Left Ventricular Assist Device Implantation and Kidney Function: Chicken, Egg, or Omelet?

Bethany Roehm and Justin L. Grodin

Durable continuous-flow left ventricular assist devices (LVADs) have transformed the treatment of advanced heart failure for more than a decade. However, these benefits are not uniform among LVAD recipients. Preim-

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plantation clinical characteristics and medical comorbid conditions have a critical influence on postimplantation outcomes. As a result, a multiorgan system multidisciplinary medical evaluation is crucial to determine the likelihood of symptomatic and prognostic benefit with LVAD implantation. Understanding the risk for deteriorating kidney function is a cornerstone of this evaluation because advanced chronic kidney disease is associated with unfavorable short- and long-term outcomes.[1-4] In particular, as the population of destination LVAD patients (who are non–cardiac transplant candidates) continues to grow, the need for managing and mitigating the risk for kidney disease progression in these individuals will become greater.

Fundamental to meeting that need is a deeper understanding of the influence of long-term LVAD support on cardiorenal interactions and kidney pathophysiology. Because of these concerns, most centers avoid LVAD implantation in patients with advanced kidney disease unless there is an expectation that kidney function will improve after receiving an LVAD or there is a more viable long-term strategy for LVAD support, such as a bridge to a simultaneous heart-kidney transplant.[5] This approach is problematic because predicting the likelihood of improvement in kidney function among those with advanced kidney disease at the time of LVAD surgery is challenging, and this practice varies across LVAD-implanting institutions.

In this issue of *Kidney Medicine*, Wettersten et al[6] sought to address this problem by assessing predictors of improvement in kidney function after LVAD implantation. To meet this aim, they conducted a retrospective analysis of 131 patients who received an LVAD at the University of California, San Diego and abstracted demographic, clinical, and hemodynamic data, as well as estimated glomerular filtration rate (eGFR) assessments using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation from the time of LVAD implantation onward.[7] Using a univariable screen, they generated a multivariable model to determine predictors of eGFR changes from the time of LVAD implantation to 1-month postimplantation. The key observations were that despite looking at 48 predictors, age, diabetes mellitus, and baseline eGFR were associated with 1-month eGFR change. These authors pointed to an unmet clinic need, concluding that it is difficult to predict change in eGFR after LVAD implantation. They further speculated that defining better predictors such as novel kidney biomarkers and imaging modalities may meet this need.

Determining preimplantation characteristics that influence changes in eGFRs after LVAD implantation from cohort studies has been challenging. This patient population is quite ill and in the midst of this illness undergo major surgery, during which other factors such as shock, anesthesia, and hypotension may influence GFR, limiting insights from such analyses. Additionally, data missingness in LVAD registries may lead to misleading observations. For example, the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry contains data for more than 27,000 durable LVAD recipients. However, many of the characteristics that might be expected to predict changes in eGFR after LVAD implantation, such as measures of albuminuria, hemodynamic parameters such as central venous pressure to pulmonary capillary wedge pressure ratio, hemoglobin A_{1c} level, and dialysis, may be incomplete.[3,8-10] However, studies that may capture these data more completely are less generalizable, of small sample size, and lacking in clinically useful predictors of outcomes.[11-13]

The findings from Wettersten et al are subject to similar limitations. In the present report, they identified that only eGFR and younger age were predictive of improvement in eGFR. Unfortunately, age and a diagnosis of diabetes are not modifiable risk factors at the time of LVAD implantation. It is also not surprising that diabetes would be associated with changes in eGFR because diabetes is the leading cause of kidney failure in the United States.[14] Also, it is reasonable to assume from a physiologic standpoint that younger patients would be more likely to have an improvement in eGFR. They have presumably larger total kidney volume, a greater number of functional nephrons, and fewer years to have developed progressive intrinsic kidney disease from chronic conditions such as diabetes and hypertension that are typically more common in older individuals.[15]

Most cohort studies that have explored the linkage between LVAD support and kidney function, including the present study, estimate GFR using serum creatinine level ($eGFR_{cr}$). Using serum creatinine level as a surrogate for GFR has limitations because sarcopenia is common in many LVAD candidates.[16] The use of creatinine-based estimating equations may overestimate actual GFR in this population. In the months immediately following LVAD implantation, patients may experience additional muscle wasting as they recover from major surgery. This could

account for apparent increases in $eGFR_{cr}$ early after LVAD implantation, a notion supported by serial measurements of cystatin-based eGFR ($eGFR_{cys}$), which is thought to be less influenced by muscle mass.[17] This could explain why the present study, much like other prior studies, saw an improvement in eGFR at 1 month that was not sustained in the longer term.[1,4,18,19]

Therefore, the confounding influence of muscle mass on $eGFR_{cr}$ questions the clinical utility of establishing predictors of change in $eGFR_{cr}$ 1 month after implantation. Though use of $eGFR_{cys}$ over $eGFR_{cr}$ may sound promising, $eGFR_{cys}$ may not yield a more accurate measurement of glomerular function than $eGFR_{cr}$ because cystatin C levels may be elevated in patients with heart failure and may not be as independent of muscle mass as previously thought.[12,20] For example, a recent study of 293 patients hospitalized for decompensated heart failure observed that both $eGFR_{cr}$ and $eGFR_{cys}$ overestimated measured urinary creatinine clearance in patients with lower muscle mass.[20] Furthermore, GFR estimates of kidney function provide an incomplete assessment of kidney physiology. Other assessments of kidney function that are needed in LVAD patients beyond GFR include albuminuria, markers of tubular function and injury, and diuretic resistance.

