

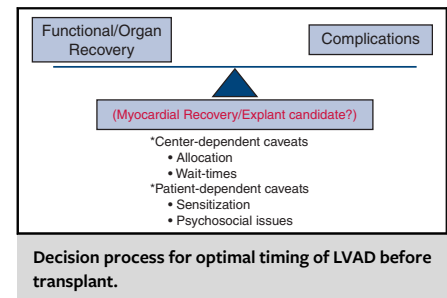
The good, the bad, the ugly: Optimal left ventricular assist device duration in bridge to transplantation



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Left ventricular assist devices (LVADs) are an important treatment option for patients with end-stage heart failure refractory to optimal medical management. Compared with medical therapy, LVADs improve quality of life and survival.^{1,2} Over the past decade, approximately 50% of patients received an LVAD as destination therapy (DT), whereas close to 25% received a device as either a bridge to transplant (BTT) or bridge to candidacy (BTC).³ In 2018, the US heart allocation system was modified in such a way that priority of patients who are stable with an LVAD was less emphasized. Since that time, there has been an increase in DT LVADs to 70% of all implants, and a decrease in the use of LVADs in the pretransplant setting. Despite this trend, the number of patients with an LVAD, regardless of implant strategy, who ultimately receive a heart transplant remains significant: BTT (60%), BTC (40%), and DT (17%).³ These observations not only call into question the role for categorization of implant strategy, but also suggest that advanced heart failure programs need to view patients with an LVAD within the spectrum of transplantation. Indeed, the common goal of prolonging survival and improving quality of life will often head down the transplant pathway independent of one's a priori LVAD designation.⁴

Within the paradigm that a large proportion of patients with LVAD will be considered for transplant, providers are routinely faced with questions regarding when to list for transplant. Unfortunately, this issue is poorly defined, dependent on multiple variables, and lacking guidance from contemporary data. Patients with LVAD receive comprehensive, multidisciplinary evaluations that often identify definitive and relative barriers to heart transplantation and influence duration of LVAD support. Ultimately, mechanical circulatory support programs must balance the benefits of circulatory support with the known complications associated with LVADs. This Commentary highlights the good, the bad, and the ugly facets of durable



CENTRAL MESSAGE

Optimal duration of durable LVAD support before transplant is a nuanced decision process that weighs the advantages of functional, organ, and psychological recovery versus the risk of adverse events.

See Commentary on page 121.

LVAD support that are utilized to determine the optimal timing of LVAD support in patients moving toward heart transplantation.

OPTIMAL TIMING OF HEART TRANSPLANTATION

Decisions regarding the optimal time to remove an LVAD or list a patient for transplant are complex and multifactorial. A key question remains largely unanswered in the modern era: Does the timing of transplant in patients bridged with an LVAD make a difference on posttransplant outcomes? Historically, several groups have reported excellent posttransplant outcomes in patients bridged with an LVAD. The multicenter, axial-flow HeartMate II (Thoratec Corp, Pleasanton, Calif) data showed equivalent survival in LVAD patients at 30 days and 1 year compared with de novo transplant recipients.⁵ In this study, 33% of patients were transplanted with a mean support duration of 151 days. No difference in mortality was seen when comparing LVAD support <30 days, 30 to 90 days, 90 to 180 days, and >180 days. Patients who received 2 or more units of packed red blood cells in 24 hours after LVAD implantation showed worse survival compared with those who received <2 U transfused blood (82% vs 94%).⁵

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Received for publication Aug 10, 2021; accepted for publication Oct 14, 2021; available ahead of print Nov 3, 2021.

