

# The Implantable Left Ventricular Assist Device: A Bridge to a Destination

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## Abstract

The Implantable Left Ventricular Assist Device (LVAD) has been in clinical use for several decades, serving originally as a therapy for bridging patients to heart transplantation (BTT). For the past fifteen years, the implantable LVAD has also served as a permanent device in patients who are not eligible for cardiac transplantation—Destination Therapy (DT). Although early results were markedly superior to optimal medical management (OMM), device durability was limited. In response, improvements in patient selection and pump design have translated into improved outcomes. As such, a broader acceptance of LVAD therapy for end-stage heart failure has been observed.

**Keywords:** Left ventricular assist device; Destination therapy

## Introduction

The desire to replace or assist the failing heart has been a challenge for more than half a century. The reason for this quest is obvious: the magnitude of heart failure is of epidemic proportions and there simply are not enough human hearts available for transplantation. As such, national organizations as well as commercial industries have invested enormous resources—financial and otherwise—to address the growing need for a therapy that for end-stage heart failure, who are not transplant eligible. The areas of investigation in this regard fell into two camps: total heart replacement versus partial heart assist.

The first use of a Total Artificial Heart (TAH) occurred in 1969 by Dr. Denton Cooley [1]. Although the patient survived the surgery, it became very apparent that there were considerable biomechanical and biological hurdles to overcome—anticoagulation, biocompatible blood-contacting surfaces, durability, infection, and so forth. Almost a decade later, in 1978, an implantable left ventricular assist device (LVAD) was used by Dr. Frazier as a Bridge-To-Transplant (BTT) for the first time [2]. The idea of a pump assist—as opposed to total heart replacement—was certainly advantageous at several levels: less parts to break down and the human heart is still in place as a “backup” in case of pump failure. In the 1980’s, the Jarvik-7™ TAH was introduced by Dr. DeVries as a permanent therapy in Barney Clark [3]. Although initial excitement was broadcasted worldwide, the frequent thrombo-embolic and hemorrhagic complications during this period lead to a serious setback in this technology. In the 1990’s, the Heartmate LVAD™ made its debut, receiving FDA approval in its pneumatic and electric versions as a BTT device [4,5]. The uniqueness of this technology was based upon a bioengineering breakthrough in the form of a textured lining to the bloodpump which eliminated the need for anticoagulation. Finally, in terms of a permanent therapy for patients ineligible for transplant, two landmark trials were undertaken around the turn of the millenium: the AbioCor™ totally implantable pulsatile electric artificial heart trial and the REMATCH Trial [6,7].

While the totally implantable electric TAH still requires further refinements and investigative analyses, the implantable LVAD has enjoyed on-going success as both a bridge and alternative to cardiac transplantation. Second generation systems are now commonly used and third generation units are embarking in clinical trials. The purpose of this report is to describe the current state of affairs related to the use of the implantable LVAD as a permanent therapy in patients suffering from end-stage heart failure.

## The First Generation Implantable LVADs

In general, the implantable LVAD is a unit that serves to assist the failing left ventricle. The typical configuration consists of an inflow cannula that drains blood from the apex of the left ventricle into the LVAD. The LVAD itself resides in a subcutaneous “pocket”—this pocket is usually in the upper abdomen under the rectus abdominus muscle in the pre-peritoneal space. The LVAD receives the blood and propels it forward into the outflow cannula that attaches to the ascending aorta. The LVAD is powered by an electric cable—“the driveline”—which exits the skin in the subcostal region and attaches to a power source. The prototype first-generation implantable LVADs were the Heartmate I (Thoratec Corporation, Pleasanton, CA) and the Novacor LVAS (WorldHeart, Inc., Salt Lake City, UT). Both units were relatively big and bulky, their durability usually less than 2 years. While the Novacor™ required anticoagulation and antiplatelet therapy, the Heartmate I™ did not. The Heartmate I™ contained a layer of sintered titanium on the interior surface of the blood pump allowing blood elements to form a neo-intima in a short period of time; once the neo-intima formed, the blood streaming through the LVAD “thought” it was in contact with itself and did not perceive the device as a foreign body. This milieu translated into an environment in which anticoagulation (e.g. coumadin) was not necessary. Both pumps were pulsatile in nature, thereby mimicking the physiology of the circulation. Although not timed to the cardiac cycle, the devices were capable of delivering 5-7 liters per minute of blood flow. And because they were not “dependent” on the cardiac cycle, they continued to pump during periods of atrial as well as ventricular dysrhythmias. Although initially designed as a BTT device, these first generation electric pumps were the “workhorses” of the FDA trials for BTT and DT. Specifically, the FDA approved the Heartmate I™ for BTT in 1998 and DT in 2002. The Heartmate I™ was also the device used during the REMATCH Trial [8]

