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Ventricular Assist Devices: Is Destination Therapy a Viable Alternative in the Non-Transplant Candidate?

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Abstract

The topic of this article, stated a more familiar way, is whether left ventricular assist devices (LVADs) are ready for 'Primetime' as a therapeutic option in and of themselves. In order to provide an update and insight on this question, we briefly review from where the field has come, and in more detail describe its current state and where we are heading. We believe the short answer to this question is 'Yes', but like many things, a short answer is not adequate. Here we attempt to deliver a more comprehensive answer, providing some historical context, outlining the great achievements that have been made, as well as the many challenges that still remain before LVADs become a truly mainstream therapy.

Keywords

Left ventricular assist device; mechanical circulatory support; rotary pumps; endstage heart failure

INTRODUCTION

Despite many medical advances and overall improving outcomes, end stage heart failure (HF) is inevitable for some patients. In a small proportion of those who suffer its ravages, HF continues to progress despite conventional therapy resulting in endstage or advanced HF. Unfortunately, despite accounting for a very small proportion of all HF patients (some estimate it at roughly 5 % of the total), this still represents a large number of individuals since the overall HF population is thought to be approximately 1 million strong [1]. While heart transplantation is the gold standard of treatment in this group with a 10-year survival greater than 50 % [2], it is not always feasible for a variety of reasons. These include common comorbidities such as pulmonary hypertension, renal failure, and severe diabetes, and a variety of other factors such as age, smoking, or psychosocial instability. Compounding these issues is the fact that there is a relative paucity of suitable donor organs relative to the growing number of potential recipients. In fact, the number of heart transplants performed annually in the United States has not meaningfully changed in nearly a decade, and while there are approximately 3,000 patients waiting for heart transplantation there are only about 2,200 transplants annually in the U.S. [2]. If these trends continue (and there appears little reason to think otherwise) transplantation may become an increasingly niche therapy available to only a few.

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In this context, there is an obvious need for alternative therapies for a large number of patients with end-stage HF. This is particularly true for elderly patients who make up a growing segment of the HF population but for whom consideration of transplantation is less likely. In fact, age was cited as the most common contraindication to transplantation among patients being treated with destination therapy (DT) LVAD in the most recent INTERMACS report, accounting for one third of all patients [3]. While experimentation continues towards medical and biologic interventions aimed at end-stage HF, by far the greatest progress has been made in mechanical circulatory support, which is now a potential option to a wide range of patients (Table 1). This success has been a long time in coming but, as we summarize below, it has now reached a critical stage where therapeutic success of Left Ventricular Assist Devices (LVADs) make them an increasingly viable option in the non-transplant candidate. Indeed, continuing and rapid advancement has brought this field to the edge of what could be an explosion in LVAD use.

HISTORICAL PERSPECTIVE

In 1964, the National Institutes of Health (NIH) started an artificial-heart program, and since that time there has been a variety of circulatory support devices in development [3]. With initial focus on short-term devices, slow and quiet progress ultimately resulted in FDA approval for the first implantable LVAD, a pneumatically driven pump, as a bridge to transplantation in 1994 [4]. Even with these very early devices, it was clear they could improve hemodynamics, reverse end-organ damage and reduce symptoms, [5] however; this came at a price of long hospital stays. By 1998, electric powered devices which were intra-corporeal and freed patients from tethering to a console were being used as a bridge to transplantation, most notably the Heartmate VE (Thermocardiosystems) [6] and Novacor (Baxter) [7]. The ability to discharge a patient home was a critical step forward which led to the field taking a great leap - testing devices in end stage patients who were not transplant candidates [8]. In 2001, the results of the REMATCH trial (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) represented a pivotal moment in LVAD development [9]. The study enrolled patients who were not transplant eligible for a variety of reasons randomizing them to either the Heartmate vented electric (HMVE/HMXVE) or optimal medical therapy. This was perhaps the sickest patient population enrolled in a clinical trial to date; participants had left ventricular ejection fraction (LVEF) of 25 % or less with New York Heart Association (NYHA) class IV symptoms despite evidence-based therapy, as well as other markers of very poor prognosis such as a peak VO_2 14ml/kg/min or IV inotropic dependence. In fact, roughly 70 % of the cohort required inotropic support.

