Rangaswami J. Anticoagulation-related nephropathy. J Thromb Haemost 2016;14:461–7.