Preoperative Proteinuria and Reduced Glomerular Filtration Rate Predicts Renal Replacement Therapy in Patients Supported With Continuous-Flow Left Ventricular Assist Devices

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Background—Renal failure requiring renal replacement therapy (RRT) has detrimental effects on quality of life and survival of patients with continuous-flow left ventricular assist devices (CF-LVADs). Current guidelines do not offer a decision-making algorithm for CF-LVAD candidates with poor baseline renal function. Objective of this study was to identify risk factors associated with RRT after CF-LVAD implantation.

Methods and Results—Three hundred and eighty-nine consecutive patients underwent contemporary CF-LVAD implantation at the Columbia University Medical Center between January 2004 and August 2015. Baseline demographics, comorbid conditions, clinical risk scores, and renal function were analyzed in patients with or without RRT after CF-LVAD implantation. Time-dependent receiver-operating characteristic curve analysis was performed to define optimal cutoffs for continuous risk factors. Forty-four patients (11.6%) required RRT during a median follow-up of 9.9 months. Patients requiring RRT had significantly worse renal function, lower hemoglobin, and increased proteinuria at baseline. Low estimated glomerular filtration rate (<40 mL/min/1.73 m^2) and proteinuria (urine protein to creatinine ratio ≥0.55 mg/mg) were significant predictors of RRT after CF-LVAD support. Dipstick proteinuria was also a significant predictor of RRT after CF-LVAD implantation. Patients with both low estimated glomerular filtration rate and proteinuria had highest risk of RRT (63.6%) compared with those with either low estimated glomerular filtration rate or proteinuria (18.7%) and those with neither of these risk factors (2.7%) at 1-year follow-up (log-rank P<0.001).

Conclusions—Estimated glomerular filtration rate and proteinuria are predictors RRT after CF-LVAD implantation and should be routinely assessed in CF-LVAD candidates to guide decision making. **(*Circ Heart Fail*. 2016;9:e002897. DOI: 10.1161/CIRCHEARTFAILURE.115.002897.)**

Key Words: acute kidney injury ■ algorithms ■ biomarker ■ blood urea nitrogen ■ renal insufficiency

Continuous-flow left ventricular assist device (CF-LVAD) therapy has become standard of care in patients with end-stage heart failure. According to the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support), the number of primary adult CF-LVAD implants has increased exponentially within the past decade.[1] Since the approval of this technology for destination therapy, medical complexity of CF-LVAD patients has also increased.[2] Because the demand far outstrips the number of heart transplants available, use of CF-LVAD therapy is expected to increase globally, including sicker heart failure populations. Therefore, proper patient selection is of utmost importance to achieve optimal outcomes while reducing the cost of care.

See Clinical Perspective

Chronic kidney disease (CKD) is a common comorbidity in patients with advanced heart failure, generally attibutable to intrinsic renal disease and cardiorenal syndrome.[3,4] Studies from pulsatile-flow and CF-LVADs have consistently showed that poor renal function before or after LVAD implantation is associated with worse clinical outcomes.[5,6] In support of these observations, serum creatinine (or blood urea nitrogen level) is the only common variable present in contemporary LVAD risk scores.[7–9] Although the importance of renal dysfunction has been long recognized in the LVAD community,

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current International Society for Heart and Lung Transplantation Mechanical Circulatory Support Guidelines do not offer any algorithms for patient selection for advanced CKD.[10] Moreover, use of a single renal biomarker may not be sufficient for renal risk stratification, particularly in patients who are just above or below the cutoff point for a given predictor such as serum creatinine. Proteinuria has been associated with increased risk of acute kidney injury in diverse patient populations; however its use in predicting poor renal outcomes in CF-LVAD patients remains unknown.

Given the significant gap in knowledge on renal risk stratification in CF-LVAD candidates, the objective of this study was to identify risk factors associated with the need for renal replacement therapy (RRT) after CF-LVAD implantation. We addressed the following 3 questions: (1) Which renal filtration parameter and cutoff level is informative for renal risk prediction in LVAD candidates?; 2) Is proteinuria a risk factor for RRT after CF-LVAD implantation?; (3) Can we identify patients who are at high-risk for need for RRT after CF-LVAD implantation using preimplantation renal function estimates?

Methods

Data Source and Study Population

Patients who underwent CF-LVAD implantation at Columbia University Medical Center between September 2004 and August 2015 were retrospectively reviewed. We included adult patients (≥18 years of age), who received either Heartmate II (HM II; Thoratec, Inc, Pleasanton, CA) or HVAD (Heartware, Inc, Framingham, MA) for bridge-to-transplantation or destination therapy indications. Patients who received total artificial hearts or investigational devices were excluded from the study. Patient characteristics at the time of CF-LVAD implantation, including patient demographics, comorbid conditions, and laboratory values, were collected. Outcome variables included post-LVAD RRT and survival on LVAD support.