REMATCH demonstrated a statistically significant decrease in risk of death from any cause with LVAD treatment, showing one-year survival of 53 % in the LVAD arm compared to only 25 % in the optimal medical management arm. It convincingly showed the horrendous natural history of end stage HF; half of the patients were dead in under six months, with only 8 % remaining by 24 months. Unfortunately, the overall survival in the LVAD group was somewhat disappointing, with a 2-year survival of around 23 %. So while the study clearly showed that mechanical support was better than medical management, it still remained to be seen if LVAD implantation would be a desirable option in the absence of transplantation (i.e., as 'destination' therapy [DT]). Similarly, the INTrEPID (Investigation of Non-transplant-Eligible Patients Who Are Inotrope Dependent) trial demonstrated benefits of LVAD implantation, most importantly prolonged survival NYHA class IV inotrope dependent patients [10]. This study utilized the Novacor, another electric, implantable, pulsatile LVAD. Patients receiving the LVAD experienced a greater survival rate at 6 and 12 months and lower rates of adverse events when compared to a non-randomized group who continued optimal medical management including inotropes. Like

REMATCH, survival was statistically superior in the LVAD group; however, the absolute survival was still low, with additional complications such as elevated stroke risk being highlighted. Despite these concerns, the results of REMATCH were acceptable for the HMXVE to obtain FDA approval as destination therapy in 2002, with Medicare approval for coverage and reimbursement coming in 2003, which began its use in select non-transplant patients. These early successes introduced destination therapy as an option, and along with continued LVAD use as a bridge to transplantation, spurred the field onward towards development of better, more durable pumps.

PROBLEMS with PULSATILES

Although the REMATCH trial demonstrated statistically significant benefit to LVAD implantation, it was clearly was not a panacea. The overall survival in the LVAD group was still too low to generate much enthusiasm about destination therapy [11]. A major part of this was a high rate of mechanical failures within one or two years after implantation [9, 12, 13]. While the Novacor pump appeared to have greater durability, it showed an even higher risk of stroke, and thus similar overall performance [14,15]. In addition, both devices were vulnerable to infection of driveline tract or pump pocket. For example, in the REMATCH trial, there was a 28 % probability of infection at three months, whereas infection accounted for 24 % of patient deaths in the INTrEPID study [9, 10].

Also problematic with these pulsatile LVADs were numerous quality of life issues. The pumps were physically large, limiting who could be considered for implantation [9] and resulting in chronic pain, early satiety, or even compression of abdominal viscera [16]. The battery life ranged from 2 to 6 hours- not quite enough for many patients to carry on their usual activities of a normal life. Finally, the cost of implantation remained high, and in combination with the suboptimal outcomes described, resulted in very poor cost effectiveness. One study estimated the cost-utility at roughly \$800,000 per quality adjusted life-year (QALY) saved,[17] and even using more favorable estimates it remained unpalatable at roughly \$350,000 per QALY [18]. Thus, while destination therapy was possible, it was neither highly desirable, nor feasible on a larger scale. Fortunately, these circumstances would change dramatically with the advent of rotary LVADs (as well as other advances), which provided significant improvements in each of these domains (Table 2). We describe these developments below with particular focus on how the prospect of LVAD as an effective destination therapy has changed.

