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CURRENT TOPICS REVIEW ARTICLE

Destination therapy: the new gold standard treatment for heart failure patients with left ventricular assist devices

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Abstract Heart failure continues to be a growing health problem, eluding large-scale improvement and treatment. Cardiac transplantation has been the gold standard treatment with high post-transplant survival rates and relatively good quality of life. However, there has been an extreme shortage of organ donations, limiting transplants to only a very small portion of patients with the condition. This led to a growing interest in alternative options for the increasing population of patients who are waitlisted or ineligible for transplantation. In recent years, ventricular assist device (VAD) technologies have advanced from pulsatile blood pumps to continuous-flow pumps that have demonstrated unprecedented post-implantation survival rates. The HeartMate II, the only commercially available, continuous flow left ventricular assist device (LVAD) in the United States and Europe, has been implanted in over 10,000 patients worldwide, setting a benchmark for biomedical modalities of advanced heart failure treatment. Thanks to the successes of contemporary LVADs, patients are able to enjoy a better lifestyle, with a significantly prolonged life span and the ability to regularly partake in physical activities. In this new biomedical generation, the usage of LVADs has begun to expand towards the treatment for a wider range of heart conditions, including earlier stages of heart failure. In fact, LVAD implantations have surpassed the number of transplants taken place annually. An increasing number of patients are considering the permanent, circulatory support with an LVAD, namely destination therapy, as a promising option for treating heart failure.

Keywords Left ventricular assist device · Destination therapy · Heart transplantation · Bridge-to-transplantation · Heart failure

Introduction

Until the recent milestone achieved by HeartMate II (Thoratec Corp., Pleasanton, CA, USA), the use of ventricular assist devices (VAD) for destination therapy remained relatively rare, despite international efforts directed towards the advancement of VAD technologies. Instead, bridge-to-transplantation (BTT) and bridge-to-candidacy were increasingly performed by VADs to increase the chance of acquiring a new heart. With assist devices like HeartMate II on the market, however, the need for patients to be bridged to heart transplantation may begin to diminish. Destination therapy—the lifelong support for advanced heart failure (AHF) patients—is becoming an increasingly promising option to consider.

This review describes how the left ventricular assist device is becoming a standard biomedical modality and is a viable option to consider over heart transplantation. These devices have demonstrated great therapeutic success that offers AHF patients a new lifestyle with a good quality of life.

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The REMATCH and HeartMate II destination therapy trial

For decades, the improvement of the quality of life (QOL) of AHF patients with mechanical circulatory support has been one of the major underlying goals of biomedical research. Instigated by the rise in prevalence of cardiovascular disorder throughout the world, efforts have been directed towards innovating support devices that encounter minimal numbers of adverse events to provide a good QOL that AHF patients otherwise have almost no chance of attaining without a new heart.

The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) was conducted from May 1998 to July 2001 to evaluate the reliability of left ventricular assist devices (LVAD) as mechanical circulatory support for patients who are ineligible for heart transplantation. Patients were evenly randomized between optimal medical management and LVAD therapy with HeartMate VE and were closely monitored for signs of improvement. Kaplan–Meier statistics estimated a 1-year survival rate of 52 % in the device group and 25 % in the medical-therapy group with a two-year survival rate of 23 and 8 %, respectively. This demonstrated superiority of VAD performance over traditional medical treatment [1].

Similarly, the HeartMate II destination therapy pivotal clinical trial, during which devices were implanted between March 2005 and May 2007, assessed the use of HeartMate II for permanent support in patients ineligible for transplantation. Patients were randomized between HeartMate II and XVE by a 2:1 ratio. Results showed a 2-year survival rate of 58 % for HeartMate II, which significantly surpassed the performance of its pulsatile predecessors, HeartMate VE and HeartMate XVE (Fig. 1) [2]. This marked a major milestone for developments in mechanical circulatory support and set a benchmark for destination therapy trials. Thoratec Inc., currently a world leader in pump technology, announced in April 2012 that HeartMate II had been implanted in over 10,000 patients all over the world and is becoming a standard therapeutic choice, as patients enjoy an excellent QOL with unimpeded mobility and minimal limitations to physical activities.

