



REVIEW

Alive Without a Pulse: Evolution of Durable Left Ventricular Assist Devices

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Abstract

Durable left ventricular assist devices (LVADs) offer a viable option for patients with advanced heart failure and have been demonstrated to be superior to optimal medical therapy in terms of both mortality and quality of life, in selected patients. However, durable LVADs can be associated with severe morbidity. Because the rates of cardiac transplantation are limited by supply, understanding of the evolution of durable LVAD support is necessary to drive innovations to optimize outcomes. Herein, we review progress in durable LVAD support in contemporary practice and propose future directions that will require additional study.

Keywords: history of LVAD, evolution of LVAD, future directions for LVAD, telemedicine, hemocompatibility for LVAD, societal determinants of LVAD

Introduction

Heart failure (HF) is a global pandemic affecting more than 26 million people; this number is expected to grow as the population continues to age [1]. Despite notable advances in medical therapy, mortality and morbidity remain high among affected individuals. This review focuses on the prevalence of stage D HF, and the effects and clinical importance of durable left ventricular assist devices (LVADs).

According to the American College of Cardiology (ACC) and the American Heart Association (AHA) HF 2022 guidelines [2], patients are considered to have stage D advanced HF when they have persistent symptoms of HF, regardless of optimal medical and device therapy. These patients may

be persistently symptomatic, or may have intolerance to guideline-directed medical therapy, refractory volume overload, or malignant tachyarrhythmias. They often become unable to maintain their original lifestyle and consequently undergo multiple hospitalizations. When a patient is considered to have stage D advanced HF, an ejection fraction <25%, and reduced functional capacity with $VO_2 < 14$ mg/kg/min, referral for advanced therapies, such as LVADs, is indicated. Notably, because of the adverse events associated with LVADs, many contraindications to LVAD placement exist, including active malignancy, age >80 years, irreversible end organ dysfunction (renal, liver, or lung), right ventricular failure, significant pulmonary hypertension, and an inability to receive adequate follow-up care (psychosocial limitations).

Although the data are limited, fewer than 260,000 patients with HF are believed to be in stage D worldwide [1]. Studies on the incidence of HF in China are scarce; however, HF is becoming more common

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in China, owing to aging of the population and the risk factors associated with high-income lifestyles. A retrospective cross-sectional study conducted in 2017 has assessed the prevalence of HF in Chinese citizens older than 25 years and found a prevalence of HF of 1.10%, equating to approximately 12.1 million people in China older than 25 years [3].

Currently, approximately 3500 heart transplantations are conducted each year in the United States; this number is limited by the supply of satisfactory hearts available. This imbalance between supply and demand leads to prolonged waiting times and ultimately to unnecessary mortality. Given the shortage of donor hearts available to patients with refractory HF, finding alternative solutions is critical. The donor pool has recently been expanded to people with hepatitis C. The opioid epidemic faced by the United States has led to patients overdosing at younger ages than ever before. Therefore, younger patients with hepatitis C now compose a greater proportion of the donor pool. With the ability to treat hepatitis C with novel therapies, more hearts have become available to people in need [4]. Another possible solution has been using donated hearts after circulatory death (DCD). Although DCD donors have long been considered a potential source to expand the pool of available hearts, advances in reperfusion technology have only recently led to a resurgence in considering these donors. According to liberal estimates, DCD may increase the donor pool by as much as 30% [5]. Despite logistical and ethical challenges, a framework is currently being implemented to use DCD hearts to expand the donor pool [6].

Fortunately, as hearts remain a limited resource for stage D HF patients, LVADs have become a viable alternative. For patients who qualify for heart transplantation, LVADs may serve as a temporary therapy until transplantation. Other patients who do not qualify for heart transplantation but meet the criteria for advanced therapy, such as LVADs, may receive device placement as a lifelong alternative (i.e., destination therapy). Finally, for patients who are critically ill and awaiting transplant candidacy decisions, LVADs may serve as a bridge therapy enabling recovery until a decision can be made. Consequently, LVADs give a second chance at life to patients who do not meet the criteria for transplantation or are awaiting a new heart.

Evolution of Left Ventricular Assist Devices

The value of implantable LVADs for patients with end-stage HF was clearly established in the REMATCH study [7], which was aimed at determining the efficacy of LVADs as a destination therapy. In that trial, a pulsatile-flow LVAD, the HeartMate (HM) XVE™, was compared with optimal medical therapy (OMT), with a primary endpoint of all-cause mortality. Patients with advanced HF (NYHA class IV, LVEF <25%) who were not candidates for heart transplantation were randomized to undergo LVAD implantation (n=68) vs. continued OMT (n=61). The results indicated 48% lower mortality in the LVAD group than the OMT group, and the difference was statistically significant (P=0.001). At 1 year, the LVAD group had a survival of 52%, as compared with 25% in the OMT group (P=0.002) [7]. This trial led to the Food and Drug Association (FDA) approval of the HM XVE in the United States. Although REMATCH clearly established the benefits of durable LVADs, the degree of associated morbidity pertaining to infections, strokes, and thromboembolisms highlighted the need for improved engineering designs. The evolution of these designs can be found in Table 1. Moreover, the HM XVE is composed of several moving parts that were not designed for long term use and consequently required frequent replacement. Design issues may potentially explain why survival benefits substantially decrease, to 28%, at 2 years in patients receiving LVAD [7].