Blood urea nitrogen and serum creatinine levels were obtained within 24 hours before device implantation. Estimated glomerular filtration rate (eGFR) was calculated using the traditional 4-variable MDRD (Modification of Diet in Renal Disease) study equation,[11] and estimated creatinine clearance was calculated using Cockcroft-Gault Equation (Table I in the Data Supplement).[12] Proteinuria was assessed quantitatively by spot urine protein creatinine ratio and qualitatively by dipstick protein levels (negative, trace, 1+ and >2+). CKD stages were defined according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines based on the eGFR levels. This study was approved by the Institutional Review Board at Columbia University.

Statistical Analysis

Continuous variables were defined as median with interquartile range and compared by Mann–Whitney *U* test. Categorical variables were summarized as percentages and were compared by Pearson χ^2 test or Fisher exact test. Nonparametric estimate of the hazard function for postimplantation RRT was performed using a Kernel-based approach.[13] Survival on CF-LVAD support was assessed using Kaplan–Meier analysis. Patients who were transplanted, explanted for recovery, or transferred to other centers were censored from the analysis at the time of these events. Those already on hemodialysis or continuous veno-venous hemodialysis before or during CF-LVAD implant surgery (n=7) were excluded from the RRT prediction analyses. Time-dependent receiver-operating characteristic curves were calculated to determine discriminatory power of continuous renal risk predictors.[14] Optimal cutoff point for each predictor was identified by using maximum value of the Youden index. Cox regression was performed to determine univariable predictors of RRT after CF-LVAD implantation. Risk factors with a *P* value <0.05 in univariable Cox regression analysis were entered into a stepwise multivariable regression model (exit criteria *P*>0.05) to determine independent predictors of RRT after CF-LVAD implantation. Correlated variables were not entered simultaneously into the multivariable model to avoid overfitting. Data were analyzed with the use of IBM SPSS Statistics software, version 22.0 (IBM Corp, Armonk, NY), and R software, version 3.1.2.

Results

Clinical Characteristics

The study population consisted of 389 CF-LVAD patients with median follow-up duration of 9.9 months (interquartile range: 4.4–21.8 months) on device support. Of those, 44 patients (11.3%) required RRT after median support duration of 8 days (interquartile range: 2–100 days). Median age of the population was 60.3 years (interquartile range: 48.1–67.5 years; Table 1). One hundred and seventy-eight patients (45.8%) had an ischemic cause of their heart failure. Patients requiring postimplantation RRT were more likely to have diabetes mellitus (45.5% versus 33.9%); however, this difference was not statistically significant. Six patients (1.5%) required RRT (continuous veno-venous hemodialysis or hemodialysis) before implantation, and 1 patient required intraoperative continuous veno-venous hemodialysis as a prophylactic approach. The majority of patients (64.0%) received a device as bridge to transplantation. There was no difference in utilization of temporary support devices between the 2 groups; 105 patients (27.5%) were supported with intra-aortic balloon pump, and 51 patients (13.4%) with Impella, ECMO, or CentriMag ventricular assist device.

More than half of CF-LVAD patients (55%) had reduced renal function at baseline, with CKD category ≥3. Patients requiring RRT had significantly worse renal function at baseline than non-RRT patients as measured by creatinine (2.00 versus 1.34 mg/dL; *P*<0.001), eGFR (35.3 versus 59.2 mL/min per 1.73 m^2; *P*<0.001), and estimated creatinine clearance (38.3 versus 62.7 mL/min, *P*<0.001). Patients who required RRT also had higher spot urine protein to creatinine ratio preoperatively (UPCR; 0.60 versus 0.18 mg/mg; *P*<0.001); however, this data point was only available in half of our study population (n=202, 51.9%).

Effect of RRT on Clinical Outcomes of CF-LVAD Patients

Of the 44 CF-LVAD patients who required postimplantation RRT, 6 patients (13.6%) had previously required RRT, whereas 38 patients (86.4%) required denovo treatment (Table 2). Of patients requiring denovo RRT, 23 patients (60.5%) required treatment within 30 days of implantation, whereas 15 patients (39.5%) required RRT >30 days after LVAD implantation. Hazard risk of denovo RRT was highest in the early postimplantation period with a steep decline within the first year of device support and remained stably low after this time point (Figure 1A). None of the patients who required RRT before LVAD had recovery of renal function. Nine patients (23.7%) requiring denovo RRT recovered, 4 of whom required early RRT and 5 of whom required late RRT.

Table 1. Baseline Characteristics of Patients With Continuous-Flow LVAD Implantation