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at which time the original model (VE™) was utilized. Upgrades in this system from the VE™ to the XVE™ model demonstrated a significant decrease in serious mechanical failures. A retrospective review of 1865 Heartmate I (1458 VE™, 407 XVE™) patients by Dowling et al in 2004 showed an 82% 1 year freedom from device malfunction [9]. A similar trial was undertaken with the Novacor™ system called INTrEPID (Investigation of Nontransplant-Eligible Patients Who Are Inotrope Dependent)—like REMATCH, LVAD survival was superior to optimal medical therapy at one year (27% vs 11%) [10] (Figure 1).

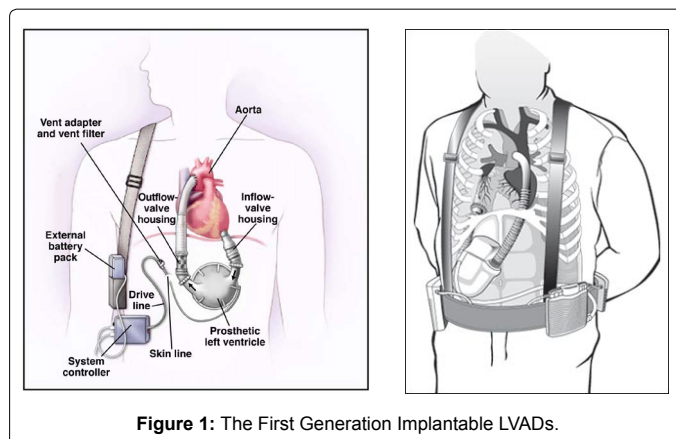
### The Second Generation Implantable LVADs

Several Second Generation LVADs were developed to address two main areas: size reduction and durability. The Heartmate II™, the Jarvik 2000™ (JarvikHeart, Inc., New York, NY), and the DeBakey HeartAssist5™ (Micromed Cardiovascular, Inc., Houston, TX) LVAD systems are revolutionary devices that changed the landscape of LVAD technology. As opposed to their predecessors, these are small axial flow pumps that are designed to deliver blood in a continuous flow fashion. As such, the circulation becomes non-pulsatile, except for some minor changes in the blood pressure related to the fact that the heart is still pumping. Patients implanted with these units are unique in the sense that they function with a *mean* blood pressure typically in the range of 60-80 mmHg. Blood pressure measurements are usually obtained with a blood pressure cuff utilizing a Doppler probe. Initial discussions about this type of circulation in the human were debated because mammalian physiology was thought to be exclusively dependent upon the presence of pulsatile flow. However, animal and clinical trials proved that this was not the case. Continuous flow devices—broadly labeled as *Rotary Pumps*—were well tolerated in chronic heart failure (CHF) patients, perhaps because CHF pathology is associated with a lower than normal blood pressure with reduced pulsatility by virtue of the disease state. Regardless of the explanation, axial flow LVADs performed admirably in both BTT and DT situations, the Heartmate II™ receiving FDA-approval for BTT in 2008 and for DT in 2010 respectively [11,12]. The obvious advantage of axial flow LVADs is its small size, allowing for a broader application in a variety of patients, including adolescents and children. More importantly, the axial flow design has translated into a marked improvement in durability. Based on clinical trial and device tracking data as of May 2013, there have been over 14,000 Heartmate II™ implants worldwide with a growing number of patients supported for more than two years (Table 1 and Figure 2) [13].