First Generation VADs

The HM XVE device used in the REMATCH study is an example of a first generation iteration based on the principle of volume displacement and pulsatile flow. Examples of other first generation devices are the HM XVE, Thoratec IVAD™, Thoratec pVAD™, and Novacor™. This class of devices includes an internal chamber and valves located on the inflow and outflow sides, thus enabling cyclic filling and emptying on the basis of pneumatic or electrical cues [8]. Some limitations of these devices include the need for substantial surgical dissection at implantation, loud pump sounds, and the need for a percutaneous outlet for air-venting. Nevertheless, these first devices were approved as a bridge-to-transplant

Table 1 Evolution of LVADs.

<p>1st Generation</p>	<ul style="list-style-type: none"> • “Pulsatile Pumps” <ul style="list-style-type: none"> • HeartMate XVE <ul style="list-style-type: none"> • CE mark 2003, FDA 2002
<p>2ND Generation</p>	<ul style="list-style-type: none"> • Continuous-flow, axial pumps • Notable Example: HeartMate II[®] <ul style="list-style-type: none"> • CE mark 2005, FDA 2008 (DT), 2010 (BTT)
<p>3RD Generation</p>	<ul style="list-style-type: none"> • All continuous-flow but distinguished by absence of contact bearings using magnetic levitation (MAGLEV) • Primarily centrifugal flow • Notable Examples: <ul style="list-style-type: none"> • HeartMate 3[™] <ul style="list-style-type: none"> • CE mark 2015, FDA 2017 (BTT), 2018 (DT) • HeartWare HVAD[®] <ul style="list-style-type: none"> • CE mark 2008, FDA 2012 (BTT), 2017 (DT)

device by the FDA in 1998. Around that time, an LVAD called the Luo-Ye VAD[™], a pulsatile volume-displacement pump, was being developed in China. This device was successfully used in the short term, albeit in a small cohort of patients, and was consequently approved by the Chinese Food and Drug Administration in 2003. As of 2013, 23 patients were supported by this pump [9].

Second Generation VADs

The next iteration of durable LVADs featured a fundamental change from pulsatile volume displacement to continuous-flow axial devices. These included the second generation HM II[™] (Figures 1 and 2), DeBakey MicroMed[™], and Jarvik 2000 Flowmaker[™]. The principal features of these devices are the presence of an axial blood flow path and a contact bearing design. Rather than relying on pneumatic compression, these devices have internal rotors and percutaneous drivelines, and are substantially smaller than their predecessors. This design relaxes several limitations regarding pericardial constraint, thus allowing more patients to be



Figure 1 Heartmate II.

eligible for implantation. In 2007, the HM II was studied in a prospective multicenter study in stage D HF patients to determine whether it might serve as a bridge-to-transplant device like its predecessor. Patients were followed until the primary endpoint