Variable	Post-LVAD RRT (n=44, 11.3%)	Post-LVAD No RRT (n=345, 88.7%)	All LVAD Patients (N=389)	*P* Value
Demographics				
Age, y	59.8 (47.0–67.1)	60.3 (48.2–67.5)	60.3 (48.1–67.5)	0.858
Female sex	9 (20.5%)	69 (20.0%)	78 (20.1)	0.943
Race/ethnicity				
White	19 (43.2%)	204 (59.1%)	223 (57.3%)	0.181
Black	14 (31.8%)	87 (25.2%)	101 (26.0%)	
Other	11 (25.0%)	54 (15.6%)	65 (16.7%)	
BMI, kg/m^2	24.7 (22.6–30.5)	25.8 (22.5–29.8)	25.8 (22.6–30.0)	0.745
Comorbidities				
Ischemic cause of HF	19 (43.2%)	159 (46.1%)	178 (45.8%)	0.716
Hypertension	20 (45.5%)	174 (50.4%)	194 (49.9%)	0.534
Diabetes mellitus	20 (45.5%)	117 (33.9%)	137 (35.2%)	0.131
Stroke/TIA	6 (13.6%)	43 (12.5%)	49 (12.6%)	0.825
CVVHD/dialysis	6 (13.6%)	1 (0.3%)	7 (1.8%)	**<0.001**
Device strategy				
BTT	26 (59.1%)	223 (64.6%)	249 (64.0%)	0.470
DT	18 (40.9%)	122 (35.4%)	140 (36.0%)	
Hemoglobin	9.6 (8.6–10.9)	11.4 (9.9–12.7)	11.2 (9.7–12.6)	**<0.001**
RDW	17.4 (15.8–19.2)	15.8 (14.7–17.7)	15.9 (14.8–17.8)	**0.001**
INR	1.20 (1.10–1.28)	1.23 (1.13–1.40)	1.23 (1.13–1.39)	0.054
Albumin	3.25 (2.73–3.78)	3.70 (3.30–4.00)	3.60 (3.20–4.00)	**<0.001**
Total bilirubin	1.30 (0.80–2.00)	1.00 (0.70–1.75)	1.10 (0.70–1.80)	0.164
ALT	18.0 (12.0–47.5)	22.0 (14.5–41.0)	22.0 (14.0–41.5)	0.365
ALP	103.0 (75.3–156.3)	84.0 (63.0–107.0)	85.0 (64.0–111.0)	**0.002**
Temporary support				
No device	21 (48.8%)	205 (60.5%)	226 (59.2%)	0.109
IABP	12 (27.9%)	93 (27.4%)	105 (27.5%)	
Impella/ECMO/CM	10 (23.3%)	41 (12.1%)	51 (13.4%)	
HMRS	2.11 (1.55–2.75)	1.48 (1.00–1.95)	1.53 (1.04–2.05)	**<0.001**
MELD-Xi score	19.3 (16.8–23.7)	14.2 (11.6–17.1)	14.9 (11.9–17.8)	**<0.001**
Renal function				
Blood urea nitrogen	43.5 (32.5–66.8)	28.0 (19.5–39.5)	30.0 (20.0–41.5)	**<0.001**
Serum creatinine, mg/dL	2.00 (1.45–2.50)	1.34 (1.00–1.67)	1.40 (1.02–1.78)	**<0.001**
BUN/Cr ratio	24.9 (18.0–30.1)	21.1 (16.8–27.3)	21.4 (16.9–27.5)	0.061
eGFR, mL/min/1.73 m^2	35.3 (29.0–50.5)	59.2 (44.7–78.3)	57.2 (41.4–76.8)	**<0.001**
CKD stages				**<0.001**
eGFR ≥90	4 (9.1%)	49 (14.2%)	53 (13.6%)	
eGFR 60–89	3 (6.8%)	119 (34.5%)	122 (31.4%)	
eGFR 30–59	24 (54.5%)	166 (48.1%)	190 (48.8%)	
eGFR <30	13 (29.5%)	11 (3.2%)	24 (6.2%)	
eCrCl, mL/min	38.3 (27.3–70.3)	62.7 (47.8–89.6)	61.2 (44.9–87.4)	**<0.001**
UPCR	0.60 (0.18–1.85)	0.18 (0.10–0.36)	0.20 (0.10–0.40)	**<0.001**
Renal size, cm	10.9 (10.1–11.8)	11.2 (10.5–11.8)	11.1 (10.5–11.8)	0.242

Values are expressed as n (%) or median (interquartile range) when appropriate. Bold values are statistically significant. ALP indicates alkaline phosphatase; ALT, alanine aminotransferase; BMI, body mass index; BTT, bridge to transplantation; BUN, blood urea nitrogen; CKD, chronic kidney disease; CM, Centrimag ventricular assist device; CVVHD, continuous veno-venous hemodialysis; DT, destination therapy; ECMO, extracorporeal membrane oxygenation; eCrCl, estimated creatinine clearance; eGFR, estimated glomerular filtration rate; HMRS, heartmate risk score; IABP, intra-aortic balloon pump; INR, international normalized ratio; LVAD, left ventricular assist device; MELD-Xi, model of end-stage liver disease excluding INR; RDW, red cell distribution width; RRT, renal replacement therapy; TIA, transient ischemic attack; and UPCR, urine protein to creatinine ratio.