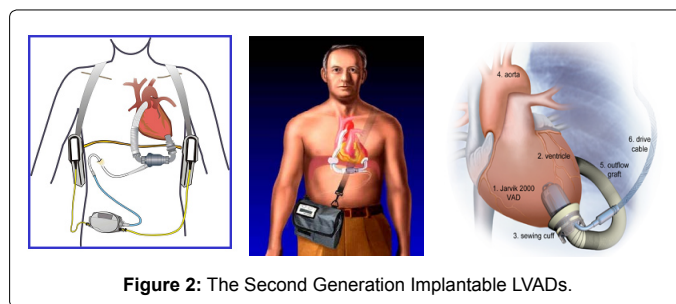
However, despite the enthusiasm regarding a broader patient application and device reliability, a side effect of the device and/or its manner of flow surfaced in the form of gastrointestinal (GI) tract bleeding. The axial flow LVADs requires formal anticoagulation with coumadin and anti-platelet therapy (i.e. aspirin, dipyridamole). Initial protocols suggested a target INR of approximately 2.5. (range 2.0–3.0). However, due to the presence of significant GI bleeding—as well as other sources including potentially life-threatening intra-cranial hemorrhage and less lethal epistaxis—some centers have modified the anticoagulation protocol to lower limits (e.g. INR 1.8 – 2.2) [14]. The hope was that the bleeding problems would disappear—they did not.

• supported ≥ 2 years: <b>1,908</b>
• Patients supported ≥ 3 years: <b>933</b>
• Patients supported ≥ 4 years: <b>398</b>
• Patients supported ≥ 5 years: <b>154</b>
• Patients supported ≥ 6 years: <b>54</b>
• Patients supported ≥ 7 years: <b>18</b>

**Table 1:** Number of LVAD patients on support for > 2 years.



**Figure 1:** The First Generation Implantable LVADs.



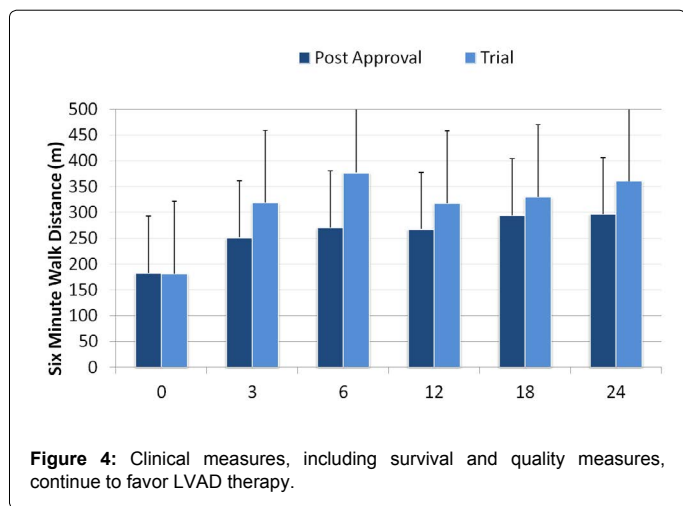
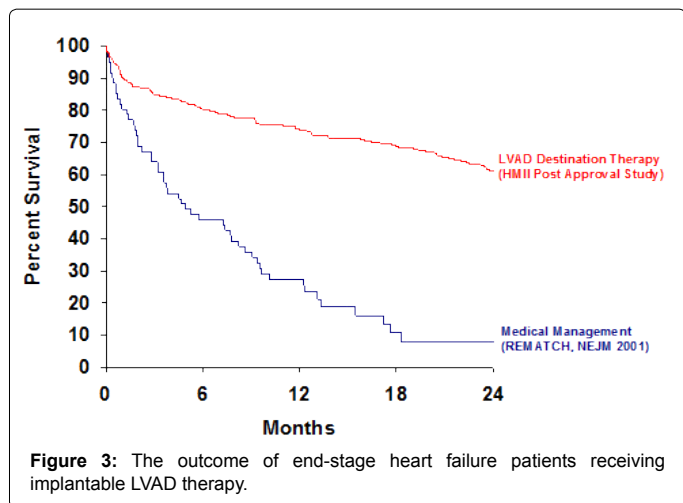
**Figure 2:** The Second Generation Implantable LVADs.