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JTCVS Open 2021;8:116-20
2666-2736

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<https://doi.org/10.1016/j.jxjon.2021.10.013>

Similarly, in a larger registry study using the United Network for Organ Sharing (UNOS) database, 1332 patients were identified during 2011-2012 as having received a continuous-flow LVAD as BTT.⁶ Patients were stratified into LVAD duration cohorts <90 days, 90 days to 365 days, and >365 days with no difference in posttransplant morbidity or mortality. In subgroup analysis, LVAD support >90 days was associated with improvement in pretransplant functional performance in these patients.⁶ Using Medicare data, 1186 (45%) of patients were identified as BTT compared with 1453 (55%) who went directly to heart transplantation without a durable device. The patients with LVAD patients were stratified into ≤31 days, 31 days to 365 days, and >365 days. Patients receiving a heart transplant within 31 days of LVAD support had significantly worse survival compared with the other cohorts.⁷

Alternatively, other studies suggest a negative influence on posttransplant outcomes in patients bridged with a durable LVAD.⁸⁻¹¹ In another UNOS database study from 2008 to 2015, propensity-matched analysis of 5486 patients with and without an LVAD undergoing heart transplantation demonstrated a higher 1-year mortality in bridged patients (9.5% vs 7.2%; $P < .001$).¹¹ Logistic regression identified reduced glomerular filtration rate and obesity as risk factors for increased mortality in transplanted LVAD patients.¹¹

With single-center and registry studies, it is difficult to determine the influence of LVAD duration on posttransplant outcomes. It seems that early transplantation after LVAD, within the first month, confers a negative influence on transplant outcomes, and that certain post-LVAD adverse events and patient factors may increase the mortality of patients with an LVAD who move on to transplant. However, these studies lack the granularity and insight to the clinical decisions on when to transplant patients with an LVAD. To answer these questions, one must consider why the LVAD was implanted in the first place.

LVAD IMPLANTATION AND TRANSPLANT: THE GOOD, THE BAD, THE UGLY

As stated, the goal of LVAD therapy is to improve survival and quality of life in patients with end-stage heart failure. Duration of LVAD support may not affect posttransplant outcomes beyond the early postoperative period, with the obligatory morbidity of a major heart operation. Conversely, a longer duration of LVAD support subjects patients to a defined risk of serious complications. Often, during the pre-LVAD evaluation period, a patient's severity of illness and definitive and relative contraindications to heart transplant dictate the decision-making process in offering LVAD therapy. Many of these variables persist after LVAD implantation and influence the duration of LVAD support.

Patients being considered for LVAD present with a spectrum of scenarios that are categorized by the Society of Thoracic Surgeons Interagency Registry for Mechanically Assisted Circulatory Support profiles of clinical presentation, ranging from cardiogenic shock to mildly symptomatic. The allocation of organs to patients in profiles 1 and 2 challenges utilization of a scarce resource. Sicker patients often have additional organ failure that precludes transplant listing. Durable LVAD has traditionally been an option for these patients to allow for other organ recovery and improve conditioning and functional status. An increasing percentage of profile 1 and 2 patients are being supported with temporary mechanical circulatory support because of the change in the US heart allocation system.¹² Furthermore, with the heart allocation system change, the number of patients listed with LVAD at the time of transplant has markedly decreased.¹³ In a recent UNOS registry study, transplanted patients with LVAD decreased to 14% compared with 47% before the allocation change, with significant decrease in 1-year survival estimate and more graft failure.¹³ These patients are foregoing durable LVAD in some circumstances while awaiting transplant with temporary mechanical circulatory.¹⁴ In patients who fail to secure a suitable donor in a timely fashion on temporary mechanical circulatory, transitioning to durable LVAD remains an option.

The Good

In addition to severity of illness, some patients with advanced heart failure have myriad contraindications to transplant—some modifiable, others not. These include multiorgan dysfunction, obesity, infection, malignancy, financial barriers, and psychosocial issues. The good part of LVAD therapy is the time it allows patients and care providers to address modifiable risk factors to heart transplantation, especially organ dysfunction. In patients with chronic heart failure, approximately 50% will have coexisting chronic kidney disease.¹⁵ Chronic kidney disease stages 4 and 5 are relative contraindications to heart transplant listing.¹⁶ The support provided by LVAD therapy transiently improves renal function in many patients who did not affect overall survival when compared with medically managed patients awaiting transplant.¹⁷ However, LVAD implantation is also associated with a negative influence on renal function, with LVAD patients who experience a severe postoperative acute kidney injury having higher mortality and impaired renal function at 1-year postimplant, and possible negatively influencing listing status.¹⁸