Table 2. Outcomes of Continuous-Flow LVAD Patients Postimplantation RRT

Variable	De Novo RRT (≤30 d; n=23)	De Novo RRT (>30 d; n=15)	De Novo RRT (All; N=38)	Preimplantation RRT (N=6)
Renal outcome				
Recovery	4 (17.4)	5 (33.3)	9 (23.7)	0 (0.0)
On CVVHD or HD	19 (82.6)	9 (60.0)	28 (73.7)	5 (83.3)
Renal transplant	0 (0.0)	1 (6.7)	1 (2.6)	1 (16.7)
LVAD outcome				
Heart transplant	4 (17.4)	2 (13.3)	6 (15.8)	1 (16.7)
Device explantation for cardiac recovery	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Death	17 (73.9)	7 (46.7)	24 (63.2)	3 (50.0)
Ongoing on support	2 (8.7)	4 (26.7)	6 (15.8)	1 (16.7)
Transferred to other center	0 (0.0)	2 (13.3)	2 (5.3)	0 (0.0)

Values are expressed as n (%). CVVHD indicates continuous veno-venous hemodialysis; HD, hemodialysis; LVAD, left ventricular assist device; and RRT, renal replacement therapy.

The majority of patients requiring denovo RRT continued to require RRT (73.7%) or underwent heart–kidney transplantation (2.6%) at the end of the study. Two patients who received combined heart–kidney transplantation after CF-LVAD support were alive and had normal cardiac and renal allograft function at the time of the this study.

Regarding LVAD outcomes, at the time of the analysis, 27 patients (61.4%) requiring denovo or preimplantation RRT died on device support, 7 patients (15.9%) underwent heart (including heart–kidney) transplantation, 7 patients (15.9%) were ongoing on device support, 2 patients (4.6%) transferred their care to outside LVAD centers, and 1 patient (2.3%) underwent device explantation for recovery (Table 2). Median hospital length of stay for patients requiring denovo RRT was significantly longer than that of patients who did not require RRT (34.0 versus 26.0 days; P=0.035). Post-RRT survival was 60.0%, 44.8%, and 34.5% at 1, 6, and 12 months of follow-up on CF-LVAD support (Figure 1B).

Prediction of RRT After CF-LVAD Implantation

Time-dependent receiver-operating characteristic curve analysis showed that eGFR calculated by the MDRD equation provided higher area under curve for predicting RRT at 1, 6, and 24 months after CF-LVAD implantation compared with serum creatinine, blood urea nitrogen, and estimated creatinine clearance (Table 3). Spot UPCR provided highest specificity for prediction of RRT at all time points. Following cutoff points were selected for each predictor based on their respective Youden index, clinical relevance, and ease of use: eGFR: 40 mL/min/1.73 m^2, UPCR: 0.55 mg/mg, hemoglobin <10 g/dL, red cell distribution width ≥16%, alkaline phosphatase ≥100 U/L, and albumin <3.5 g/dL. Although many of these laboratory values were predictive of RRT after LVAD implantation, only UPCR and eGFR were significant predictors of postimplantation RRT in a multivariable model (Table 4). Time to event analyses have demonstrated that freedom from postimplantation RRT was lower in patients who have both low eGFR (<40 mL/min/1.73 m^2) and proteinuria (UPCR ≥0.55 mg/mg) (63.6%), compared with those who have 1 (18.7%) or none (2.7%) of these 2 risk factors at 1-year follow-up after CF-LVAD implantation (log-rank P<0.001; Figure 2).

Predictive Ability of Qualitative Dipstick Proteinuria Data

Given the use of UPCR in predicting need for post-LVAD RRT, we hypothesized that the preimplantation dipstick proteinuria may also serve as a useful screening tool to identify patients at risk for postimplantation acute kidney injury. As compared with UPCR, preimplantation urinalysis data were available in the vast majority of CF-LVAD patients (n=362, 93.1%), which allowed us to cross-validate our findings with UPCR data. One in every 4 CF-LVAD patients had evidence of dipstick proteinuria before device implantation: 33 patients had trace (9.1%), 48 patients had 1+ (13.3%), and

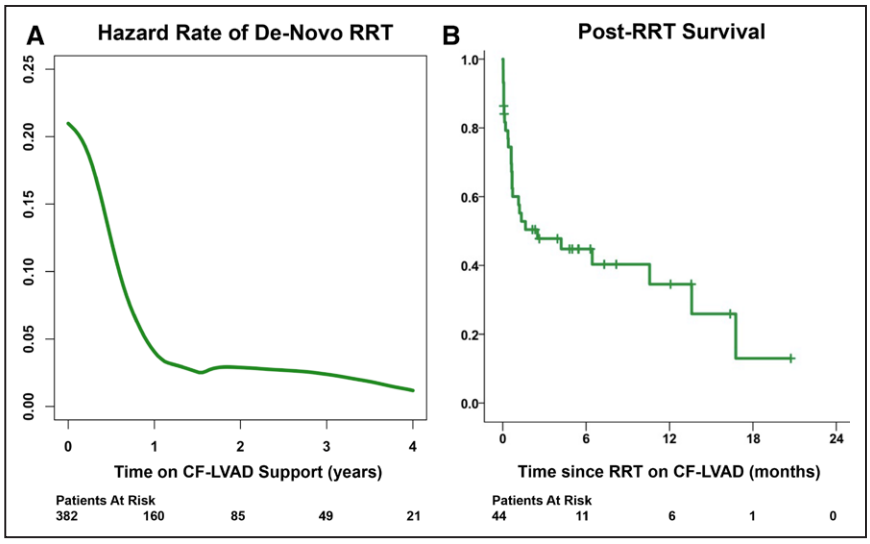

Figure 1. Incidence and outcomes of post–left ventricular assist device (LVAD) renal replacement therapy (RRT). **A**, Instantaneous risk of postimplantation RRT. **B**, Post-RRT survival on device support.