The precise mechanism for this adverse condition remains elusive, but may be related to von Willibrand Factor (vWF) and the development of acquired Von Willibrand disease [15]. However, other mechanisms may be responsible and the treatment is still enigmatic [16].

Despite the presence of adverse events, the outcome of end-stage heart failure patients receiving implantable LVAD therapy remains superior to optimal maximal medical therapy (OMM) (Figure 3) [16]. Clinical measures, including survival and quality measures, continue to favor LVAD therapy with results that continue to trend in a favorable direction [17] (Figure 4). Yet, if a truly long-term device is to challenge the “durability” of a heart transplant—which currently equates to a 50% 10-year survival—then even more novel technology is required.

### The Third Generation Implantable LVADs

The idea of a mechanical device that may address the epidemic of heart failure is one of the “holy grails” of medicine. In the United States alone, the prevalence of heart failure exceeds 5.7 million, with almost 600,000 new cases diagnosed each year. The annual cost exceeds 34 billion dollars and the five year survival is approximately 50% [18]. These staggering and sobering statistics have forced clinicians to seek solutions beyond medications for the most advanced stages (i.e. NYHA Class IV and Stage D) since heart transplantation can only provide therapy to a fraction (e.g. 2000 patients) of the overwhelming demand. Furthermore, the ever increasing longevity of the population will result in more end-stage heart failure patients being ineligible for a natural organ simply on the basis of an age cutoff. As such, implantable LVAD technology is currently at the stage where devices are virtually indestructible. The third generation LVADs is designed so that the only moving part—a centrifugal rotor—is suspended in a magnetic field thereby eliminating any “wear and tear”. The basic configuration is the same as the first and second generation LVADs—that is, inflow from the left ventricle and outflow to the aorta—however, the LVAD itself



remains small and without contacting surfaces—a bearing less design (Figure 5).

Among the first Third-Generation LVAD to be tested clinically is the Heartware HVAD™ (HeartWare, Inc, Framingham, MA). This miniature implantable LVAD is designed to be placed intrapericardially, thereby eliminating the need for an “LVAD pocket”. The ADVANCE Trial, a multi-institutional study examining the HVAD™ compared to another commercially available LVAD as a BTT demonstrated non-inferiority with a successful outcome in 90.7% of the investigational pumps [19].

Similarly, the Heartmate III™ is designed in a magnetically-levitated field and has been undergoing design changes for over a decade. The initial *in vitro* description and laboratory animal experiments of this device were encouraging [20]. Further testing and refinements in design may ultimately include an induced pulse mode, a transcutaneous energy transfer (TET) configuration, and a modular connection for upgrading without replacing the LVAD [21]. A clinical trial for the Heartmate III™ is forthcoming.

