Innovation With Experience Using Implantable Left Ventricular Assist Devices

Deborah D. Ascheim, MD; Annetine C. Gelijns, PhD; Eric A. Rose, MD

The National Institutes of Health’s artificial heart program, initiated in 1964, has generated sustained and coordinated efforts by industry and academic engineers and investigators to create and develop mechanical circulatory support devices to prolong and enhance the lives of patients with advanced heart failure. These efforts have been supported by a combination of federal, industry, and philanthropic funding. By the mid 1990s, left ventricular assist devices (LVADs), the direct offspring of the program, received Food and Drug Administration marketing approval to support patients awaiting cardiac transplantation. Favorable results in this bridge to transplant population encouraged the design of the multicenter REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial to evaluate the efficacy and safety of long-term LVAD support in patients with chronic end-stage heart failure (stage D). Compared with optimal medical management (n=61), LVAD implantation (n=68) doubled the 1-year survival (from 25% to 51%) in a terminally ill, transplant-eligible population. Moreover, these patients had a significant improvement in quality of life and functional status compared with their medical counterparts. On the basis of these results, the Food and Drug Administration allowed initial commercialization of LVADs as a “destination therapy” (DT) in late 2002, and the Center for Medicare and Medicaid Services approved the therapy for coverage and reimbursement in 2003. In addition to proving the concept that LVADs could improve survival and quality of life of a defined severely ill population, REMATCH documented an array of limitations in device performance, durability, and clinical management. The concerns raised have resulted in limited adoption of DT clinically, although efforts are refocused toward developing improved selection and clinical management of device recipients and a new generation of devices.

Clinicians and policy makers alike have recognized that LVADs are highly complex therapeutic modalities. Each of the devices reflects highly sophisticated engineering, integrating moving components with blood-surface interaction and controllers designed to mimic physiological responses. The surgical implantation of LVADs is highly specialized, requiring expertise and collaboration on the part of the surgeon and the other members of the operative team, including anesthesiologists, perfusionists, and nurses. Similarly, the perioperative, intensive care, and long-term care requires collaborative expertise on the part of cardiologists, the surgical LVAD team, and intensivists. These factors are exacerbated by the severity of illness of patients with advanced heart failure. The complexities of providing LVAD therapy, compounded by the high costs of the intervention, stimulated policymakers to create an infrastructure to allow for careful dissemination of the therapy. LVAD centers were required to be accredited by the Center for Medicare and Medicaid Services before they could implant DT patients. At the same time, recognition of the sophisticated nature of the therapy raised questions about the effectiveness and safety of the device as it disseminated to a broader set of patients and providers.

One established method of evaluating clinical effectiveness is to evaluate the association between the volume of interventions and clinical outcomes. This relationship has been explored across multiple treatment interventions over the past 2 decades, with particular interest paid to its utility in understanding outcomes in high-risk surgical interventions. The fundamental motivation in evaluating factors such as volume, which may impact clinical outcomes, is to stimulate quality improvement efforts that ultimately translate into better outcomes.

In this issue of Circulation: Heart Failure, Lietz et al. take the first step in addressing this important issue by evaluating the relationship between center volume and clinical outcomes in the use of the HeartMate XVE for DT between 1998 and 2005. In the first 3 years following Food and Drug Administration approval, only some 300 DT patients were implanted with an LVAD in 63 centers. Lietz et al’s research suggests that there is a learning curve within centers for DT LVAD therapy. Moreover, the authors found that higher center volume was associated with clinical outcomes, although when adjusted for severity of illness, DT center volume may not be an independent predictor of outcome. The authors acknowledge that rigorous risk adjustment models are critical in conducting volume-outcome studies. There is, however, no adequately validated risk score for this patient population. Previously derived heart failure scores such as the Heart Failure Survival Score proved an insensitive predictor when applied to the REMATCH dataset, and predictive rigor of the Seattle Heart Failure Score in a population with this severity of illness has yet to be corroborated. Lietz et al used a DT Risk Score they had previously

Article see p 3

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From the Department of Health Policy (D.D.A., A.C.G., E.A.R.) and the Cardiovascular Institute (D.D.A., E.A.R.) of Mount Sinai School of Medicine, NY.

Correspondence to Deborah D. Ascheim, MD, Department of Health Policy, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1077, New York, NY 10029. E-mail deborah.ascheim@mssm.edu

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derived on a subset of the patients analyzed in the current study.¹⁸

One of the most intriguing implications of their findings is that institutional experience is an important factor in shaping the outcomes of LVAD therapy. This raises important questions as to what other factors, such as patient selection, process of care, and device issues, may contribute to defining the institutional experience. The authors highlight the likely contribution of patient selection to outcomes; a relationship that seems to have already evolved in this young field. The patient population enrolled in the REMATCH trial, at the inception of the DT, was unprecedented in heart failure clinical trials with respect to their severity of illness. Despite iterative modifications to the patient selection criteria over the course of the trial, the disease severity of those enrolled remained profound. The post-REMATCH era, however, has seen a gradual shift in patient selection with improving outcomes over the same period of time.⁸ Also intriguing in their current article is the finding that more experienced centers tended to implant patients with lower risk scores. This implies an evolution in know-how with regard to selection of DT candidates, and awareness among clinicians of the importance of considering potential predictors of outcome in the selection of patients for this therapeutic intervention.

The clinical management of DT patients is another factor that undoubtedly contributes to defining institutional experience, and the complex nature of this interaction in the DT population is further complicated by ongoing changes in management. Both postoperative and long-term management of these patients continues to evolve, particularly with respect to the prevention and management of several key adverse events associated with LVADs including infection, bleeding, and clotting. Despite progress in management, infection remains the most important cause of death in LVAD patients and serves as a reminder that more rigorous evaluations of processes of care, and their relationship to outcomes, are crucial.

Understanding the outcomes of LVAD therapy as it is applied more broadly in clinical practice, and the factors that contribute to successful and poor outcomes, is critical. The National Institutes of Health has supported the collaboration of stakeholders in the field to create a unique infrastructure to coordinate, federally supported convergence of premarket trials, and postmarketing outcomes analyses is unique to this extremely dynamic field. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) provides a robust dataset with which to validate risk-adjustment models.

Finally, mechanically circulatory support is a highly innovative field. The HeartMate XVE, the device investigated in REMATCH, has undergone numerous changes since it was first introduced in the market, and new generations of axial and centrifugal flow LVADs have entered clinical trials for bridge to transplant and DT. The expectation that the newer LVADs will have improved device reliability and require fewer device replacements seems to be borne out by current events. In December 2008, the field of DT therapy reached another milestone with the announcement that the HeartMate II, axial flow LVAD, is superior to the HeartMate XVE for DT based on the interim analysis of the ongoing clinical trial. The expectation is that this device will be approved by the Food and Drug Administration in the following year and will stimulate more rapid dissemination of DT therapy. Therefore, this first volume-outcomes study is a snapshot of experience with a device that will soon likely be outdated, but only because of the learning to date. Ongoing critical evaluation of this complex learning process is essential for continued improvement in LVAD technology and its therapeutic applications.

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