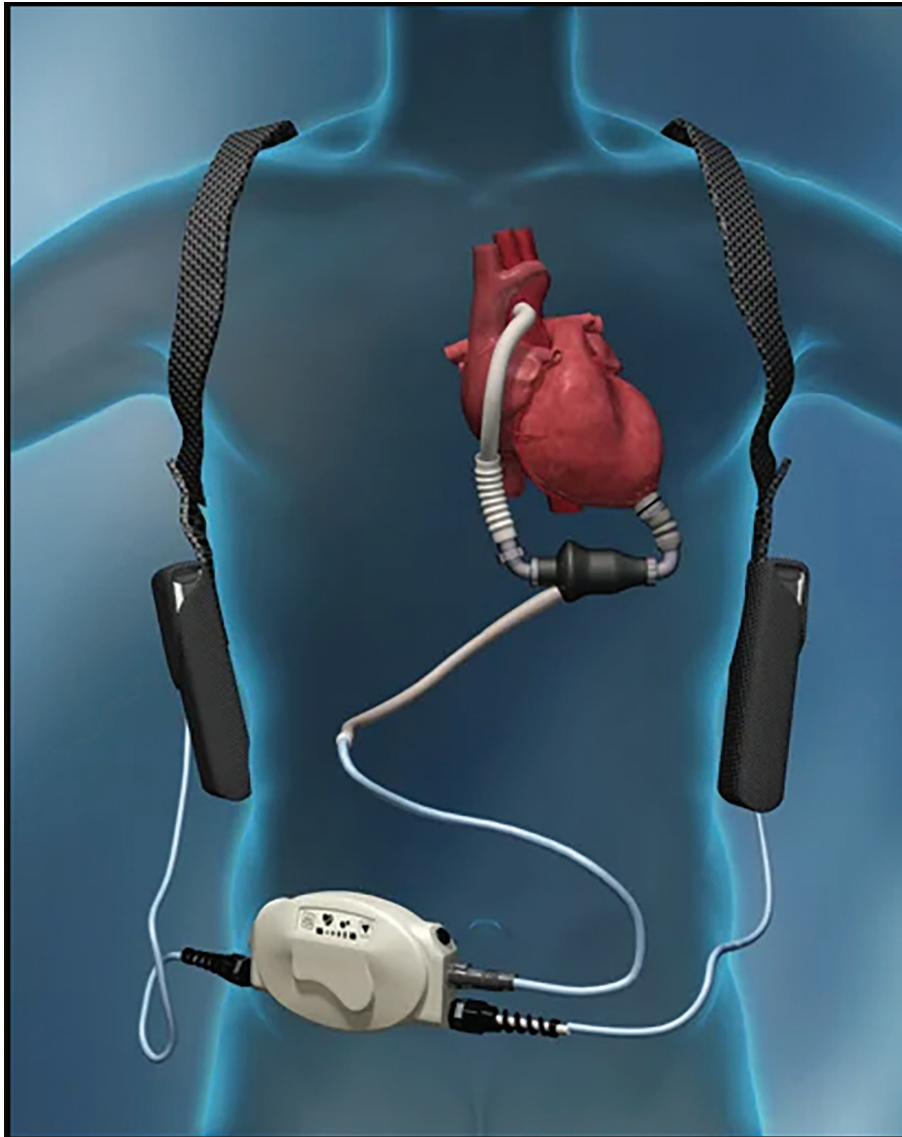


Figure 2 Heartmate II Schematic.

of cardiac transplantation, cardiac recovery with explantation of the LVAD, or ongoing device support for more than 180 days. At 6 months, 75% of the patients survived, and the number had decreased to 68% at 1 year [10]. The trial was extended to 18 months with additional enrollees and indicated a survival of 72% at 18 months, with benefits of improvements in NYHA class symptoms [11]. On the basis of these promising results, the FDA approved the HMII as the first continuous flow LVAD as a bridge-to-transplant device.

The pivotal trial that demonstrated the effectiveness of the HM II for destination therapy was performed 2009. This head-to-head randomized controlled trial implanted patients with the HM II

vs. the HM XVE™ in a 2:1 ratio. This study provided one of the first direct comparisons of continuous flow devices with pulsatile flow in a randomized fashion. The primary endpoint was 2-year survival without stroke or reimplantation/repair of the LVAD. Among the 200 patients enrolled (134 to HMII vs. 66 to XVE), 46% of the HM II patients met the primary endpoint, as compared with 11% of the XVE patients, representing a statistically significant difference. Moreover, survival at 1 and 2 years favored the HM II (68% and 58%, respectively, compared with 55% and 24% in the XVE group). The HM II, compared with the pulsatile comparator, resulted in similar improvements in NYHA class symptoms and better overall quality of life changes. Moreover,

the HM II resulted in lower rates of arrhythmias, right HF, infection, and end-organ dysfunction than the XVE [12]. These findings provided sufficient evidence for the FDA to approve the HM II for destination therapy in 2010 and ultimately led to the HM II's supplantation of the HM XVE as the predominantly preferred LVAD.

Third Generation VADs

One commonly observed issue with the second generation axial LVADs was an elevated rate of pump thrombosis. The third generation LVADs were designed specifically to address this issue. The HeartWare HVAD™, one of the first third generation LVADs, uses centrifugal flow, weighs only 140 g, and is intrapericardially placed. At the time, the HeartWare HVAD was the only LVAD that could be placed in a minimally invasive manner through small thoracotomy incisions [13]. Like prior models of the LVAD, the HVAD was tested as a bridge-to-transplant device in the ADVANCE trial. The trial compared the HVAD with all other commercially available devices on the market and assessed survival, transplantation, or explantation at 180 days. The HVAD was successful in 90.7% of patients, as compared with 90.1% of patients receiving the commercially available devices, and showed non-inferiority to the intrapericardial centrifugal pump [14]. Evidence indicated improved quality of life and, more importantly, decreased pump thrombosis in the HVAD group. These findings led to FDA approval of this bridge-to-transplant therapy in 2012.

When the HVAD was approved as a bridge-to-transplant device, the ENDURANCE trial was conducted to compare this device with the already established axial flow Heartmate II. In this multicenter, randomized trial, patients who were ineligible for transplantation were assigned 2:1 to HVAD vs. Heartmate II. The primary endpoint was survival at 2 years without stroke or LVAD malfunction. A total of 55% of the HVAD group and 57.4% of the HM II group reached the primary endpoint at 2 years, thereby indicating non-inferiority between devices. The adverse events of bleeding, arrhythmias, end organ dysfunction, and infections were similar between groups. Alarming, however, the patients receiving HVAD had greater risk of ischemic and hemorrhagic stroke than the HM II group (29.7% vs. 12.1% in the HM

II group). This difference was attributed to higher systemic blood pressure at the time of implantation in the HVAD group. A supplemental trial comparing stroke within the first 12 months with improved blood pressure control indicated no statistical significance of ischemic or hemorrhagic stroke between the groups. Nonetheless, the overall rate of survival was similar between groups, at 60.2% and 67.6%, respectively, and 80% of participants clinically improved to NYHA class I or II [15].

