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A Roadmap for Evaluating the Use and Value of Durable Ventricular Assist Device Therapy^{*#}

Sarah Ward, MD^{†1}; Qixing Liang, BS^{†1}; Francis D. Pagani, MD PhD¹; Min Zhang, PhD¹; Robert Kormos, MD²; Keith D. Aaronson, MD MS¹; Andrew Althouse, PhD²; Brahmajee K. Nallamothu, MD MPH¹,
Donald S. Likosky, PhD¹

¹University of Michigan, Ann Arbor, MI;

²University of Pittsburgh, Pittsburgh, PA

[†]Dr. Ward and Mr. Liang contributed equally to the development of this work.

Running Title: Use and value of LVAD Therapy

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Address for Correspondence:

Donald S. Likosky, PhD

Department of Cardiac Surgery

Frankel Cardiovascular Center

University of Michigan

1500 East Medical Center Drive

Ann Arbor, MI 48109

Office phone: 734-232-4216

Fax: 734-764-2255

Advanced heart failure (HF) impacts more than 250,000 Americans, and is characterized by severe limitations in survival, functional status and quality of life (1). Patients with advanced HF become refractory to guideline-directed medical therapy (GDMT) and a majority will die within 2-years of diagnosis in the absence of advanced surgical therapies (2, 3). Cardiac transplantation (TXP) is the most successful surgical therapy to extend survival and improve symptoms for selected patients (4). However, the majority of patients with advanced HF are not candidates for TXP given restrictive criteria imposed by a limited supply of donor hearts. Durable left ventricular assist devices (LVADs) offer patients with advanced HF an alternative therapeutic option as either a bridge to transplantation (BTT) or as destination therapy (DT).

Utilization of durable LVAD therapy has grown dramatically in the past decade and now exceeds TXP as the dominant surgical treatment modality for advanced HF refractory to GDMT (5). Rapid dissemination of durable LVAD therapy has occurred as a consequence of: 1) a growing population of eligible recipients; 2) improvement in durable LVAD technology that has increased its acceptance by providers and patients; and 3) significantly fewer supply limitations compared to TXP.

There is an urgent need to understand the determinants of LVAD utilization. The rapid and continuing growth of durable LVAD therapy for patients with advanced HF requires a timely understanding of potential determinants in order to inform targeted health care policies and ensure responsible and equitable dissemination of this life-prolonging technology. This review will focus on LVAD utilization in the adult population.

Potential Determinants of LVAD usage

We introduce a conceptual model (**FIGURE 1**) as a paradigm for how to evaluate the value of durable LVAD therapy. Our model integrates multiple factors determining LVAD use, including

technology innovation, insurer, market-, provider- and patient-level factors. Each determinant is inter-dependent and likely contributes to overall clinical outcomes and healthcare spending. As *value* is defined as a clinical outcome achieved per dollar spent, each of these determining factors should be considered when evaluating the value of durable LVAD therapy.

Improvements in Technology (Transformative and Iterative)

Improvements in durable LVAD technology represents the primary factor driving use, particularly following transformative changes in device design. This is evidenced by the rapid adoption of continuous flow pump technology (over that of pulsatile technology) following approval by the United States Food and Drug Administration (FDA) of the HeartMate II (Abbott Laboratories, Abbott Park, IL) for BTT indication in 2008 and for DT indication in 2010 (6, 7) (**FIGURE 2**). The Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS), a National Heart, Lung and Blood Institute-sponsored registry created to record the evolution of LVAD therapy and to assess and improve patient outcomes, now includes over 20,000 patients, with nearly 100% of these patients receiving continuous flow pumps in the most recent era (8). Utilization also increases with iterative improvements in LVAD technology that decrease the burden of device-related adverse events. Recent data from the MOMENTUM 3 trial have demonstrated a significant reduction in pump thrombosis risk for the HeartMate 3 (Abbott Laboratories, Abbott Park, IL) compared to the HeartMate II (9). As the risk of pump thrombosis has been a major barrier to greater durable LVAD adoption, particularly in those with less advanced stages of HF (10), the impending commercialization of the HeartMate 3 will likely lead to greater adoption, and perhaps broadening of clinical use among less ill patients. If iterative device-related improvements can be similarly achieved in reducing the risk of stroke (to approximately 5% or less per year), further significant expansion of this therapy will likely follow (10). Further iterative or transformative improvements in technology (e.g., fully implantable systems) are needed to decrease the rates of device-related infections, as infection rates remain high in both the recent ENDURANCE and MOMENTUM 3 clinical trials (9, 26).