Table 3. Receiver-Operating Curve Characteristics of Laboratory Values for Prediction of Postimplantation RRT in CF-LVAD Patients

Variable	Area Under the Curve	Optimal Cutoff by Youden Index	Sensitivity, %	Specificity, %
RRT at 1 mo				
eGFR, ml/min/m^2	0.797	38.2	70	86
Creatinine, mg/dl	0.788	1.87	70	85
eCrCl, ml/min	0.786	38.4	61	88
BUN, mg/dl	0.757	33	83	61
Hemoglobin, g/dl	0.745	9.6	65	79
UPCR, mg/mg	0.733	0.54	66	88
Albumin, g/dl	0.692	3.5	74	57
RDW, %	0.683	16.1	83	57
ALP, U/L	0.612	98	56	66
RRT at 6 mo				
eGFR, ml/min/m^2	0.742	38.2	63	86
Creatinine, mg/dl	0.739	1.87	63	85
eCrCl, ml/min	0.706	38.4	52	88
BUN, mg/dl	0.708	50	45	89
Hemoglobin, g/dl	0.722	9.6	63	80
UPCR, mg/mg	0.758	0.54	68	89
Albumin, g/dl	0.716	3.2	57	77
RDW, %	0.676	16.1	79	57
ALP, U/L	0.632	98	56	66
RRT at 12 mo				
eGFR, ml/min/m^2	0.706	38.2	56	86
Creatinine, mg/dl	0.714	1.87	61	86
eCrCl, ml/min	0.658	38.4	46	88
BUN, mg/dl	0.695	37	59	71
Hemoglobin, g/dl	0.709	9.6	62	80
UPCR, mg/mg	0.726	0.54	65	90
Albumin, g/dl	0.727	3.2	57	77
RDW, %	0.659	16.1	75	57
ALP, U/L	0.629	69	91	31
RRT at 24 mo				
eGFR, ml/min/m^2	0.741	43.5	65	78
Creatinine, mg/dl	0.709	1.81	56	86
eCrCl, ml/min	0.673	47.3	59	77
BUN, mg/dl	0.707	36	67	69
Hemoglobin, g/dl	0.671	9.6	53	80
UPCR, mg/mg	0.732	0.54	56	90
Albumin, g/dl	0.619	2.9	32	88
RDW, %	0.625	16.1	69	57
ALP, U/L	0.665	94	64	64

ALP indicates alkaline phosphatase; BUN, blood urea nitrogen; CF-LVAD, continuous-flow left ventricular assist device; eGFR, estimated glomerular filtration rate; eCrCl, estimated creatinine clearance; RDW, red cell distribution width; RRT, renal replacement therapy; and UPCR, urine protein to creatinine ratio.

12 patients with >2+ proteinuria (3.3%; Table 5). Dipstick proteinuria categories correlated well with the UPCR levels. Only 5.2% of patients with negative dipstick required RRT at 1-year follow-up. However, 12.2% of patients with trace proteinuria, 17.3% of patients with 1+ proteinuria, and 50.0% of patients with >2+ proteinuria went on to require RRT at 1 year after LVAD implantation (log-rank $P<0.001$). Dipstick proteinuria was independent predictor of requiring RRT after CF-LVAD implantation, after adjustment for the preimplantation eGFR level (hazard ratio 2.84 for ≥trace proteinuria, hazard ratio 3.13 for 1+ proteinuria, hazard ratio 5.87 for >2+ proteinuria; all $P<0.01$). This effect remained consistent across all patient subgroups including diabetics and those who were on an angiotensin converting enzyme inhibitor or angiotension receptor blocker at the time of device implantation (Figure I in the Data Supplement). Freedom from RRT after CF-LVAD implantation was significantly lower in patients who have both low eGFR (<40 mL/min/1.73 m^2) and dipstick proteinuria (≥trace), compared with those who have 1 or none of these 2 risk factors (Figure 3).

Discussion

This study evaluated clinical risk factors associated with postimplantation renal failure requiring RRT in CF-LVAD patients because application of this technology rapidly expands to a sicker patient population. Our principal findings are as follows: (1) preimplantation eGFR provides a superior estimate of post-LVAD RRT compared with other markers of renal clearance; (2) preimplantation proteinuria is an independent risk factor for post-LVAD RRT either assessed quantitatively by UPCR or qualitatively by urinalysis; and (3) combining eGFR and proteinuria may allow for identification of patients who are at high risk for RRT after CF-LVAD implantation. Taken together, these findings suggest that combination of eGFR and degree of proteinuria could substantially improve risk assessment of patients for CF-LVAD therapy.