In contrast to the devices discussed above, third generation durable LVADs are also continuous flow devices but primarily have a non-contact bearing design, which theoretically mitigates the risk of friction and energy loss between the device and blood. Among the third generation durable LVADs, an additional distinction can be made between those in which the blood takes a centrifugal course versus an axial course (Incor). The primary difference between centrifugal and axial pumps is in the design of the impeller. In axial pumps, the inlet and outlet paths are parallel to the impeller, which propels blood forward. In contrast, in centrifugal pumps, the impeller is perpendicular to the outlet path, and blood moves at 90° to the axis of the impeller [16]. To additionally minimize mechanical contact that might contribute to friction and result in energy inefficiency, levitation of the impeller is used in all third generation durable LVADs, which take advantage of hydrodynamics (VentrAssist) or magnetic forces (HM 3™, HVAD, Levacor™).

The HM 3 (Figure 3) is an intra-pericardial centrifugal pump that shifts its rotor speed to create an artificial pulse (Figure 4). The aim of this design was to prevent blood stasis and decrease the rate of pump thrombosis. The Momentum 3 trial, conducted to assess these functions, was a randomized controlled trial enrolling patients receiving either bridge-to-transplant or destination therapy, and implanting the Heartmate 3 vs. the HM II. The primary endpoint was survival free of disabling stroke, or reoperation to replace the device within the first 6 months of implantation. A total of 86.2% of the patients in the HM 3 cohort reached the primary endpoint, as compared with 76.8% of the HM II cohort, representing a statistically significant difference. The need for reimplantation was also lower in the HM 3 group. More importantly, pump thrombosis occurred in no patients in the HM 3 group, as compared with 10.1% in the HM II



Figure 3 Heartmate III.

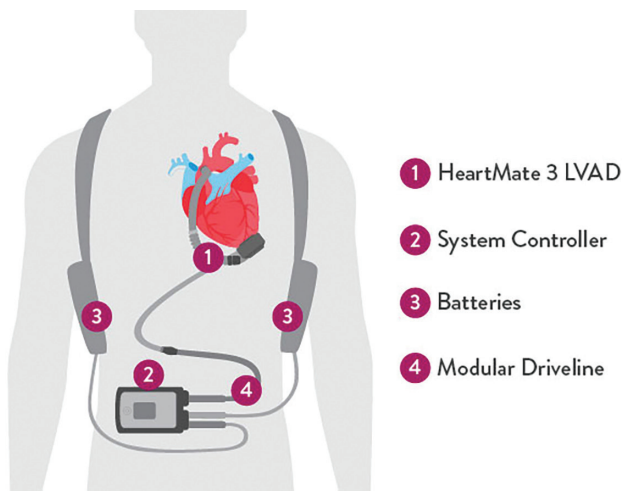


Figure 4 Heartmate III Schematic.

group [17]. Moreover, the patients were followed for 2 years to assess the primary endpoint. Again, in the HM 3 group compared with the Heartmate II group, more patients reached 2 years without a disabling stroke or requiring pump reimplantation, and the overall stroke rate was lower [18]. These studies led to the FDA approval of HM 3 as a bridge-to-therapy device in 2017 and as a destination therapy in 2018 [13]. A summary of the seminal LVAD clinical trials can be found in Tables 2 and 3.

LVAD Use

A comprehensive analysis of patient outcomes indicates the strides made in LVAD technology in

the preceding decade. The advances are particularly remarkable given the changes in the United States transplant allocation system in 2018. In most patients currently receiving LVADs, the treatment is considered a destination therapy rather than a bridge-to-transplant therapy. In the post-allocation change era, despite the presence of high-risk features such as renal dysfunction, advanced age, and high BMI, the survival outcomes associated with durable LVAD support have been excellent [19]. In addition, durable LVADs have prolonged the need for transplantation when used as a bridge to transplant. Both of these observations reflect substantial improvements in the rates of adverse events in the context of LVAD technological advancements, when compared to their predecessors. Although a decrease in implant volume by as much as 23.5% had been achieved in 2021, with respect to the peak implantation rates in 2019, this decrease is likely to reflect the effect of the COVID-19 pandemic as well as the increasing donor pool due to drug overdoses, hepatitis C donors, and DCD donors [19].

The evolution of LVADs described above reflects experiences primarily in the United States and Europe. However, the legitimate need for the development of LVADs applies worldwide, as indicated by the absence of sufficient hearts for transplantation. The same principle applies to the Chinese population: both donor supply and expertise with transplantation are limited, and only 2 of 46 institutions conduct more than 30 transplantations annually. LVAD development in China has been shown to have successful outcomes in animal models and in a limited sample of patients. Examples of LVADs include both axial (FW-11™, VAAP™, BJUT-II™) and magnetically levitated centrifugal (ChinaHeart VAD™) devices [20]. Similarly to the United States, in China, the burden of durable LVAD implantation for all patients who may benefit from the procedure depends on clinical and surgical expertise, cost, and optimal post-implantation care.

Mechanism of Action

In contemporary practice, the continuous-flow magnetically levitated HM 3 is the most implanted durable LVAD in the United States, and is used in 92.7% of all implantations [19]. In contrast to

Table 2 Summary of LVAD Trials.