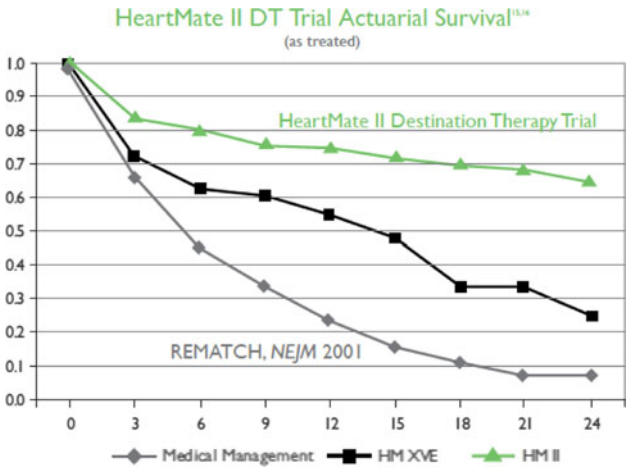

Fig. 1 Kaplan–Meier analysis of survival in groups that received left ventricular assist devices (LVAD) and optimal medical management (OMM). The LVAD (HeartMate XVE) group had a 1-year survival rate of 52 %, while the OMM group had a rate of 25 %; the 2-year survival rates were 30.9 and 8 %, respectively. [20] The 2-year survival rate of patients with HeartMate II was 58 % [2]

LVAD therapy in Japan

Until 2009, the Organ Transplant Law proved to be a large barrier between patients and organs, stringently restricting the procurement of organs to those who have garnered familial permission. Furthermore, due to a cultural opposition against cadaveric donors, the waiting period for donated hearts exceeded 800 days, which necessitated the government to approve reliable devices that would support patients for this length of time. Government approval of LVADs for the Japanese market, however, had proven to be dilatory by nature [3]. In fact, the Toyobo VAD was the only device in the market until 2009, excluding the short existence of Novacor. Although there was a great urgency for a reliable bridge-to-transplantation device to be on the market, con-temporary implantable VADs only became available for patients in 2009.

BTT therapy was introduced in the United States in 1992 starting with Abiomed 5000 (ABIOMED, Inc., Danvers, MA). The United States then approved the HeartMate VE for destination therapy in 2002 after its dependability as permanent support was demonstrated in the REMATCH trial. On the other hand, the Japanese Ministry of Health, Labor, and Welfare (MHLW) had not approved for the commercialization of a contemporary implantable BTT device until 2009, excluding Novacor, which was approved and soon pulled off the market due to fiscal burdens in 2006. This left patients with a small range of options, including the Toyobo (currently Nipro) VAD, which had been designed almost 30 years ago as a pulsatile, paracorporeal device.

Clinical trials for BTT indication in Japan with HeartMate VE were finally initialized in 2001, almost 5 years after it was approved for BTT in the United States. Between November 2001 and June 2003, five patients with New York Heart Association (NYHA) class IV end-stage heart failure who were supported with HeartMate VE were evaluated for improvement during the bridging period. All five patients improved to NYHA class I or II, with a 1-year survival rate of 100 %. This prospective, multicenter trial

indicated that the HeartMate VE could effectively bridge patients to heart transplantation in Japan [4].

Between 2009 and 2010, an auspicious period for the improvement of cardiac therapy in Japan, the parliament voted to revise the Organ Transplant Law to increase the number of donor organs in the registry. Concurrently, the HeartMate XVE (Thoratec), DuraHeart (TerumoHeart, Ann Arbor, MI, USA), and EVAHEART (Sun Medical, Nagano, Japan) LVADs were approved for BTT. The Jarvik 2000 and HeartMate II are currently pending approval [5]. The first successful case involving DuraHeart for BTT in Japan was reported in 2010, with the bridging period spanning 437 days [6].