A similar influence has been observed in patients presenting with liver dysfunction. LVAD therapy has been shown to improve preexisting acute hepatic failure as early as 1 month post-LVAD implantation with comparable survival rates.¹⁹ Although, as seen in patients who develop

postoperative acute kidney injury, the development of postoperative hepatic dysfunction is associated with increased early and midterm morbidity and mortality.²⁰ Likewise, LVAD therapy can have positive postoperative effects on patients with pulmonary hypertension as a contraindication to transplant. Pulmonary hypertension may be present in 40% to 75% of patients with advanced heart failure.²¹ LVAD support has been shown to improve pulmonary vascular resistance in these patients and permit heart transplant candidacy in patients initially deemed ineligible.²² Despite early reductions in pulmonary vascular resistance, pulmonary arterial remodeling is often delayed or incomplete in patients with secondary pulmonary hypertension and associated with increased posttransplant mortality.^{22,23} A benefit of LVAD therapy is the improvement in end-organ function to allow reappraisal of transplant eligibility. The positive influence of LVAD therapy in end-organ recovery appears to happen early during the postoperative course, within the first 1 to 3 months after implant, which can influence the duration of LVAD support and timing of listing.

Supplementary to end-organ recovery, LVAD therapy is associated with body recovery and functional improvement. LVAD therapy has been shown to significantly improve nutritional status and reduce malnourishment when compared with the preoperative heart failure state.²⁴ In patients supported with LVAD, exercise capacity significantly increases 6 to 12 months postimplant regardless of preoperative Intermacs profile or heart failure etiology.²⁵ Taken altogether, improvements in end-organ function, nutritional status, and functional improvement represent the good of LVAD therapy and translates to improved health-care related quality of life for these patients.^{26,27}

The Bad

Despite the many positives of LVAD therapy, the bad part of LVAD support is the association of the device with an array of adverse events. LVADs have well-defined complication profiles that commonly include infection, bleeding, and stroke. The number and rate of these complications increase proportionally to the duration of LVAD support. Once an LVAD-related complication occurs, patients are often upgraded in transplant listing status and mortality is significantly increased.²⁸ Furthermore, a device-related infection appears to be specifically deleterious, with increased 1- and 10-year mortality posttransplant.²⁹ The community awaits more studies with contemporary pumps that detail the reasons for status upgrade and their associated outcomes.

The fully magnetically levitated HeartMate 3 (Abbott Cardiovascular, Abbott Park, Ill) LVAD is the dominant durable device and has an improved adverse event profile compared with prior, axial-flow devices, including

significant reductions in pump thrombosis, strokes, bleeding, ventricular arrhythmias, and hospital readmissions.³⁰ The reduced complications associated with this device may limit the number of status upgrades for device-related complications in LVAD patients awaiting transplants and influence waitlist duration, optimal timing of transplant, and posttransplant outcomes. In addition, more robust utilization and knowledge of the HeartMate 3 might alter the perceived notion that one must transplant a patient with an LVAD prophylactically before adverse events arise. The full effect of fully magnetically levitated LVADs with fewer complications, particularly with the current heart allocation system, remains to be seen because limited data are available.

In the absence of an LVAD-related complication, the mere presence of an LVAD in patients bridged to transplant has been associated with increased risk of primary graft dysfunction and prolonged posttransplant vasoplegia.^{31,32} Avoiding complications associated with LVAD therapy is imperative to improve posttransplant outcomes. To avoid LVAD-related complications, limiting the duration of LVAD support seems intuitive. Steffen and colleagues³³ investigated the optimal timing of transplant in patients supported with continuous-flow LVADs from 2004 to 2013. In this study of 285 patients, posttransplant survival was improved when occurring within 9 months of LVAD implantation.³³ Survival decreased as the duration of support exceeded 9 months.³³ Heart transplant before the onset of LVAD-related complications is essential to transplant survival.