IMPROVED SURVIVAL

Continuous flow LVADs represent a large step forward in terms of durability, and thus, survival, most convincingly demonstrated by the HeartMate II (HMII) destination therapy trial [19]. Numerous continuous flow devices have in fact been tested and/or marketed as a bridge to transplant options including (but not limited to) devices from DeBakey [20], Jarvik [21], Ventrasist [22], and most recently the Heartware HVAD [23] which has completed a successful bridge trial (ADVANCE) [24] and has an ongoing destination trial. However, by far the most evidence currently available pertains to the HMII, and this is the only device with extensive data outside of the bridge to transplant indication. The HMII was studied both as a bridge [25] and as destination therapy [19]. The goal of the latter trial was to determine the safety and efficacy of the HMII as destination therapy compared to the HMXVE, which was the only approved destination therapy device at that time. The primary endpoint was survival free from disabling stroke and repair/replacement of the device, which was significantly better in the HMII group compared to the HMXVE (46 % vs 11 %; $P<0.001$), as was the two-year overall survival of 58 % and 24 %, respectively, ($p=0.008$) [19]. Interestingly, the survival curve in the HMXVE arm of this trial was nearly super-

impossible on that provided in the REMATCH study. This fact underscores the consistency of these data and strongly implies a remarkable survival advantage of continuous flow LVAD therapy when compared to optimal medical therapy (Figure 1); a point nicely summarized in an accompanying editorial cleverly titled 'Rise of the Machines' [26].

Adding to this success is the continued improvement in outcomes with continuous flow LVADs over time. When one compares survival in the original HMII bridge to transplant cohort, [25] to the later cohort within that study,[27] and finally to the HMII post-marketing study,[28] what is seen is that the 6 month survival progressively increased in those groups from 79 % to 84 %, to an impressive 91 %, respectively. These improved outcomes are present despite the fact that most patients implanted were still critically ill; 61 % of the patients in the post-approval study were INTERMACS category 1 or 2 (defined as cardiogenic shock or decline on inotrope support). Similarly, the ADVANCE trial which utilized the Heartware HVAD showed outstanding short and medium term outcomes with 94 % survival at 6 months, albeit with a somewhat lower risk cohort. While these results are from bridge to transplant patients, it still importantly illustrates that survival among LVAD treated patients continues to improve. While there are fewer data currently available specific to destination patients, a similar comparison can be made; examining the initial HMII DT trial cohort [19] to the later enrolled patients [29] and the most recent INTERMACS report, [30] reveals one year survivals of 68 %, 74 %, and 77 %, respectively. In summary, the survival of patients with current continuous flow LVADs is remarkably better than that with older pulsatile pumps, and there is good evidence that these survival rates have continued to improve as greater clinical experience is gained with these devices.

REDUCED MORBIDITY

In addition to the significantly improved probability of survival discussed above, other clinical endpoints have also improved in the era of continuous flow devices. As mentioned, neurologic events and infections were common complications, and patients continued to have frequent hospitalizations. Device-related infections are of course important in all LVAD use, but particularly important in the setting of destination therapy when transplantation is not available as a rescue option. The experience with the HMII has shown reduced incidence of stroke, lower rates of re-hospitalizations and reduced risk of driveline infections compared to the HMXVE [19]. For example, the rate of device-related infections was 0.48 per patient year in HMII patients compared to 0.90 in XVE patients ($p=0.01$).

Although most outcomes were significantly improved, there remained areas of concern. Bleeding appeared to be more frequent with continuous flow support, particularly gastrointestinal bleeding [31,32]. This has improved somewhat as lower INR goals have been adopted [33] due to data suggesting acceptable safety, in terms of thromboembolic complications, and of less intense anticoagulation [34, 35]. However, this remains an area of active investigation in order to further reduce risk and improve long-term outcomes.

ENHANCED QUALITY OF LIFE

An extremely important aspect of the effectiveness of destination LVAD therapy is how it affects the patient's quality of life. This tends to receive less attention than raw survival, however, if one queries advanced HF patients, impairment in functional capacity and quality of life considerations are just as important if not more so than longevity. There is very convincing data from both the bridge to transplant and destination trials that LVAD support significantly improves quality of life compared to advanced stage HF, across a variety of devices including pulsatile pumps [9,10,23,26]. The largest and longest data again comes from the HMII experience. While pulsatile pumps clearly improve quality of life, the HMII was still able to show significantly better changes in Minnesota Living with Heart Failure

and Kansas City Cardiomyopathy Questionnaire scores compared to the HMXVE ($p=0.03$, 0.06 , respectively) [19]. Furthermore, focusing specifically on quality of life and functional capacity utilizing the entire HMII trials experience, Rogers and colleagues [37] were able to show that patients achieved drastic improvements across a wide variety of measures, which were not only statistically significant but clinically meaningful as well. Equally important, these improvements appeared durable through 24 months of device support. Table 3 summarizes changes in the measure of quality of life and functional status associated with continuous flow LVAD implantation.