Trial	Number of Patients	Strategy of Use	Comparison	Patient Population	Outcome
REMATCH (2001)	129	Destination therapy	Heartmate XVE versus medical therapy in a prospective 1:1 allocation	NYHA class IV for 60 days, LVEF <25% and peak VO_2 (<14 mL/min/kg), or IABP or IV inotrope dependent	Improved 1 year survival with HM XVE compared with medical therapy (52% vs. 25%; $P=0.002$)
INTREPID (2007)	55	Destination therapy	Novacor LVAD and optimal medical therapy in transplant ineligible patients	NYHA class IV patients unable to wean off of inotropic support	Superior survival with NOVACOR compared with medical therapy at 6 (46% vs. 22%; $P=0.03$) and 12 months (27% vs. 11%, $P=0.02$)
HM II (2007)	133	Bridge to transplant	Prospective, randomized 2:1 HM II vs. Heartmate XVE	NYHA class IIIB or IV symptoms for at least 45 days, LVEF <25% and peak VO_2 (<14 mL/min/kg), or IABP (for 7 days) or IV inotrope dependent (for 14 days)	Superior 1-year (68% vs. 54%, $P<0.001$) and 2-year (58% vs. 24%, $P=0.008$) survival with the HM II compared with the XVE
ADVANCE (2012)	137	Bridge to transplant	Prospective, nonrandomized HVAD comparison with 499 patients from the iINTERMACS registry	Transplant eligible patients bridged with durable LVAD	Non-inferiority of the HVAD compared with FDA-approved LVADs for survival, transplantation, or ventricular recovery ($P<0.001$; 15% non-inferiority margin)
ENDURANCE (2012)	446	Destination therapy	Prospective, DT patients randomized 2:1 HVAD vs HM II	NYHA class IIIB or IV despite optimal medical therapy, LVEF <25%	Non-inferior for survival free from stroke or device failure; more strokes in HVAD (29.7% vs. 12.1%) but less device malfunction (8.8% vs. 16.2%)
MOMENTUM 3 (2019)	1028	Destination therapy, bridge to transplant, or bridge to candidacy	Prospective, 1:1 randomized to HM 3 vs. HM II	Advanced heart failure deemed to require durable LVAD support	Improved survival at 2 years free of stroke or malfunction (74.7% vs. 60.6%, $P<0.01$)

Table 3 Strengths of LVAD Trials.

Trial	Strengths	Interesting Takeaways
REMATCH (2001)	First study showing efficacy of durable LVAD therapy compared with medical therapy alone	Limited options for medical therapy at the time of study
INTREPID (2007)	Improvement in survival for transplant ineligible patients with NOVACOR VAD	Small sample size
HM II (2007)	First definitive evidence of improved survival with continuous-flow devices compared with pulsatile flow-devices	CF-LVAD found to be superior for survival and associated with a better adverse event profile; validation of use for patients being bridged to transplant
ADVANCE (2012)	HVAD established as a viable alternative for patients awaiting transplant compared with LVADs commercially available at the time	Comparison to a patient population already implanted with LVADs rather than prospective randomization
ENDURANCE (2012)	Non-inferiority for the primary endpoint established in a large patient sample	Raised a concern for harm that ultimately resulted in HVAD recall by the FDA
MOMENTUM 3 (2019)	Seminal trial demonstrating the superiority of the most widely used contemporary durable LVAD	Primary endpoint comprising a composite of survival free of stroke or re-operation rather than survival alone Improved safety profile with the HM 3

its previous competitor, the HeartWare HVAD, it has been shown to contribute to fewer infections, less thrombosis, and less significant arrhythmias [21]. These diminished adverse events have contributed to impressive short-term life expectancy comparable to that with cardiac transplantation. Consequently, the current American AHA/ACC/HFSA society guidelines include a class 1A recommendation to consider durable LVAD for patients with stage D, NYHA class IV HF dependent on inotropes or temporary mechanical circulatory support. For patients not meeting these criteria but still experiencing NYHA class IV symptoms after maximal guideline-directed medical therapy, the current AHA/ACC/HFSA guidelines include a class 2A recommendation for durable LVAD support [2].

The components of the HM 3 include the inflow cannula, pump housing, outflow graft with bend relief, and a percutaneous driveline. The pump consists of an inflow cannula placed in the apex of the left ventricle and an outflow cannula located in the aorta. Blood enters the inflow cannula and exits the outflow cannula in the aorta, thus allowing blood flow to the rest of the body. The pump is attached to a driveline cable that exits the abdomen and connects to a controller outside of the body. The controller allows patients or medical providers to operate the LVAD by changing speeds to modify output, and provides alarm notifications of possible

malfunction. The LVAD is run on rechargeable batteries for mobile use, and it can be plugged into an electrical outlet during sleep.