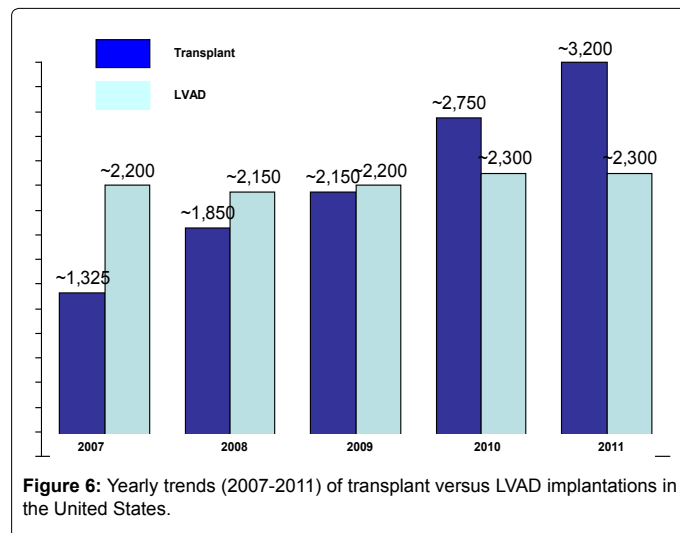
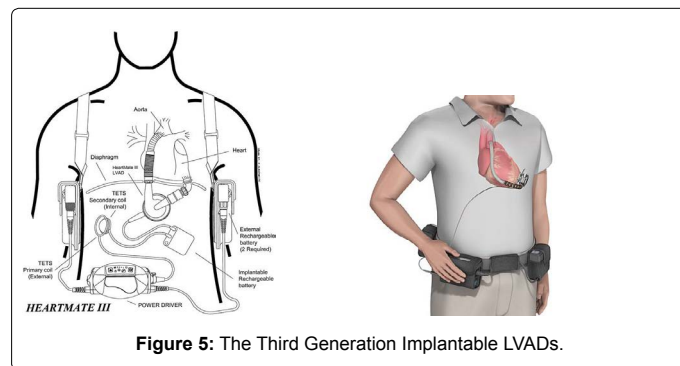
### DT-LVAD Eligibility Criteria

In the United States, the Centers for Medicare and Medicaid Services (CMS) govern eligibility for DT-LVAD implantation from a governmental insurance point of view. These guidelines (Table 2)

have evolved, and will continue to evolve, as the experience grows and allocation of public spending is defined and re-defined [22]. The clinical criteria are much broader and include a variety of conditions that advanced heart failure specialists are familiar with (e.g. all the cardiomyopathies, intractable arrhythmia, and acute states that fail to reverse.) Furthermore, the “insurance criteria”—as important as it is for payment coverage—does not address the risk stratification of the eligible patients, a factor that weighs heavily on outcomes including length of stay (LOS) and complexity of care. For example, the LOS can vary from weeks to months, depending upon pre-operative status of the patients and post-operative events. The costs associated with these variables are substantial and can range from several hundred thousand to several million dollars per patient. In one study, the average total hospital cost per patient for the pre-LVAD, LVAD and post-LVAD was \$585, 513 (range \$132,640-\$1,247,299) [23]. In addition, there are occasions where patients are transitioned from short-term external LVADs to long-term implantable LVADs as a permanent therapy in patients who are not transplant eligible—an expense that can double the aforementioned costs. As such, there is public policy makers who would debate the cost-effectiveness of this therapy, arguing that the money spent on this advanced (and expensive) treatment is better used elsewhere [24]. Clearly, the bridge to a destination is complicated and deserving of both clinical and financial refinements (Figure 6).

### Conclusion

In summary, the field of mechanical circulatory support continues to evolve and improve to the extent that a worldwide registry—



a.	New York Heart Association (NYHA) Class IV Heart Failure
b.	Not eligible for heart transplantation
c.	Have failed to respond to optimal medical management (including beta-blockers, and ACE inhibitors if tolerated) for at least 45 of the last 60 days, or have been balloon pump dependent for 7 days, or IV inotrope dependent for 14 days; and,
d.	Have a left ventricular ejection fraction (LVEF) < 25%; and,
e.	Have demonstrated functional limitation with a peak oxygen consumption of $\leq 14$ ml/kg/min unless balloon pump or inotrope dependent or physically unable to perform the test.

**Table 2:** Centers for Medicare & Medicaid Services (CMS) Guidelines for Destination Therapy LVAD Implantation.

INTERMACS—is now firmly established to record implant and outcome data, its first report published in 2008 [25]. Furthermore, a Destination Therapy Risk Score (DTRS) has helped define patients preoperatively in an attempt to improve some conditions that are associated with adverse events [26]. The efforts by industry as well as by the physicians and surgeons have made LVAD therapy for end-stage heart failure an excellent option, something to be considered when traditional therapies fail to control the disease.

### Conflict of Interest Statement

The authors declare that there is no conflict of interest regarding the publication of this article.

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