There are other important, though more difficult to quantify, quality of life considerations that have also improved. For example, the HMII takes up a volume of 63ml and weighs 280g, whereas the pulsatile flow HMXVE displaces 450ml and weighs 1250g. This clearly results in greater patient comfort and also allows smaller patients to be considered. Another great advantage is that the pump is essentially silent, reducing the unwanted attention and stigma associated with noisy, pulsatile pumps. Unrelated to pump advances, improvements in battery technology have made a difference in patients' lives as well. The latest iteration of Heartmate system batteries has a greatly extended life of 10–12 hours, allowing patients to essentially complete an entire day's activities without having to plug in, a critical issue contemplating this device as a long-term treatment for HF. Finally, there is even evidence that psychological well being and sexual function improve after LVAD placement [38].

IMPROVING COST EFFECTIVENESS

Cost is a critical issue in all aspects of today's health care, and it's definitely a subject that needs to be addressed in detail if LVAD therapy is contemplated as a broad approach to advanced heart failure in non-transplant candidates. As noted above, early cost-effectiveness analyses of LVAD therapy suggested a very poor cost utility, particularly in the setting of destination therapy. First generation LVADs had an average first year cost of more than \$220,000 (2001 dollars) which compared poorly to one year costs of cardiac transplantation at that time [39]. The costs of LVAD placement have indeed decreased with time and the migration to continuous flow devices. Slaughter and colleagues compared implantation costs in REMATCH to those of the HMII in the destination trial and found a nearly 50 % decrease in average costs (\$193,812 vs. \$384,260, $p<0.001$) [40]. Because the incremental cost effectiveness of LVAD therapy will change depending on device longevity and reliability, this aspect has changed even more. A recent analysis showed the cost-utility of the HMII as destination therapy as \$198,184 per QALY [41]; an astounding improvement compared to estimates just a decade earlier of roughly \$800,000 [17]. The incremental cost per life year saved (not QALY) appears even more compelling, estimated at \$167,208 per life year. So while LVAD as destination has not yet reached what is generally considered cost-effective level, it is not far off of the upper limit (often considered \$100,000 per QALY) and is certainly headed in the right direction.

REMAINING CHALLENGES

Despite the many advances described above, there are of course a variety of issues still limiting success with LVADs as destination therapy. Most prominent is the fact that device-related infections will always be an issue as long as a drive line is required, so a primary focus of current development is devoted to enhancing technology related to transcutaneous charging and battery/electronics size. Bleeding and thrombotic phenomena also remain an issue, thus defining optimal anticoagulation regimens, better identifying individual risk of thrombus or bleeding, and developing new pumps that are more biocompatible all remain active research questions. Finally, LVAD patients still require a substantial amount of care

and are often hospitalized; additional work is needed in order for this technology to be adopted outside specialized centers.

Despite the shortcomings in existing devices, many experts are already asking whether mechanical support has a role in less ill patients. This is tempting because some of these patients still have poor prognoses, and implantation in a more stable patient should reduce peri-operative risk. At least part of the answer should be gleaned from the upcoming multi-center Randomized Evaluation of VAD Intervention before Inotropic Therapy (REVIVE-IT; [clinicaltrials.gov NCT01369407](https://clinicaltrials.gov/ct2/show/study/NCT01369407)) trial. This is an NIH funded effort to define the safety and benefit of LVAD therapy (utilizing the Heartware HVAD) in less advanced HF patients, who do not meet current LVAD indications, yet have a poor prognosis. Similarly, a non-randomized comparison is underway focusing on the HMII device in patients who meet current indications but are not inotrope dependant. This study, titled Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients (ROADMAP, [clinicaltrials.gov NCT01452802](https://clinicaltrials.gov/ct2/show/study/NCT01452802)) is a prospective, multi-center, non-randomized, observational study to compare the outcomes in patients undergoing HM II implantation to similar patients supported with optimal medical management only. Hopefully these two endeavors will inform us whether LVAD usage should potentially move upstream to less severely ill patients.

