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EDITORIAL

# Left Ventricular Assist Devices and Renal Ramifications

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Left ventricular assist devices are well-established therapy for end-stage heart failure with reduced ejection fraction. Durable left ventricular assist device (LVAD) implantation carries a Class I recommendation for patients with advanced heart failure with reduced ejection fraction who are inotropic dependent or require temporary mechanical support. There is a Class IIa recommendation for those patients with persistent New York Heart Association Class IV symptoms despite optimal guideline-directed medical therapy.[1]

See Article by Roehm et al.

Contemporary LVADs include the continuous flow axial (CF-axial) pump, centrifugal flow hybrid levitation (CF-hybrid) pump, and the centrifugal full-magnetic levitation (CF-maglev) pump. Currently, the CF-maglev pump is the only US Food and Drug Administration–approved LVAD implanted in the United States. In the MOMENTUM 3 (Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3) trial, the overall 5-year survival rate for CF-maglev LVAD versus the CF-axial LVAD was 58.4% and 43.7%, respectively. Among patients with LVADs as destination therapy or not receiving heart transplants, the 5-year survival in the CF-maglev LVAD versus the CF-axial LVAD was 51.5% and 36.0%, respectively. Renal dysfunction, defined by an increase in creatinine of 2 mg/dL or greater or the requirement for sustained hemodialysis for 90 days, occurred in 15% of CF-maglev patients.[2] Among 14 226 LVADs implanted between 2016 and 2020, early (≤90 days postimplant) and late (≥90 days postimplant) renal dysfunction occurred in 9.1% and 4.9% of patients, respectively.[3]

Preimplant renal dysfunction predicts higher mortality after LVAD implantation,[4] and end-stage renal disease is a contraindication to LVAD.[5] In a study of Medicare beneficiaries with end-stage renal disease, 51.6% of patients who underwent LVAD therapy died during the index hospitalization, and the survival rate was <20% at roughly 2 years.[6] Another study of Medicare beneficiaries demonstrated a 1-year mortality of 61.5% among patients with end-stage renal disease.[7] Renal replacement therapy after LVAD therapy also carries a significant mortality risk with a 1-month survival of 74.7% and a 1-year survival of 45.3% in a single-center study. Pre-existing renal disease, specifically proteinuria and an estimated glomerular filtration rate (eGFR) <45 mL/min per 1.73 $m^2$, and a mean right atrial pressure to pulmonary capillary wedge pressure ratio ≥0.54 were predictors of renal replacement therapy after LVAD placement.[8] In another study, patients with a combination of preoperative proteinuria (urine protein to creatinine ratio ≥0.55 mg/mg) and low GFR (<40 mL/min per 1.73 $m^2$) had a 63.6% risk of renal replacement therapy after LVAD placement.[9]

Renal dysfunction is common in patients with advanced heart failure. In a systematic review, the 1-year

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mortality was 38% in patients with heart failure with any renal impairment and 51% among those with the moderate–severe disease.[10] The cardiorenal syndrome describes the bidirectional, maladaptive interaction between the heart and kidneys. The cardiorenal syndrome pathophysiology is complex, and increased venous pressures, reduced renal perfusion, right ventricular dysfunction, and neurohormonal adaptations are thought to be the underlying mechanisms for renal dysfunction.[11] While left ventricular unloading with LVADs improves cardiac output, reduces venous pressure, and potentially improves right ventricular function, renal trajectories can vary postimplantation.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Roehm and colleagues evaluated the change in eGFR in LVAD recipients over 2 years.[12] This single-center study conducted at Tufts University included patients receiving LVADs from January 2010 to December 2017. Patients on hemodialysis or those who received prior LVADs were excluded. Estimated renal function was measured using the Chronic Kidney Disease Epidemiology Collaboration 2009 creatinine equation. Baseline eGFR was defined as the median of all eGFR values obtained 30 days before LVAD implantation, and patients were stratified into 3 groups: baseline eGFR ≥60 mL/min per 1.73 $m^2$, 30 to 59 mL/min per 1.73 $m^2$, and <30 mL/min per 1.73 $m^2$. The primary outcome was a change in eGFR over time, and secondary outcomes included a 30% change in eGFR from baseline, all-cause death, and heart transplantation during the 2-year follow-up period. A joint model was constructed to examine changes in eGFR over time while accounting for informative censoring related to the competing risks of death and heart transplantation.

A total of 288 patients received durable LVADs during the study period. The LVADs implanted during this period included the CF-axial LVAD and the CF-hybrid LVAD; 59% were implanted as a bridge to transplant. The majority (92%) had eGFR ≥30 mL/min per 1.73 $m^2$, with a median baseline eGFR of 60 mL/min per 1.73 $m^2$. Patients were predominantly male (79%) and White (81%), 39% had ischemic cardiomyopathy, and 42% had diabetes. A higher percentage of patients with lower eGFR had ischemic cardiomyopathy and diabetes.

Within each eGFR group, most patients had either an improvement or stable renal function, with only 6% (16 patients) experiencing a 30% or greater decrease in eGFR. Thirty patients (10.4%) required renal replacement therapy postoperatively, of whom 17 (56.7%) had died by 6 months. One-year survival was 83% among those with baseline eGFR ≥60 mL/min per 1.73 $m^2$, 73% among those with baseline eGFR 30 to 59 mL/min per 1.73 $m^2$, and 67% among those with baseline eGFR <30 mL/min per 1.73 $m^2$ ($P$=0.13). In the joint model analysis adjusted for age, sex, and baseline eGFR, men did not have an increase in eGFR and experienced a decline of 5 to 10 mL/min per 1.73 $m^2$ over the first year, followed by stable function over the subsequent year. Conversely, women had an increase in eGFR of ~5 mL/min per 1.72 $m^2$ in the first year, followed by a return to baseline values.