DuraHeart is the first, magnetically driven, centrifugal LVAD that eliminates contact between the impeller and the driving mechanism, consequently reducing the likelihood of thrombus and hemolysis. In 2011, it was reported that eight Japanese patients, who were supported by the Toyobo LVAD, switched to DuraHeart via bridge-to-bridge therapy. The apical cuff was not replaced because its size was equivalent to that of DuraHeart, eliminating potential complications that may arise from cuff replacement and reducing operation time. All exchanges were performed safely, but three patients had complications due to infections observed prior to the exchange on the Toyobo VAD cannulation site [7]. This suggests that patients currently supported by Toyobo VAD in Japan may consider the option of switching to DuraHeart—effectively undergoing bridge-to-bridge therapy—to enjoy the advantages of a newer LVAD model.

The status of cardiac transplantation

Cardiac transplantation has been the gold standard treatment for advanced heart failure patients who are not amenable to other treatments, such as valvular surgery, coronary artery bypass grafting, or LV volume reduction therapy. It has been associated with the greatest survival benefits for patients in all demographics that are eligible for the operation. Unfortunately, there are not enough donors available for every AHF patient, and patients may be ineligible for transplantation if they are over 60 years old, have severe irreversible pulmonary hypertension, or other life-threatening conditions that would severely affect the life expectancy regardless of transplantation. The average waiting period for a donor in the United States is approximately 6 months, allowing patients to be bridged to transplantation in a rather short period of time with a VAD [8], while the waiting period in Japan can exceed 2 years.

There have been multiple studies on the QOL of post-transplant patients in the United States, based on both short-term and long-term data, which date as far back as 1993. In Japan, however, there have been no studies that account for the QOL of these patients. Surveys that compare post-LVAD implant QOL and post-heart transplant QOL are warranted. They will have important implications for the viability of permanent LVAD support.

The evolution of LVAD technologies

As exemplified by the REMATCH and HeartMate II destination therapy trials, patients supported by recent LVADs have had unprecedented survival rates. The use of contemporary devices has increasingly become an attractive choice for AHF patients with contraindications to transplantations that can be gradually remedied. This "bridge-to-candidacy" strategy can eventually allow patients to be put on the transplant list.

Recently, however, prospects of LVADs as a viable alternative to heart transplantation are becoming more realistic, as the miniaturization and increased durability of these devices have rendered them safer and more effective (Fig. 2). Second-generation LVADs have distinguished themselves from their predecessors with the advent of the rotary blood pump, allowing blood to be channeled with a continuous flow. The compact design supersedes the previously bulky model and eliminates the reservoir chamber and valves that effectively removes many potential sites of infection (Fig. 3). The lack of a pusher plate or valves also decreases the chance for mechanical failure [9]. HeartMate II is currently the most successful second-generation

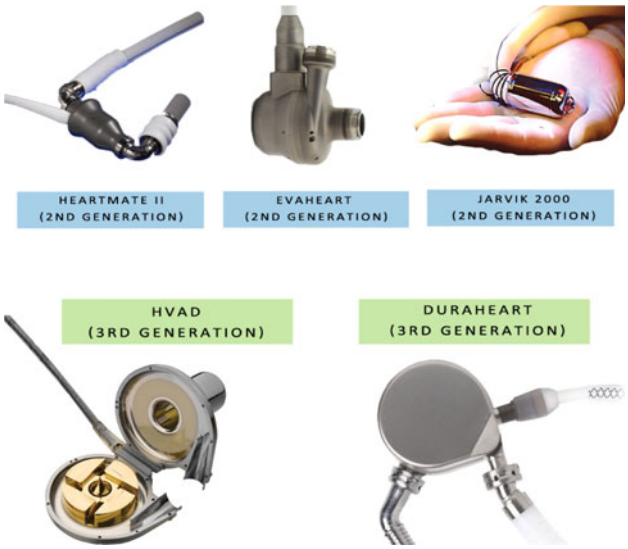

Fig. 2 Second and third generation left ventricular assist devices. *Top left* HeartMate II by Thoratec Corp, *Top middle* EVAHEART by Sun Medical, *Top right* Jarvik 2000 by Jarvik Heart Inc., *Bottom left* HVAD by HeartWare International Inc., *Bottom right* DuraHeart by TerumoHeart