Insurer Factors (Public vs Private)

Healthcare spending for the care and management of HF is staggering, and represents the second largest expenditure for the Centers for Medicare and Medicaid (CMS) (1). The CMS National Coverage Determination (NCD) continues to have significant impact on LVAD utilization, as exemplified by the inclusion of DT as an approved indication in 2002. Consequently, LVAD usage for DT increased from 14.7% of total LVAD volume in 2006-7 to 41.6% in 2013, even as the total annual LVAD implantation volume increased about 10 fold during the same period (11). Changes in indications for durable LVAD therapy could arise as a result of the MOMENTUM 3 trial design (12). The MOMENTUM 3 trial eliminated BTT and DT designations as requirements for study participation and assessed eligibility for enrollment based upon symptoms, treatment modalities and/or physiologic factors. Outcomes were then assessed based upon short (i.e., 6 months) and long term (i.e., 2 years) support. Future decisions by CMS as to whether BTT and DT designations will be required to meet requirements for reimbursement could potentially have a significant impact on LVAD usage. Although the NCD provides criteria for reimbursement coverage for durable LVAD therapy, the NCD is not uniformly applied by private or public (Medicaid) insurance plans resulting in less or more restrictive criteria influencing availability of coverage (13, 14). This practice likely creates inequities in access and use across geography and different patient subgroups.

Public insurance has been a means for a significant number of patients to gain access to advanced HF therapies. Compared to those with private insurance, patients requiring public insurance have been shown to have worse health care outcomes (15, 16). While studied in other areas of medicine, the role of insurance type on health outcomes has not been extensively studied within the durable LVAD population (15, 16). Recent data have documented greater access to heart transplantation for states adopting the Affordable Care Act, in part, attributed to increased access to Medicaid services (15). This benefit was demonstrated for African-Americans but not Hispanic or Caucasians populations (17). In reference to LVAD therapy, individual state-run Medicaid plans do not uniformly recognize DT indication for LVAD

therapy, creating a significant obstacle for economically disadvantaged patients relying on Medicaid services to receive DT (18). Whether access to durable LVAD therapy has been increased in states that have adopted the Affordable Care Act and expanded Medicaid access is unknown (19).

Market Factors

Market-level factors may have a greater influence in the dissemination of LVAD therapy as compared to TXP, given the significantly fewer barriers to initiating new LVAD programs. Given their expertise in delivery of other HF therapies (e.g., TXP), tertiary medical facilities have disproportionality been early adopters of LVAD therapy. A new era in durable LVAD therapy began following the FDA approval of the HeartMate II for BTT in 2008, with increased proportion of durable LVADs subsequently implanted at non-academic, non-TXP facilities (late adopters) (20). A recent analysis based upon INTERMACS data has documented equivalent outcomes between TXP and non-TXP centers, suggesting that factors beyond traditional center designations (e.g., TXP, non-TXP) may contribute to patient outcomes (20). Further work is warranted to: 1) characterize populations served by these emerging centers and determine whether emerging centers are addressing unique patient populations or improve access to LVAD therapy; 2) analyze the role of market forces in influencing the threshold for durable LVAD use and value, and (3) analyze the role of market forces in providing access and increased value to patients receiving durable LVAD therapy, especially among our most vulnerable populations.

Provider Factors

Provider factors at both the hospital- and physician-level should be taken into account. Hospital-level factors to consider include the availability of board certified HF specialists, annual procedure volume and the offering of TXP services at that center. Moreover, there are considerable direct and indirect costs that are associated with establishing a successful LVAD program within a hospital, that may serve as a barrier to the initiation or maintenance of a LVAD program.

Individual provider factors also play a key role in the utilization of LVAD therapy. Dissemination of medical knowledge is paramount as durable LVAD therapy requires a high degree of provider specialization and expertise. Medical expertise is required as there are many unique aspects to LVAD therapy, such as surgical implantation and device operation and management. Provider knowledge has been cited as a barrier to dissemination of other high technology medical therapies, such as the use of implantable cardiac defibrillators (21, 22). Provider knowledge may thus play an important role in patient referral patterns for LVAD therapy. An additional consideration is the regulatory requirements of individual providers. For example, individual LVAD providers are subject to less stringent requirements as compared to TXP. For a center to perform LVAD therapy for DT, the NCD requires that a surgeon implant only 10 devices over a 3 year period (23) despite evidence suggesting a higher volume threshold to optimize outcomes (31, 32). By comparison, the United Network of Organ Sharing (UNOS) requires that a surgeon to have performed at least 20 heart transplants as primary surgeon or first assistant during an approved thoracic surgical residency, 12-month heart transplant fellowship or within the first two years of clinical practice to qualify as surgical director of a heart transplant program (24). Additional training requirements for surgeons implanting LVADs are not specified in the NCD, despite more comprehensive recommendations from The Society of Thoracic Surgeons (25). Additionally, as other markets in cardiac surgery (i.e., coronary artery bypass grafting) continue to decline, there may be an increase in the number of surgeons who pursue additional training to meet the NCD requirements to provide durable LVAD therapy.