Geometrically, the HM 3 has a total size as much as one-third smaller than the HM II, and it can fit within the pericardium without the need for a pocket. The device is fully magnetically levitated, such that a contactless and frictionless rotor decreases the risk of shear stress from friction [22]. Software programming inherently enables changes in pump speeds for fractions of a second, thus allowing for additional protection against stasis and conferring the unique feature of an “artificial pulse” on the HM 3. Specifically, this feature is present at a rotor speed above 4000 RPM. Every 2 seconds, the rotor decreases the flow by 2000 RPM for 0.15 seconds, then increases the flow by 4000 RPM for 0.20 seconds before returning to the set speed [23].

Important advances in surgical techniques have allowed for more efficient implantation and post-implantation patient outcomes. Traditional surgery for HM 3 implantation uses the full median sternotomy approach, which confers excellent surgical exposure and favorable control of the surgical field. However, a less invasive approach with bilateral small thoracotomies in the right second and left fifth intercostal space has been shown to be equally successful and to be associated with less right ventricular failure, less need for transfusion, and shorter

intensive care unit and hospital lengths of stay [24]. Importantly, a sternal-sparing approach such as this one may aid in keeping the right-ventricular geometry intact, owing to less pericardial dissection, and in minimizing mediastinal tissue.

To understand the HM 3 pump's parameters, the hemodynamic milieu in which this device must perform must be considered. Fundamentally, the flow across the device is proportional to the speed of the impeller, and is inversely proportional to the pressure difference across the inflow (i.e., the left ventricle) and outflow grafts (i.e., the aorta). As such, the flow across the device increases during ventricular systole and decreases in ventricular diastole for the same impeller speed. However, these changes are very small with respect to the hemodynamic milieu of the HM 3 and do not necessarily reflect the macrohemodynamics observed by the evaluating clinician.

Clinically meaningful changes in hemodynamics observed by a patient or clinician are better represented on a macro level by the relationship between the pump head pressure and pump flow (HQ curves). These curves are unique to each pump and to each operating speed for that pump. Although the relationship between the head pressure experienced by the pump and subsequent pump flow is usually linear, understanding the unique HQ curve in which each type of device operates is important, because it determines afterload sensitivity and the need to potentially titrate afterload-reducing agents. Although the HM 3 operates at the flat portion of the HQ curve in most clinical situations, it operates at a steeper portion at higher flows, in contrast to both the HVAD and HM II devices [23].

These fundamentals of LVAD function determine the pump parameters that can be reviewed and interpreted. The HM 3 LVAD displays the pump speed, which is the only parameter that can be adjusted by clinicians. It also displays the pump flow, but this readout is an estimate based on the relatively linear power-flow relationship. Pump power is also displayed and, for the HM 3, represents the power needed for the rotor to generate flow. In contrast, for other LVADs, the estimated power displayed may represent the total power needed to operate the device rather than being isolated to the power needed to generate blood flow. Finally, the pulsatility index (PI) is also displayed. The PI can range between 1 and 10, with lower values representing

greater LVAD support and higher values representing a greater contribution of native systolic function. The PI represents the variations between maximum and minimal power over a 15-second period. Because flow is directly associated with power, as postulated by power-flow curves, variations in the PI may be normal or abnormal depending on the clinical context. In all clinical situations, changes in the PI that occur in rapid succession merit careful investigation to rule out pathology.

Common pathology and responses can be predicted on the basis of the aforementioned discussion on pump function and display parameters. For instance, hypovolemia is similar to RV failure, in that the left ventricular preload is reduced. This state may manifest as diminished flow through the LVAD and changes in the PI depending on the mean aortic pressure, as governed by the HQ curves discussed above. In contrast, hypervolemia or significant aortic regurgitation would decrease the differential across the pump and might actually increase average flows, and the PI would be dependent on mean arterial pressure. Inflow and outflow graft obstructions can also occur; inflow graft obstruction from a thrombus would manifest as increased power output if the rotor is involved. Outflow graft obstruction might be more insidious and could potentially be present in a substantial portion of patients receiving HM 3 [25], possibly because of the accumulation of debris, either internally or externally. Diagnosis may frequently require additional imaging, including computed tomography scans of the graft. Outflow graft obstructions may manifest as diminished total flows and a low PI [23].

Adverse Events

Compared with the HM II, the HM 3 has been associated with significantly lower amounts of device thrombosis, debilitating strokes, and bleeding, although infection, right ventricular failure, and the arrhythmia burden are similar between devices [26]. These findings are consistent with long-term follow-up data [27]. Although the HM 3 decreases the risk of device thrombosis or embolic stroke, antithrombotic therapy is initiated shortly after implantation to further minimize this risk. Typically, IV heparin is started as soon as no evidence of bleeding is observed post-operatively. After the chest tubes

have been removed, aspirin and coumadin can be started. Of course, the risk of bleeding must be considered for every individual patient. Furthermore, the remaining burden of adverse events can be challenging for both clinicians and patients.