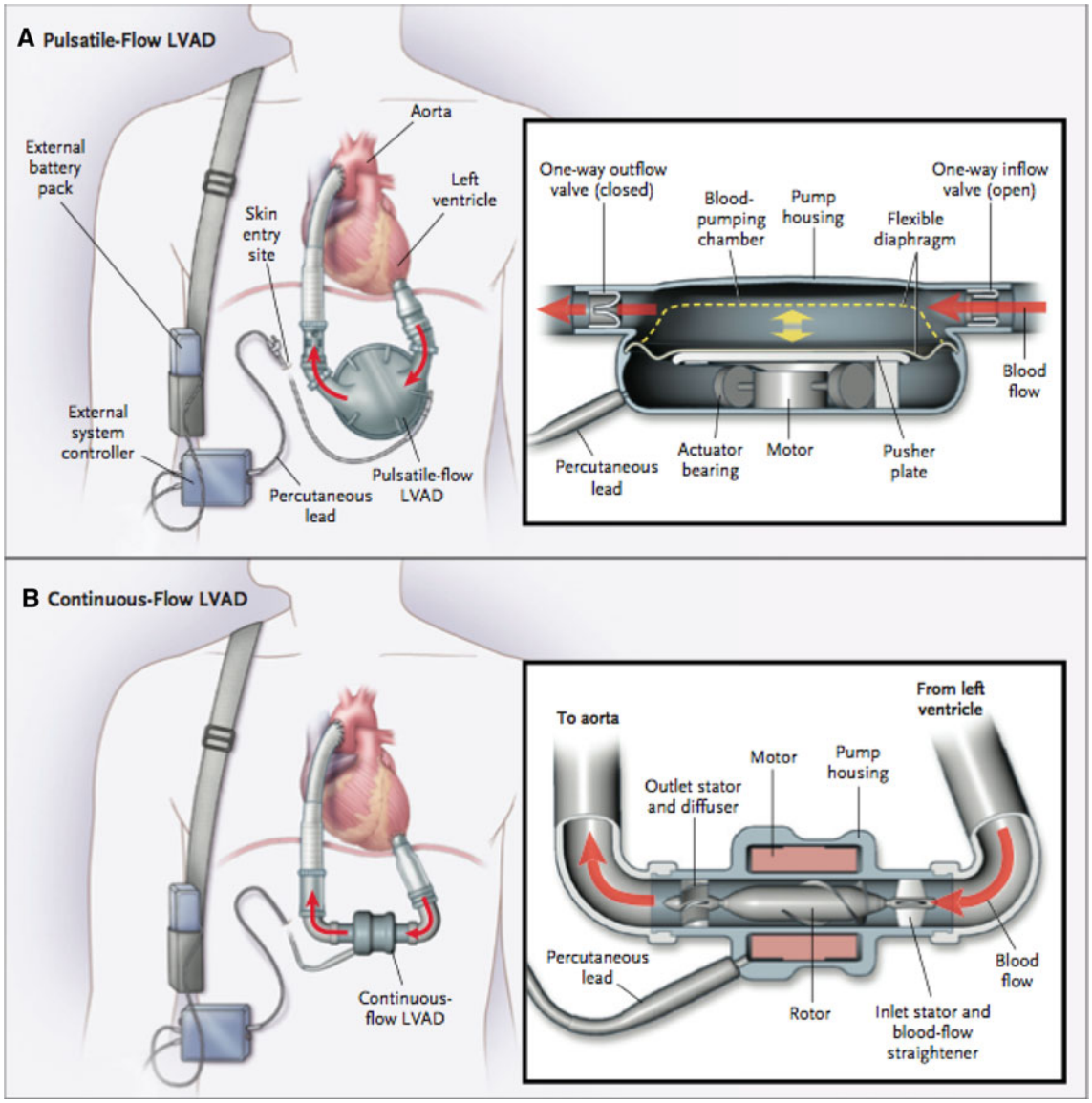

Fig. 3 **a** The first-generation design of a pulsatile flow LVAD; **b** the second-generation design of an axial, continuous-flow LVAD [2]