There are several methodologic considerations worth noting in the present report. First, the investigators defined an improvement in eGFR as any positive number after subtracting the implantation eGFR from the follow-up eGFR, although small increases in eGFR at follow-up may not necessarily be clinically significant or carry prognostic value. Second, LVAD patients are a highly selected population subject to secular trends in care and differences in clinical practice between institutions and providers, limiting the generalizability of these observations.[21] Third, the retrospective nature of this study inadequately captures additional factors beyond objective clinical data that may either influence a clinician's decision to recommend an LVAD or have additional influence on kidney failure over time. Fourth, eGFR on the day of LVAD implantation is an inadequate benchmark to determine a patient's homeostatic eGFR. For example, eGFR can be labile in patients with advanced heart failure before LVAD implantation due to myriad factors, including hemodynamic changes, administration of nephrotoxic medications, and possible acute tubular necrosis in shock. These dynamic changes make it difficult to ascertain the cause, the stability, and what is clinically modifiable when observing changes in eGFR in this setting. Fifth, estimates of changes in eGFR at 1 month postimplantation are limited because they may numerically represent regression to the mean and not true improvement or worsening. Finally, the interpretation of the association of baseline factors with long-term trajectories in eGFR is limited by a survival bias for patients that neither died nor experienced a heart transplantation. Death and heart transplantation would be informative censors in this case that might influence the interpretation of long-term kidney function.[22]

Box 1. Key Next Steps to Advance Research in Predictors of Kidney Function in LVAD Recipients

- Multidisciplinary collaboration between nephrologists, cardiologists, pathologists, and radiologists
- Multi-institutional collaboration to improve quantity and quality of data
- Longitudinal studies of measured GFR to circumvent pitfalls of creatinine and cystatin
- Identification of novel biomarkers
- Development and use of imaging modalities
- Study of other markers of kidney function such as tubular function, albuminuria, and diuretic resistance

Abbreviations: GFR, glomerular filtration rate; LVAD, left ventricular assist device.

In the present report, 6 patients died in the first month, patients who may have been more likely to experience a decline in GFR had they lived.

Despite these limitations, the present study explores characteristics that might help clinicians understand factors that may influence eGFR after LVAD implantation. Prior studies were limited such that they examined the overall eGFR trajectory after LVAD implantation without establishing predictors, except for a small handful of studies that examined predictors of severe acute kidney injury or declines in eGFR after LVAD implantation. These studies found that serum or plasma neutrophil gelatinase-associated lipocalin (NGAL), a marker of tubular injury and acute kidney injury, body mass index, and prior sternotomy were associated with kidney dysfunction after LVAD implantation.[11-13,23] Much like age, prior sternotomy is not a modifiable risk factor. Similarly, although body mass index seems modifiable, it may not be practical to do so in a patient with advanced heart failure. Though NGAL level could be a useful marker of tubular function providing additional physiologic insights, it is not widely commercially available and norms in the LVAD population would need to be established.

The ideal LVAD recipient with comorbid kidney disease is a patient whose kidney function will improve or not worsen rather than plummet after LVAD surgery; identifying these individuals remains a significant challenge. An initial step in the evaluation process should incorporate better ways to identify those who truly have experienced an increase or decrease in GFR after LVAD surgery rather than eGFR given the limitations of current biomarkers used to estimate GFR. We agree with Wettersten et al that there is need for novel biomarkers and imaging modalities to identify intrinsic kidney disease that is unlikely to be reversible after LVAD implantation. Ideally, such testing would be done prospectively and involve a consortium of LVAD centers with collaboration between nephrologists, cardiologists, clinical pathology, and radiology. Finally, researchers need to look beyond GFR when discussing changes in kidney function in LVAD patients. Tubular

function and diuretic resistance may also be of significant prognostic importance in LVAD patients (Box 1).

Despite its limitations, the present report is a step toward a better understanding of the predictors of changes in eGFR in LVAD patients and highlights the current limitations of retrospective analyses in LVAD patients. This study underscores the need for advances that will empower clinicians to make better informed decisions regarding LVAD candidacy and have more meaningful discussions surrounding shared decision making with potential LVAD recipients with kidney disease.

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