

# VAD therapy 20/20: moving beyond the myopic view of a nascent therapy

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The past five years have seen remarkable growth in the use of durable, continuous flow left ventricular assist devices (LVAD) with associated improvements in mortality, quality of life, functionality and end-organ function. To sustain the growth of this important therapy, the LVAD community must now address key issues focused around the costs of LVAD care, refined patient selection, and reducing complications associated with this therapy. In this perspective piece, we discuss many of these issues.

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The groundwork for today's durable mechanical circulatory support devices dates back to the 1960s. Over the ensuing decades, innovations in technology, enhanced patient selection, improvements in management and the development of multidisciplinary teams focused on mechanically assisted circulation have revolutionized this field. We are now in a unique era in the surgical management of heart failure characterized by the rapid adoption of durable, continuous flow left ventricular assist devices (LVAD).

In the United States alone, over 2,500 LVADs were implanted in adults in 2013 compared to 338 in 2007 (1). Most anticipate this number will continue to rise, resulting from the expansion of LVAD implant centers and further acceptance of the therapy by the general cardiovascular community. The rapid uptake of this technology was spurred by the Food and Drug Administration approval of the HeartMate II device (approved in 2008 for bridge-to-transplant therapy and in 2010 for destination therapy) and the HeartWare HVAD (approved in 2012 for bridge-to-transplant therapy). Beyond these regulatory changes, the real drivers of this paradigm shift are the efficacy and durability of contemporary devices in the face of limited treatment options for patients with advanced heart failure.

As with most innovations in medicine, the Pandora's Box of unanticipated consequences is now becoming

clearer. Current issues facing the LVAD community are focused around the costs of LVAD care, refined patient selection, and reducing complications associated with this therapy including bleeding, stroke, and infections. Only some of these issues were predictable. In the following, we consider key questions that must be addressed by the LVAD community in the next five years to sustain the growth of this important therapy.

## Reducing adverse events

While adverse event rates for continuous-flow LVADs are significantly reduced compared to older, pulsatile pumps, the rates remain unacceptably high. Within one year of device implantation, 70% of patients in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) have experienced a major adverse event, most commonly bleeding, infection, and/or arrhythmias (2). Data like this from registries and from clinical trials have provided common definitions and baseline event rates that will allow focused initiatives to reduce adverse events in LVAD patients.

Part of the solution to these problems will come from improved medical therapy and device innovations. For example, newly available oral anticoagulant therapies

for stroke prevention in patients with non-valvular atrial fibrillation have improved safety and efficacy compared to warfarin (3), but their use is currently limited in more high-risk settings such as mechanical heart valves (4). More data are needed to understand the use of novel oral anticoagulants in patients with LVADs and antidotes will be necessary prior to broad application in this patient cohort. Totally implantable power sources analogous to current implantable cardioverter defibrillators should also offer reduced infection risk compared to systems connected via percutaneous driveline and will likely have a positive impact on patient acceptance and quality of life.

In addition, engineers, physicians and surgeons must develop a better understanding of the biology involved with the blood–biomaterial interface to reduce the risk of thrombosis as well as the physiologic effects of continuous flow on mucosal surfaces. Our current understanding of the pathophysiology of LVAD thrombosis and the development of arteriovenous malformations in the gastrointestinal tract is quite limited (5,6). The delicate balance between bleeding and thrombosis challenges even the most experienced clinician and adherent patient.

Stroke also remains one of the most dreaded adverse events following LVAD implantation and is associated with significant morbidity and mortality. The annualized combined risk of hemorrhagic and ischemic stroke with continuous flow LVADs is 0.18 events per patient-year (7). Recovery from ischemic stroke is common whereas hemorrhagic stroke is frequently a fatal event in VAD-treated patients. More investigation is needed to understand the relative importance of device design, implantation technique and post-implant management on reducing stroke risk.