LVAD for BTT and destination therapy and is the only commercially available, continuous flow LVAD in the United States and Europe. While post-transplantation data indicates similar survival rates between those implanted with second-generation and first-generation devices, the group implanted with second-generation devices experienced lower early rejection rates and infection rates during VAD therapy [10, 11]. The interagency registry for mechanically assisted circulatory support (INTERMACS) reported that the number of implanted, continuous-flow LVADs significantly exceeds that of pulsatile-flow devices, according to data collected between June 2006 and December 2008, as well as between January 2009 and June 2010 (Fig. 4). Third-generation LVADs also utilize rotary blood pump technology. Its distinguishing feature, however, is its hemodynamically or magnetically levitated pieces that reduce the friction caused by rotation. DuraHeart, a third-generation device, was recently approved for BTT in Japan in 2010. Further studies on whether third-generation devices demonstrate significantly improved clinical outcomes than second-generation devices are warranted.

In 2010, the EvAluation of the HeartWare LVAD System for the Treatment of ADVANCed Heart FailurE (ADVANCE) evaluated the HeartWare HVAD (HeartWare International, Inc., Framingham, MA)—a third generation, compact device—for BTT indication in the United States [12]. The HVAD provides flows up to 10 L/min in a relatively small and lightweight device [13], and thanks to these qualities can allow for pericardial placement, limited

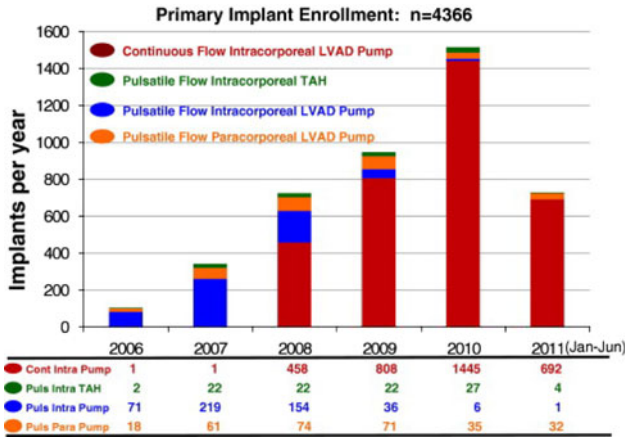

Fig. 4 The number of implantations of various LVAD models and total artificial hearts between 2006 and June 2011 [22]

cardiopulmonary bypass time, a small diameter percutaneous driveline, and elimination of an abdominal pump pocket, which are beneficial features that have not existed in other models. ADVANCE results suggested similar frequency in adverse events as HeartMate II and indicated a 180-day survival rate that exceeds 90 %. Furthermore, the comparison between HVAD performance and the data for the control group provided by the NIH-sponsored INTERMACS Registry is a novel approach towards clinically investigating the performance of future devices. It may be an approach that can be incorporated into Japanese pivotal trials when data is further collected by the Japanese registry for mechanically assisted circulatory support (J-MACS). The HVAD is also undergoing another randomized clinical trial called the Evaluation of the HeartWare Ventricular Assist System for Destination Therapy of Advanced Heart Failure (ENDURANCE) in the United States, which is investigating the performance of HVAD in comparison with other continuous flow devices for destination therapy [14].

The evolution of devices is also observed during the period in which clinical trials are being conducted. During the REMATCH trial, for example, device modifications, including the addition of parts and release of pressure, increased survival benefits of patients during the enrollment period. In fact, between the first and second year, there was a 15 % improvement in survival rate in patients receiving the device who were enrolled in the second half of the trial compared with those who were enrolled in the first half [15]. Thoratec Inc. soon replaced HeartMate VE with HeartMate XVE, which had modified features of the former that proved to benefit patients during REMATCH [16]. Further improvements in survival benefits in devices are anticipated as innovative strategies are being implemented and device modifications are routinely introduced in practice. While the improvement of the survival rate of post-transplant patients remains difficult, the constant evolution of LVAD technologies are inevitably going to assist the rise of LVADs as the next gold standard therapy for heart failure.