The authors should be commended for their work, which complements other studies assessing renal outcomes after LVAD implantation. The primary finding was that most patients have stable renal function within the first 2 years of LVAD therapy, even after considering competing risks. While renal dysfunction may be a relative contraindication to LVAD support, the study's findings suggest that renal dysfunction, even advanced, may not necessarily be an absolute contraindication to LVAD support. Furthermore, the differences between men and women may shed light on sex-based differences in LVAD support. The study did not demonstrate a significant difference between eGFR and mortality, although there were only 22 patients (8%) with eGFR <30 mL/min per 1.73 $m^2$, and the survival was 67% among this cohort.

The primary limitations of this study include that it is a single center with a more homogeneous population than is represented in INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). In addition, the LVADs in this cohort are not currently implanted. However, both short- and long-term data from the MOMENTUM 3 trial did not suggest significant differences in renal function between the axial versus centrifugal flow pump. The authors used a sophisticated statistical joint model to address the changes to GFR over time and to account for those patients who could not contribute GFR data because of death or heart transplantation before the end time of the study. It is informative that differences in GFR patterns over time were noted between men and women. Yet the authors included factors selected a priori into their model, which limits the findings to the variables selected. The differences between men and women may be because of distinct differences between their sexes that were not explored in this study. For instance, men in this cohort were statistically more likely to have ischemic cardiomyopathy, while women were more likely to have nonischemic cardiomyopathy. Interestingly, the GFR patterns, when compared between the 2 cardiomyopathies, paralleled those of their respective associated sexes. This leaves open the question of other notable differences that may be contributing to differences in eGFR patterns between men and women. As the authors conclude, larger studies are indeed needed to address this important question.

The present study is unique in that it accounts for the competing risks of death and heart transplantation when describing changes in GFR over time, a limitation

that may bias results. The findings of this study mirror what other investigators have demonstrated. In a retrospective multicenter cohort study of 400 patients that included axial and centrifugal flow LVADs, renal function initially improved in all chronic kidney disease groups and then regressed to baseline levels. Patients with an early improvement in renal function were younger and more likely in shock, and these patients had improved survival rates over a 2-year follow-up.[13] Likewise, in a study of 59 patients supported with LVADs over 3 years, the hepatic function remained in the normal range for the duration while renal function transiently improved and then returned to baseline. Older age, ischemic cardiomyopathy, and late right ventricular failure were risk factors for progressive renal failure.[14]

Utilizing INTERMACS data that included pulsatile pumps and continuous pumps, Brisco and colleagues reported an early improvement in renal function followed by a decline in renal function over the subsequent year. Of note, poor survival was associated with both marked improvement and worsening in eGFR.[15] The former finding may result from significant inflammatory insult and progressive sarcopenia postimplantation. The impact of muscle wasting is an essential factor mediating renal function assessment. Serum creatinine, used to measure renal function, may be reduced by muscle wasting, which is common in end-stage heart failure. Cystatin-C, an endogenous protease inhibitor less influenced by muscle mass, has been used to determine renal function and is associated with outcomes among patients with advanced heart failure.[16] In a study by Pinsino and colleagues, cystatin-C was compared with serum creatinine in patients with advanced heart failure undergoing LVAD therapy. Among 116 patients undergoing LVADs, creatinine-based eGFR improved early post-LVAD, whereas cystatin-C-based eGFR remained stable and correlated to a composite of in-hospital mortality, renal replacement therapy, or severe right ventricular failure.[17] The authors demonstrated that muscle mass, assessed by chest computed tomography, decreased post-LVAD placement, and this reduction correlated to a decline in serum creatinine. Significant gains typically follow the early decrease in skeletal mass over the subsequent 6 months of LVAD support.[18]

The presumption that LVADs improve cardiorenal syndrome is thus questioned by the aggregate data implicating more complex cardiorenal interactions. More recently, Walther and colleagues identified 5 eGFR trajectories among 4615 patients implanted between 2016 and 2017. Trajectories in the first 2 groups were similar to the current study. However, the third group identified patients with likely intrinsic renal disease with a postimplant decline followed by sustained low renal function. A fourth group demonstrated significant improvement; these patients were likely to have acute decompensated heart failure with associated renal dysfunction (type 1 cardiorenal syndrome). Finally, the fifth and smallest group had severe postimplant renal injury, followed by recovery in survivors.[19]

Despite improved long-term LVAD outcomes with the current US Food and Drug Administration–approved device, there is ongoing focus on mitigating complications and morbidity. Renal function is a crucial determinant of outcomes. The decline in renal function over time may be multifactorial because of right ventricular dysfunction, venous congestion, reduced pulsatility, and/or ongoing maladaptive neurohormonal mechanisms.[20] Furthermore, the influence of race and sex on LVAD outcomes becomes essential, as demonstrated in this current study. Additional investigation is necessary to understand the mechanisms that lead to these outcome differences and how to truly measure renal function in the context of inflammation and sarcopenia that accompanies advanced heart failure.

## ARTICLE INFORMATION

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### Disclosures

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