### **Expedited regulatory pathways**

The current nomenclature utilized in the United States to describe device implant strategy, e.g., bridge-to-transplant and destination therapy, are no longer clinically relevant and hinder the approval process for new devices. Data from INTERMACS highlight that device strategies change over time (8). For example, 44% of bridge-to-transplant patients still on support were no longer listed for transplantation 24 months following implant. Further, 15% of destination therapy patients had been listed by transplant or deemed eligible for transplant by 12 months. A more logical approach for the evaluation of new devices might be to test and approve devices for short- (six months) and long-term (24 months) support rather than a future therapy that is unpredictable (9). To date, the most commonly utilized

implant strategy in INTERMACS is “bridge-to-candidacy” (1), an implant strategy not currently recognized by the Food and Drug Administration or payers. The realities of contemporary heart failure care coupled with the beneficial effects of LVAD support on the heart failure phenotype and the potential for detrimental adverse events of mechanically assisted circulation are not well-aligned with predicting a patient’s ultimate “destination.” The call to change the regulatory pathways and LVAD “indications” dates back many years but remains unresolved (9,10).

### **Are the costs of mechanical circulatory support sustainable?**

Beyond safety and efficacy, the LVAD community must acknowledge cost effectiveness as an important metric in device evaluation. Current estimates suggest that there may be >250,000 LVAD-eligible patients in the United States that are not being treated (11), but it is not clear that society can afford to provide LVAD care for all of these patients. A recent analysis of cost data from patients included in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial and HeartMate II Destination Therapy trial determined that the incremental cost-effectiveness ratio for patients with a continuous-flow LVAD relative to those with a pulsatile device decreased 75% to \$190,184 per quality-adjusted life year (12). Although not meeting definitional cost-effectiveness metrics in the US, this represents a remarkable improvement and suggests that cost-effectiveness can be achieved with reduction in the long-term management costs of the therapy coupled with extension of life with high measured quality.

More data are needed to understand the true cost of VAD therapy as well as the cumulative costs of alternative advanced heart failure treatments. Expansion of multidisciplinary teams to comprehensively review all therapeutic choices for an individual patient is needed. As an example, patients with advanced heart failure and severely compromised hemodynamics are commonly upgraded to a bi-ventricular pacing system prior to LVAD referral. In many instances, this expensive intervention is ineffective at favorably altering the clinical course. The cardiovascular community is challenged by a lack of risk stratification tools to predict the advanced heart failure population likely to respond to the upgrade. Implant trends, expansion of the therapy into a less sick and other novel populations, device innovations, and totally implantable systems will predictably increase the overall cost of mechanically assisted circulation

and may force cost containment practices onto the LVAD community. The solutions to this problem are not straightforward. In addition to improved devices, enhanced patient selection with consideration of novel biomarkers and measures of frailty may assist the clinical decision-making.

### End-of-life and mechanical circulatory support

The inevitability of death has challenged VAD patients, their families and the clinical care team. However, clinical experience and research do not delineate the best methods to provide adequate end-of-life care for patients supported with an LVAD. There are multiple reasons why end-of-life care for patients on an LVAD is complex. Many LVAD-related adverse events challenge the clinician's ability to prognosticate. As an example, the life expectancy of a patient with recurrent gastrointestinal bleeding on an LVAD that is not a candidate for transplantation is poorly understood. Additionally, strategies to incorporate end-of-life decisions and LVAD management are not well integrated into routine post-VAD care pathways, nor is there a body of evidence to provide guidance. Finally, the issues surrounding withdrawing LVAD support require an individualized and a multidisciplinary approach. For example, the process of disconnecting an LVAD for a patient on hospice care requires training and an understanding of the device alarms. For many of these issues, there is an opportunity for multidisciplinary teams to organize and provide care to this growing patient population. The LVAD community must embrace this issue and support new educational and research opportunities to improve this practice.

### Conclusions

The past five years have seen remarkable growth in the use of LVADs and impressive reductions in mortality for patients with advanced heart failure treated with LVAD therapy. These favorable changes have been accompanied by improvements in quality of life, functionality and end-organ function. However, the therapy remains imperfect. Collaborative initiatives between clinicians focused on VAD care, clinical consultants, trialists, engineers and industry will be required to realize and fulfill the ultimate potential of LVAD therapy. The rapid expansion of patients supported on these devices for prolonged periods combined with standardized data collection in registries have provided invaluable tools to understand the residual challenges that will need to be addressed as mechanically assisted circulation moves into the mainstream of clinical care.

### Acknowledgements

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