Postimplantation renal failure requiring RRT has devastating consequences on the quality of life and outcomes of CF-LVAD patients. Mortality risk is substantially increased after CF-LVAD implantation, similar to what was demonstrated in patients who received first-generation pulsatile-flow LVADs.[15] Recovery of renal function is infrequent, and survivors commonly transition from continuous veno-venous hemodialysis to long-term hemodialysis, which limits their quality of life. Vascular access issues pose a challenge because maturation of arteriovenous fistula or grafts can be difficult in the setting of continuous flow.[16] Moreover, erythrocyte-stimulating agents used in this population can predispose patients to device thrombosis.[17] Therefore, every effort should be made to assess renal risk in patients with borderline kidney function before CF-LVAD implantation.

Patients with serum creatinine ≥3.5 mg/dL (or greater than 3 times of upper limit of normal) were excluded from all contemporary CF-LVAD trials, including Heartmate II BTT (Thoratec Heartmate II Left Ventricular Assist System for Bridge to Cardiac Transplantation), Heartmate II DT

Table 4. Predictors of Postimplantation RRT in CF-LVAD Patients

	Univariable Analysis		Multivariable Analysis	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
UPCR ≥0.55 mg/mg	9.93 (4.05–24.4)	**<0.001**	7.26 (2.74–19.3)	**<0.001**
eGFR <40 mL/min/1.73 m^2	6.53 (3.41–12.5)	**<0.001**	5.56 (2.14–14.4)	**<0.001**
Hemoglobin <10 g/dL	3.95 (2.07–7.55)	**<0.001**	…	…
RDW ≥16%	3.09 (1.50–6.36)	**0.002**	…	…
ALP ≥100 U/L	2.75 (1.44–5.24)	**0.002**	…	…
Albumin <3.5 g/dL	2.27 (1.20–4.31)	**0.012**	…	…

Bold values are statistically significant. ALP indicates alkaline phosphatase; CF-LVAD, continuous-flow left ventricular assist device; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; RDW, red cell distribution width; RRT, renal replacement therapy; and UPCR, urine protein to creatinine ratio.

(Thoratec Heartmate II Left Ventricular Assist System for Destination Therapy), ADVANCE (Evaluation of the Heartware Left Ventricular Assist Device for the Treatment of Advanced Heart Failure), and ENDURANCE (A Clinical Trial to Evaluate the Heartware Ventricular Assist System).[18–20] However, scientific evidence supporting the use of a serum creatinine cutoff of 3.5 mg/dL is limited. Our data suggest that MDRD eGFR is superior to rest of the renal filtration parameters tested for prediction of postimplantation renal failure. This is not unexpected because MDRD equations are derived from patients with varying degrees of renal function and validated against glomerular filtration rate measured from the renal clearance of 125I-iothalamate.[11] Interestingly, we found 40 mL/min/1.73 m^2 as the optimal eGFR cutoff value for CF-LVAD patients, which is identical to the 2006 criteria recommended by the International Society for Heart and Lung Transplantation as a relative contraindication for heart transplantation listing.[21]

A novel finding of the current study is identification of proteinuria as an independent predictor of RRT in CF-LVAD patients. Proteinuria is a reflection of glomerular barrier defect and impaired reabsorption by the renal tubular system, which contributes to CKD progression through intrarenal activation of the complement system.[22] Large epidemiological studies have suggested that the presence of proteinuria may be an independent risk factor of acute kidney injury in the general population, irrespective of the eGFR levels.[23–25] In addition, dipstick proteinuria was shown to be a risk factor for postoperative acute kidney injury in patients undergoing coronary artery bypass grafting or valve surgeries.[26,27] Our findings suggest that proteinuria determined either qualitatively or quantitatively can be used for risk stratification in CF-LVAD patients. Interestingly, even low-grade proteinuria can increase renal risk because the UPCR cutoff identified in our analysis was 0.55. In a large sample of patients with New York Heart Association class II–IV, dipstick proteinuria defined as 1+ was present in 8% of patients and associated with increased mortality.[28] In our CF-LVAD cohort, 16.6% of patients had evidence of 1+ proteinuria on a urine dipstick. This may