The Ugly

The ugly related to LVAD support and determining the optimal duration of support before transplant are the many patient-related variables that are difficult to control or predict and often dynamic. These include psychosocial issues common in patients with advanced heart failure such as substance abuse, family or caregiver support, relocation, noncompliance, and financial limitations. Active substance abuse in patients with an LVAD has been associated with increased mortality and overall poor outcomes.³⁴ Whereas past or remote use is not detrimental to survival and opens the possibility of earlier transplant listing.³⁵ Patient noncompliance, although not a risk for increased mortality, has been associated with increased hospital readmissions and post-LVAD nonadherence.³⁶ Many of these variables can raise concerns among mechanical circulatory support programs when evaluating patients for transplant listing and influence the duration of LVAD support; however, there is no defined right time period for resolution of these variables to move to transplant.

Lastly, a subset of patients may exhibit myocardial recovery after LVAD implantation. Independent predictors

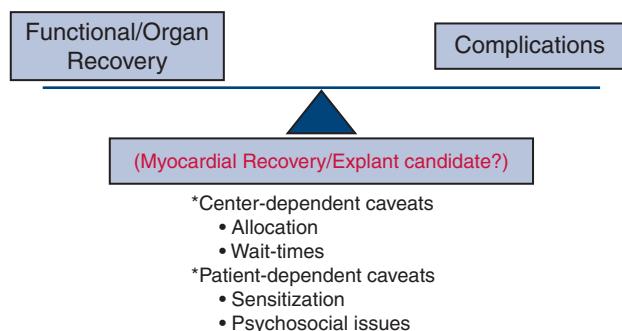


FIGURE 1. The decision process regarding optimal timing of left ventricular assist device (LVAD) support before transplantation weighs the benefits of functional, organ, and psychologic recovery from advanced heart failure versus the risks associated with the well-known adverse event profile of durable LVADs. Within this paradigm there are several other important elements in the formula, including the possibility of myocardial recovery, center-dependent factors such as waitlist management and allocation strategies, and patient-dependent factors such as sensitization and psychosocial issues.

of myocardial recovery include younger age, nonischemic etiology, normal renal function, and a shorter duration of heart failure. These same predictors make this subset of patients ideal for heart transplantation barring other contraindications.³⁷ Reverse remodeling with LVAD support combined with a standardized pharmacological regimen improved LVAD explantation with chronic heart failure.³⁸ Is there a duration of LVAD support that should be allotted to potential recovery patients before transplant listing? Using turn-down echocardiograms and right heart catheterizations, our group showed that early improvement in reverse remodeling and ventricular function occurred most often within the first 6 to 9 months after LVAD implant and was sustainable in a subset of patients.³⁹ This timeline for potential recovery corresponds with that of organ recovery, body recovery, modifying barriers to transplant, as well as limiting potential complications of LVAD.

CONCLUSIONS

Determining the optimal duration of LVAD support as BTT is fine balance between these good, bad, and ugly variables that also must consider region- and center-specific limitations (Figure 1). Implanting an LVAD is a major operation with significant morbidity and mortality. It is prudent to allow these patients to recover from surgery because the recovery process varies among patients and is often dictated by their preoperative condition. Transplanting a patient before recovery, and <30 days since LVAD implant, will lead to poor outcomes. The LVAD allows time for end-organ recovery, functional recovery, and modifiable contraindications to transplant to be addressed while the patient is supported. Because the duration of LVAD support increases, so will the possibility

of adverse events. Therefore, transplanting before 9 to 12 months (and as early as 1-3 months) post-LVAD could limit complications and improve posttransplant outcomes. Additionally, patients with the potential of myocardial recovery often declare themselves within a 6- to 9-month time period. Lastly, there are many psychosocial variables that are dynamic and affect duration of LVAD support before transplant. There is no defined or optimal time period for resolution of these variables that affect duration of support and eligibility for transplant listing.

A limitation to these recommendations is the caveat that no prospective data are currently available. Furthermore, the majority of registry and observational data available pertains mostly to HeartMate II (Abbott Cardiovascular, Abbott Park, Ill) devices. The improvement in complication profiles with fully magnetically levitated durable LVADs may alter the optimal duration of LVAD support in patients bridged to transplant. Moreover, with more patients transplanted at status I or II, fewer organs are actually available for durable LVAD patients in the status III or IV range, therefore necessitating a nonmodifiable increase in support duration. Hence, further research is warranted with the latest generation of durable LVADs and the recent changes to the US heart allocation system to better understand duration of support in the current era.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: heart transplant, left ventricular assist device