Gastrointestinal bleeding (GIB) can be a particularly challenging complication with substantial associated morbidity, and has been found to be present in almost one-third of patients with durable LVADs [28]. The etiology of an increase in GIB is likely to be multifactorial, and acquired von Willebrand factor deficiency from shear stress through the impeller and the need to use anticoagulation to prevent pump thrombosis are suspected to be major contributors. Management is determined primarily on the basis of the patient's stability and may require endoscopic treatment. In the absence of successful management, several agents can be used, although none have robust evidence supporting their widespread use [28]. These agents may include somatostatin analogues, anti-angiogenic agents, and even von Willebrand factor concentrate. A paradigm shift regarding the need for antiplatelet agents in patients receiving the HM 3 may occur, pending the results of the ARIES HM3 study [29]. The cessation of antiplatelet agents required after HM 3 implantation may decrease the future burden of GIB.

Strokes are common after durable LVAD implantation and remain an unacceptably high cause of morbidity and mortality. Initial estimates of stroke incidence in the continuous-flow LVAD era were as high as 10%, and were generally equally divided between hemorrhagic and ischemic strokes [30]. However, stroke risk is as much as one-third lower in patients receiving HM 3 than HM 2 treatment. Potential pathophysiologic factors, in addition to patient comorbidities, that may contribute to increased stroke risk center on the effect of non-pulsatile blood flow along with diminished autoregulatory mechanisms governing cerebral blood supply [31].

Infections in patients receiving durable LVAD therapy are common in the presence of an implanted heart pump. Driveline infections are the most common LVAD infection overall and tend to occur after the immediate post-operative period. The most common pathogens tend to be skin flora, among which *Staphylococcus aureus* is most frequently observed. Multi-drug resistant organisms are similarly common in this patient population. Prevention

is focused on excellent driveline care with weekly dressing changes. The use of chlorhexidine cleaning solution has been shown to be particularly effective in decreasing driveline infections, in contrast to povidone-iodine [32]. Treatments for identified driveline infections include a short course of antibiotics, chronic suppressive antibiotics, surgical debridement, or even progression to cardiac transplantation [33]. Further information regarding infection prevention and treatment has been previously reviewed [34].

Valvular dysfunction across all valves is almost certainly a consequence of deranged loading conditions and structural remodeling in patients undergoing durable LVAD therapy. The aortic valve is particularly prone to dysfunction because of continuous flow physiology; unloading the left ventricle necessitates a higher transvalvular gradient that precludes regular aortic valve opening. Valvular changes may result, thus leading to leaflet dysfunction, aortic sinus changes, fusion of valve leaflets, and worsening aortic insufficiency [35]. For patients with more than mild aortic insufficiency at the time of LVAD implantation, surgical techniques to avoid future worsening of aortic insufficiency may involve approximating the aortic nodules with a "Park" stitch, oversewing the valve completely, or replacing the native valve with a surgical valve. These techniques are dependent on surgical considerations and expertise, and no discernible superiority has been reported for one method over the others. Subsequent worsening of aortic insufficiency may be treated with repeated surgery, although percutaneous techniques, such as percutaneous aortic valve replacement or percutaneous occlusion of the aortic valves, are also emerging options [36].

Cost Effectiveness of Medical Care and LVADs

The cost of LVAD development, placement, and post-operative care can financially ruin patients, their families, and medical systems. The cost effectiveness of LVAD therapy for a patient is not directly proportional to the growth of the implanting centers themselves. With increasing LVAD implantation, needs arise for both pre-implantation and post-implantation invasive and non-invasive testing, as well as associated costs

of creating and maintaining a multi-disciplinary team and costs of hospitalizations. Low resource healthcare systems will have difficulty in maintaining this level of care. An integrative analysis of these cost effectiveness variables remains to be performed but would be expected to influence the ability to provide life-saving care to all patients in need.

One recent development that may increase accessibility to healthcare is telemedicine. Telemedicine shows promise in delivering quality care, despite lacking the specialized equipment previously believed to be required for comprehensive patient assessment [37]. Telemedicine may further contribute to the cost effectiveness of durable LVADs in the future. Improved provider education and continued advancements in telemedicine capabilities may allow patients to remotely access quality care, even when they are located far from specialized medical centers. Additional refinement of telemedicine's capabilities remains ongoing; for instance, implantable pressure-sensing devices may allow for more frequent hemodynamic measurements and the ability to adjust medications without an in-person visit [38]. However, the applicability and generalizability of these strategies to different countries worldwide will necessarily be contingent on the medical structures already in place.

Goals of care remain a critical aspect of both cost-effective care and ensuring that patients undergoing LVAD placement understand the extent to which their lives will be affected. To assist in decision-making, consultation with providers specializing in palliative care to ensure that goals of care are adequately defined and LVAD implantation is desired is intuitively logical. However, in clinical practice, overall integration with palliative care in the context of LVAD implantation discussion remains objectively low [39]. Individual goals of care should be recognized to differ among national and international regions. For instance, the roles of cultural and spiritual factors in Asian patients may specifically need to be considered during the decision-making process for LVAD support [40]. In particular, strict adherence to expected gender roles has been shown to affect attitudes toward durable LVAD support in this patient population [41]. If resources are not available to address each individual in a comprehensive manner, then durable LVAD implantation is unlikely to improve objective and subjective quality of life,

even if it improves total mortality over medical therapy alone. In regions of the world with limited access to healthcare technology and innovation, this factor becomes as important as cost-effectiveness, health literacy, and financial feasibility.