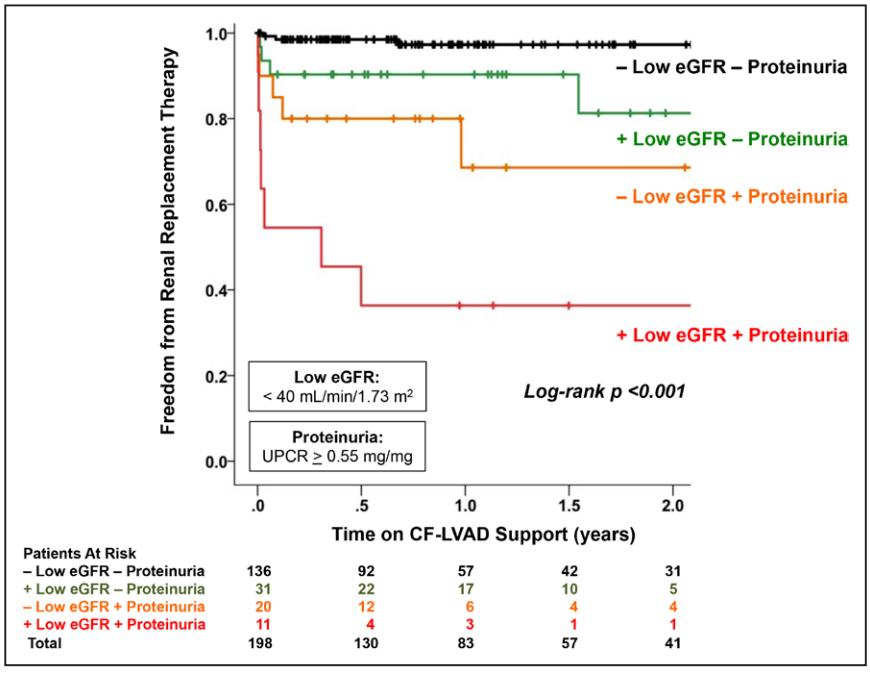

Figure 2. Freedom from post–left ventricular assist device (LVAD) renal replacement therapy (RRT) based on preimplantation estimated glomerular filtration rate (eGFR) and spot urine protein to creatinine ratio (UPCR). Low eGFR defined as eGFR <40 mL/min/1.73 m^2 and proteinuria defined as UPCR ≥0.55 mg/mg.

Table 5. Use of Dipstick Proteinuria in Renal Risk Prediction of CF-LVAD Patients

	n (%)	UPCR	RRT at 1 y, %
Proteinuria level (n=362)			
Negative	269 (74.3)	0.16 (0.09–0.33)	5.2
Trace	33 (9.1)	0.29 (0.10–0.52)	12.2
1+ proteinuria	48 (13.3)	0.34 (0.15–0.66)	17.3
>2+ proteinuria	12 (3.3)	1.61 (0.22–2.91)	50.0

Values are expressed as n (%) or median (IQR) when appropriate. CF-LVAD, continuous-flow left ventricular assist device; RRT, renal replacement therapy; and UPCR, urine protein to creatinine ratio.

indicate that CF-LVAD cohort represents a sicker patient population with more advanced renal disease compared with a general heart failure population.

Perioperative patient management plays a major role in prevention of post-LVAD renal failure requiring RRT. In our institution, we routinely perform preoperative right heart catheterization, intensive care unit monitoring, and hemodynamic optimization in patients with poor baseline renal function before LVAD surgery. Intravenous diuretic therapy, escalation of inotropic support, and use of temporary mechanical support devices may further improve hemodynamics and renal function even in patients who are deemed clinically stable. Close attention is paid to postoperative vasoplegia and right ventricular failure, both of which may significantly increase risk of post-LVAD renal failure. Early intervention through optimization of right ventricular filling, escalation of inotropic and pressor support, speed optimization with serial echocardiograms, and use of percutaneous right ventricular support devices may help restore hemodynamics and significantly reduce need for RRT in this population.

Study Limitations

This is a retrospective analysis of a large institutional clinical data registry with known limitations inherent to such study design. UPCR data were only available in half of our CF-LVAD patients, which limited our statistical power in terms of identifying other potentially important risk factors for RRT. Moreover, the number of events was small, limiting our ability to fit additional variables that could be relevant into the multivariable regression model. Given the single-institutional nature of this study, our model should be validated externally by other implanting centers, and proper eGFR and UPCR cutoff levels should be determined in larger patient cohorts. We used equations for eGFR and estimated creatinine clearance, although actual measurement of glomerular filtration rate may provide a more accurate assessment of renal function. Although UPCR is demonstrated to be as accurate as 24-hour urine proteinuria, the accuracy of estimating proteinuria from a random urine specimen may be diminished if creatinine excretion is substantially lower than normal, such as in cachexia, which is not uncommon in CF-LVAD candidates. Because this was a retrospective investigation, we did not have the chance to investigate potential use of other emerging biomarkers of kidney injury such as cystatin C, neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and liver-type fatty acid-binding protein, which can potentially provide prognostic information beyond eGFR and proteinuria in CF-LVAD candidates before device implantation.[29]

In summary, our findings suggest that preimplantation proteinuria and low eGFR are associated with increased risk of renal failure after CF-LVAD implantation. Patients with both risk factors have >50% risk of requiring RRT within 1-year after CF-LVAD implantation. Proteinuria should be routinely checked in CF-LVAD candidates—particularly those with borderline renal function to guide decision making. Patients who are at high risk should be informed of their