A new era with ventricular assist devices

As VAD therapy has gradually entered mainstream practice, INTERMACS was established as a joint effort between the National Heart, Lung, and Blood Institute (NHLBI), the Centers for Medicare and Medicaid Services (CMS), and the FDA in 2006 to monitor the growth of device utilization. There has been an almost 10-fold increase in the number of VADs used for lifelong support in transplant-ineligible patients [17]. According to INTERMACS data, the percentage of devices implanted for destination therapy increased from 8.4 % in 2006 to 13.8 % in 2010 (Table 1) [18]. J-MACS is currently being developed to track the progress of device usage in Japan as well.

VADs have thus been raising therapeutic standards for AHF patients, and will soon reach the survival expectations observed post-transplant. With devices like HeartMate II supporting thousands worldwide, new hope for improving the lives of those diagnosed with advanced heart failure without the worry of waiting for a donor is disseminating. In fact, HeartMate II currently provides support for almost 4500 patients in the United States, a number significantly higher than the number of heart transplants, which is

Table 1 Strategy for device implant—adult primary implants: INTERMACS, June 2006 – December 2008; January 2009—June 2010 [22]

Device strategy	June 2006–December 2008 No. (%) ($N = 1.138$)	January 2009–June 2010 No. (%) ($N = 1,542$)
Bridge-to-transplant, listed	529 (46.5)	632 (41.0)
Bridge-to-candidacy	468 (41.1)	663 (43.0)
Likely	312 (27.4)	447 (29.0)
Moderate	102 (9.0)	178 (11.5)
Unlikely	54 (4.7)	38 (2.5)
Destination therapy	96 (8.4)	213 (13.8)
Bridge-to-recovery	32 (2.8)	16 (1.0)
Rescue therapy	13 (1.1)	9 (0.5)
Other	0 (0)	9 (0.5)
Total	1,138 (100)	1,542 (100)

typically around 2000 cases. The United States has thus entered a generation in which LVAD implantation surpasses transplantation for a greater population of AHF patients.

Unlike previous, standard medical therapy, the performance of contemporary LVADs are now able to offer a healthy, prolonged lifestyle for AHF patients who have been restrained from physical activities. In Japan, however, the amount of organ donations still remains low, and currently the average bridging period still exceeds 2 years, gradually increasing despite the revision of the Organ Transplant Law. As of December 2010, there had been 89 heart transplantations since 2002, among of which 80 of them were bridged with an LVAD. Of these patients, the average waiting time was 960 days [19]. Furthermore, the survival rate of post-transplant patients is very high in Japan compared with the worldwide averages—86, 79, 72 and 51 % (1, 3, 5, and 10-year survival rates, respectively) [20]. The 10-year patient survival rate in Japan was approximately 95 % ($n = 89$), far better than the world average [19]. Thus, bridging therapies may be the primary usage of LVADs for another few years in Japan. Destination therapy may become a common option for heart failure patients later in the future as the amount of organ donations remain low and LVAD technologies continue to evolve.

Adaptations in medical practice to the rapid development of LVADs have been demonstrated in the form of a gradual shift in patient selection. There have been discussions on the degree of heart failure that should qualify patients for implantation or transplantation candidacy. While the amount of donors in the registry remain relatively low worldwide, the percentage of status II heart failure patients that undergo transplantation remain low as well, as donors are reserved for those who are in worse conditions. This highlights an area of expansion for LVAD usage. In fact, a pivotal trial, Randomized Evaluation of VAD InterVEntion before Inotropic Therapy (REVIVE-IT), will soon evaluate the usefulness of LVADs for less sick patients [21].

Conclusion

As LVADs continue to evolve through miniaturization and increased durability, the prospect of minimally invasive LVAD implantations as a means to avoid riskier transplant operations and concomitant complications is becoming a reality. Smaller device models also are more suitable for smaller patients, who may have otherwise not been able to consider implantable VADs due to their small abdominal cavity size. With the dearth of donor organs, we are preparing ourselves to integrate non-biological alternatives for the benefit of advanced heart failure patients who may consider or are required to consider options other than transplantation. Destination therapy may soon become the gold standard option for a larger population of heart failure patients, of various statuses, in the future.

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