Future Directions

As technology improves, patients will experience fewer adverse events, and their survival will lengthen. Long-term survival with the HM 3 is currently approaching 60% at 5 years, exceeding that of its axial flow-pump competitors, primarily because of a decrease in hematologic events [27]. Although pump thrombosis remains relatively low with the HM 3, stroke and bleeding events remain high. One area currently being evaluated is the need for antiplatelet and anticoagulation. The ARIES HM3 trial, a global, prospective, randomized, double blind, placebo-controlled, non-inferiority trial, is comparing standard coumadin with aspirin vs. coumadin with placebo post-implantation in patients receiving HM3. The trial is currently ongoing; however, if the risk of pump thrombosis is non-inferior between groups and the rate of GI bleeding decreases, the risk of bleeding adverse events in the future may significantly improve.

Additional technological improvements will further improve results. The power source of the HM 3 remains an issue. The HM 3 LVAD uses 14-volt lithium-ion batteries, which can provide 17 hours of support and require approximately 4 hours to charge, thus posing a substantial burden on patients and caregivers, particularly those living in rural areas with inconsistent electricity. Additional work to maximize the efficiency of the batteries remains ongoing. Initial iterations of durable LVADs were not considered more cost-effective than medical therapy, with a cost of approximately \$200,000 per quality-adjusted life year [2]. Continued improvement in battery life is expected to be a key contributor to the cost-effectiveness of durable LVAD therapy.

One unavoidable fundamental feature of the HM 3 and all prior iterations of durable LVADs is the connection to an external driveline. Despite the aforementioned evidence strongly supporting the use of durable LVADs in transplant ineligible patients, patients must still undergo cardiac surgery, be

permanently tethered, and be subject to debilitating complications. A fully implantable left ventricular assist device would be ideal for durable mechanical support. Removing a percutaneous drive line and allowing for wireless charging would significantly decrease the risk of infection rates and enable higher quality of life. Although several devices are currently under development (Abbot FILVAS™, Corvion™), widespread use in clinical practice remains a future goal rather than a near reality.

Enhanced risk stratification for LVAD candidates is another method for maximizing survival in these patients. The HM 3 risk score (HM3RS) is used to predict 1- and 2-year survival after HM 3 implantation, and should be used during the patient education process. This risk-score uses age, presence of prior valvular procedures or coronary artery bypass grafting, plasma sodium, BUN, left ventricular end-diastolic diameter <5.5 cm and a RAP/CVP >0.6 to provide estimates of survival [42]. Use of these risk factors will ideally improve patient outcomes and quality of life.

As HF management and monitoring improves, patients requiring LVADs will have improved quality of life and fewer hospitalizations. Approximately 20% of patients receiving LVADs continue to experience HF symptoms post-implantation. Despite medical management with diuretics and goal directed medical therapy, patients may experience HF exacerbation and hospitalizations. Right heart catheterization is used to assess hemodynamics to optimize medications and VAD speeds; however, this method is invasive and is not always routinely available. Another technology beginning to play a major role in HF monitoring is pulmonary artery pressure (PAP) sensors, such as CardioMEMS. In the INTELLECT-2HF trial, patients with HM II and HM 3 LVADs were implanted with CardioMEMS and had their PAP monitored, and those with lower PAP were found to have improved 6-minute walk test outcomes and fewer HF exacerbation hospitalizations [43]. Although the study had no control group, it does suggest that PAP monitoring in patients receiving LVADs may play a major role in improving quality of life.

Although the HM 3 is available in the United States, locally produced VADs will increase cost-effectiveness and availability to countries worldwide. One such example is the CH-VAD™, which

is currently in production as China's first magnetically suspended centrifugal VAD. This device has lower thrombotic and hemolytic complications than the HM II and was approved for marketing in 2021 [44]. To date, it has been placed in at least 50 patients, but it continues to undergo clinical trials in the United States.

Ultimately, durable LVADs have evolved with advances in the understanding of stage D cardiomyopathy. Although they perform better than optimal medical therapy, they are not without risk. Patients effectively trade one disease process for another. In summary, a durable LVAD can be the right device for the right patients, who are unable to receive cardiac transplantation because of contraindications or lack of availability of donors. However, choosing the right patients can be a particularly challenging task; medical criteria must be met, but the individual goals of care must also be confirmed to ensure that post-implantation care, support, and quality of life are acceptable. On a broader level, we believe that this device cannot be sustained by low-resource healthcare systems, independently of patient factors. This situation may change over time, with the development of a fully implantable device, utilization of telemedicine, and an additional decrease in post-implantation adverse events. Unfortunately, marked improvements in these categories may be many years away. In the interim, VADs remain a costly but effective alternative for patients with stage D cardiomyopathy who are unable to undergo heart transplantation. In countries such as China, independently developed durable LVADs, such as the CH-VAD, that are compatible with the unique healthcare landscape and surrounding cultural beliefs, will be the most cost-effective option.

Acknowledgments

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Conflict of Interests

Leway Chen MD, MPH: Consultant for Abbott, **Anas Jawaid MD:** None. **Eric Czinn MD:** None.

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