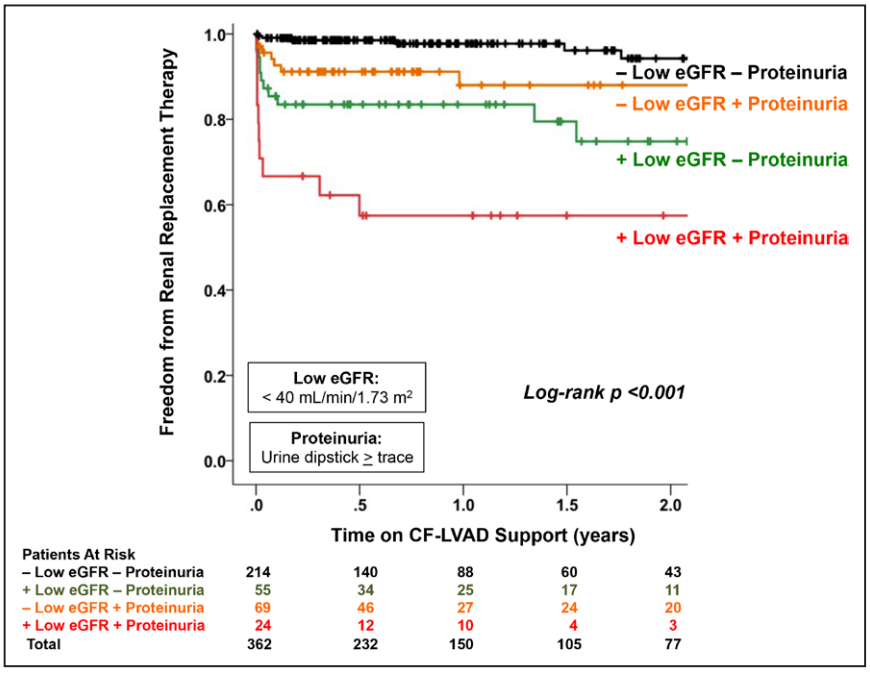

Figure 3. Freedom from post–left ventricular assist device (LVAD) renal replacement therapy (RRT) based on preimplantation estimated glomerular filtration rate (eGFR) and dipstick proteinuria. Low eGFR defined as eGFR <40 mL/min/1.73 m² and proteinuria defined as ≥trace dipstick proteinuria.

risk of renal complications and dialysis dependency—which may affect their decision on device therapy. Careful hemodynamic optimization before and after device implantation may reduce risk of renal failure and improve outcomes in these patients.

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Disclosures

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CLINICAL PERSPECTIVE

Because the approval of continuous-flow left ventricular assist devices (CF-LVADs) for destination therapy indication, the number and medical complexity of patients receiving this treatment option has substantially increased worldwide. Despite improvements in care and outcomes of these patients, post-LVAD renal failure requiring renal replacement therapy (RRT) is not infrequent and leads to significant morbidity and mortality in affected individuals. Current International Society for Heart and Lung Transplantation mechanical circulatory support guidelines do not offer any decision-making algorithms for CF-LVAD candidates with poor baseline renal function. In the present study, we performed a comprehensive analysis of our institutional data set to identify clinical risk factors associated with development of post-LVAD RRT. Our analysis suggested that glomerular filtration rate estimated by the MDRD study (Modification of Diet in Renal Disease) equation provided superior estimate of post-LVAD RRT compared with other traditional markers of renal clearance, including blood urea nitrogen, serum creatinine, and estimated creatinine clearance. Multivariable risk prediction model identified poor renal function (eGFR <40 mL/min/1.73 m^2) and proteinuria (urine spot protein creatinine ratio ≥0.55 mg/mg) as significant predictors of post-LVAD RRT. Patients with both risk factors at the time of CF-LVAD implantation carried 64% risk of RRT at 1-year follow-up. Future studies are warranted to validate these findings in larger patient populations. Our results suggest that proteinuria should be routinely assessed in CF-LVAD candidates to guide clinical decision making.

Preoperative Proteinuria and Reduced Glomerular Filtration Rate Predicts Renal Replacement Therapy in Patients Supported With Continuous-Flow Left Ventricular Assist Devices

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Formulas used to estimate renal clearance and LVAD mortality risk

Estimated Glomerular Filtration Rate (MDRD):

MDRD eGFR = 186 x (serum creatinine mg/dl)$^{-1.154}$ x (age in years)$^{-0.203}$ x (0.742 if female) x (1.212 if Black)

Estimated Creatinine Clearance:

CG eCrCl = [(140 – [age in years]) x Weight (kg) x (0.85 if female)] / (72 x serum creatinine mg/dl)

Heartmate II Risk Score:

HMRS = (0.0274 x [age in years]) + (0.723 x [albumin g/dl]) + (0.74 x [serum creatinine mg/dl]) + (1.136 x [INR]) + (0.807 if total center LVAD volume is less than 15)

MELD-XI (MELD excluding INR):

MELD-XI = 5.11 Ln (total bilirubin mg/dl) + 11.76 Ln (serum creatinine mg/dl) + 9.44

Supplemental Figure 1. Subgroup analysis of post-CF-LVAD need for renal replacement therapy (RRT). A summary of interactions between subgroups and proteinuria is presented. The *p*-values for interaction indicate there are no significant interactions that could account for the increase in need for RRT in patients with proteinuria.