SUMMARY AND CONCLUSIONS

There are a number of considerations that must be taken into account before a given treatment is accepted for broad usage in a given population. First, therapeutic success needs to be objectively demonstrated, not just in terms of survival but also in terms of patient-centered outcomes such as quality of life and functional capacity. Of course safety needs to be shown with an acceptable risk-benefit profile. And finally, cost-effectiveness needs to be considered in order for the therapy to be financially sustainable and responsible. Not long ago, a mechanical heart pump satisfying these criteria would have seemed a pipe dream. However, as described above, contemporary continuous flow LVADs appear to have a good chance of satisfying these criteria. That is not to say that these devices are now ready to be routine, or mainstream. All the outcomes above are achieved in the setting of specialized centers with large multidisciplinary teams, devoted to advanced heart failure treatment. Truly widespread or routine LVAD use as a destination awaits further technological and surgical developments allowing lower risk patients to receive real benefit from low-maintenance devices implanted using lower risk procedures. However, today's devices are indeed reasonable therapy for end-stage heart failure patients who are not transplant candidates but are otherwise viable candidates based on comorbidities. This is part of why the total rate of LVAD implants has doubled since 2008,[30] and this appropriate growth will require greater knowledge and familiarity with LVAD therapy throughout the entire health care system, as more patients live longer with these devices.

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Figure 1.

Survival curves for REMATCH (9) and HeartMate II Destination (19) trials. From *N Engl J Med*, Fang JC, "Rise of the machines--left ventricular assist devices as permanent therapy for advanced heart failure," Volume 361, Pages 2282-5. Copyright ©2009 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Table 1

Inclusion and Exclusion Criteria for LVAD as Destination Therapy (19)

Inclusion criteria
<ul style="list-style-type: none">• Left ventricular ejection fraction < 25%• Peak oxygen consumption of less than 14 ml/kg/min, or less than 50% predicted value• NYHA class IIIB or IV symptoms, or dependence on inotropes
Exclusion criteria
<ul style="list-style-type: none">• Irreversible, severe renal, pulmonary, or hepatic dysfunction• Active infection• Inability to safely manage LVAD post-implant

Table 2

Contrasts between Contemporary Left Ventricular Assist Device and First Generation as Destination Therapy

Characteristic	Destination therapy 2002 (e.g. Heartmate XVE, Novacor)	Destination therapy 2011 (e.g. Heartmate II, Heartware HVAD [*])
Pump Physical Attributes	HMXVE: 1250g, 450 ml, audible	HMII: 280g, 63ml, inaudible HVAD: 145g, 50 ml, inaudible
Implant Cost (U.S. dollars)	\$384,260 (inflation adjusted) (40)	\$193,812 (40)
Cost-utility (dollars/QALY)	\$802,700 (17)	\$198,184 (41)
Device-related Infection Rate	0.9 events/patient-year (19)	0.27 events/patient-year (29)
Battery Life	4 – 6 hours	~ 10 hours
2 Year Survival	23% (9)	63% (29)

^{*} Not approved for destination, trial ongoing.

Table 3

Functional Status and Quality of Life changes after Continuous Flow LVAD Implantation.

Measure	Clinically Meaningful Change	Continuous Flow LVAD Change
Six Minute Walk Test	25M (42)	113M – 146M (24,37)
NYHA Functional Class	1 NYHA Improvement	80% 2 Improvement (37)
Metabolic Equivalent Task Score (METs)	1 MET Improvement	60% 1 MET Improvement (37)
Minnesota Living with Heart Failure score	5 points (43)	40 points (37)
Kansas City Cardiomyopathy Questionnaire	5 points (44)	32 – 39 points (23,24,37)