Patient Factors

The influence of patient factors is perhaps the most studied aspect of the determinants of LVAD use. Patient factors associated with limited access to LVAD therapy include age >65 years, female sex, black race, admission to a non-academic center and geographic region (26). Data from clinical trials and large patient registries (i.e., INTERMACS) have identified patient characteristics that influence outcomes following LVAD implantation that educate providers and patients as whether to pursue durable LVAD

therapy (5). Individual patient factors are intimately associated with each of the other determinants of LVAD utilization including technology, insurance coverage, market and provider factors in ways that have yet to be studied.

Why a Conceptual Model? Disparities as a Consequence of Non-Rational Use

A conceptual model may serve as a useful lens for evaluating real-world problems, and affording frameworks for informing health policies. As an example, we describe how our model may help to evaluate existing disparities in LVAD utilization.

To date, large public and private payers have not instituted policies to ensure equity in LVAD use. Although not well studied to date, disproportionate access to LVAD therapy has likely resulted, especially among vulnerable populations (e.g., age, sex, race, ethnicity, geography and socioeconomic status). For example, women represent one of the largest potential growth areas for LVAD therapy. While the prevalence of HF is relatively equal among men and women, more women die from HF every year (27, 28). Advances in technology have produced smaller pumps that theoretically eliminate size barrier as an impediment to smaller women receiving LVADs (29). Recent data has documented equivalent survival in patients with a small body size and supports LVAD use in this population (29). Despite these advances, women continue to receive fewer LVADs than men and remain underrepresented in clinical trials (9, 30). Women are also more likely to receive LVAD therapy later in the course of their disease, thus reducing the potential benefit of this therapy (31, 32). Non-rational LVAD use in conjunction with spending on this therapy may worsen already existing healthcare disparities. Thus, careful attention to the various determinants of LVAD utilization is needed in order to ensure equitable access for vulnerable populations.

Conclusion

LVAD use has significantly increased over the past decade and is now on the precipice of dramatic dissemination to a broader population of patients with advanced HF. We provide a conceptual

framework to serve as the foundation for: (1) evaluating this effective, yet expensive therapy, and (2) informing health policymakers. Transformative device technology, along with the NCD, are likely the most important factors contributing to greater LVAD use. While yet understudied, market-, provider- and patient-level factors likely influence LVAD use, although may lead to disproportionate use of this therapy, especially among our most vulnerable populations. Beyond LVAD use, we posit that our conceptual framework may also help guide the evaluation of similar costly but life-prolonging technologies (e.g., transcatheter aortic valve replacement), with the goal to develop policies that ensure their rationale use and dissemination.

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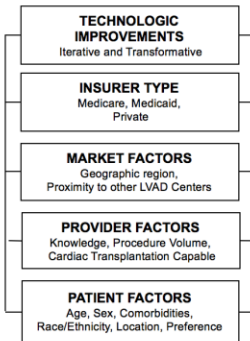
Figure 1 Legend

Our conceptual model integrates several factors determining LVAD use, including technology, insurer, market-, provider- and patient-level factors. Technologic improvements can be iterative, such as the incremental improvements to reduce the rate of adverse events, or transformative, as evidenced by the shift from pulsatile to continuous flow LVADs. Insurer type has enormous implications for affecting trends in LVAD utilization (e.g., the inclusion of DT as an indication in the CMS NCD led to a surge in VAD utilization beginning in 2008). Market-level factors account for proximity of alternate centers, which may influence thresholds for LVAD use depending on local or regional competition. Provider-level factors account for procedure volume as well as the offering of transplant services, as these may affect clinical outcomes. Patient-level factors include characteristics such as age, sex, race, comorbidities, geography and patient preference.

Figure 2 Legend

Key clinical trials for LVADs are represented as a function of annual LVAD volume (source INTERMACS registry). Of note, the corresponding year of each clinical trial represents the date of publication of major findings from the trial. While recent trials from 2017 (i.e., HeartWare HVAD ENDURANCE, ENDURANCE II, HeartMate 3 MOMENTUM) are displayed, procedural volume has yet to be published by INTERMACS for the years 2016 and 2017.

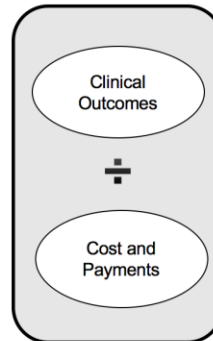
DETERMINANTS of LVAD Utilization



**Rates and
Patterns of
LVAD Therapy**



VALUE of LVAD Utilization



LVAD Volume in relation to Key Clinical Trials

