Advanced Heart Failure and Left Ventricular Assist Devices- Are we there yet? - A Review of the Literature

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Abstract

Left ventricular assist devices (LVADs) have revolutionized therapy for patients with Stage D heart failure (HF) with reduced systolic function (HFrEF) with improved survival benefits but also meaningful changes in quality of life and functional capacity. With technological advances and improved durability of devices, length of survival has significantly improved. With continued organ donor shortage, LVADs frequently serve as a substitute for cardiac transplant as destination therapy, particularly among the elderly. This review provides an overview of the present status, indications and advances in LVADs.

INTRODUCTION

The incidence and prevalence of patients with Heart failure (HF) is increasing at alarming rates. HF has become one of the largest cardiovascular epidemics of modern times. With an aging population; advancement of therapies and improved survival of patients with HF and ischemic heart disease, this is going to continue to be a major epidemic [1-3]. HF is a global problem with an estimated prevalence of 38 million patients worldwide and that number continues to rise. It is the most common diagnosis among hospitalized patients aged ≥ 65 years of age and in high-income nations. Despite the significant advancements in HF therapy, the prognosis of HF remains poorer than that of most malignancies. Approximately 50% of the HF population has HF with reduced systolic function (HFrEF). A small subset of these patients (0.5-5%) of patient with HF respond poorly to standard guideline directed medical therapy (GDMT) and progresses to chronic advanced HF [4,5]. Among patients with extremely poor prognosis, due to advanced age and co morbidities, palliative care had been the only option. Even though heart transplantation is an excellent treatment option for patients who are good candidates; the availability of suitable donor remains a limiting factor.

Patients with Stage D HF (advanced HF) have a poor short-term survival and have a very small chance of receiving a transplant. The emergence of continuous flow (CF) left ventricular assist devices (LVADs) hold the greatest promise for these patients. It does so by augmenting the circulation to meet the body's physiological needs thereby improving survival and improving quality of life.

The American Heart Association (AHA)/ American College of Cardiology (ACC) guidelines for 2013 provides a Class Ila Level of recommendation (Level of Evidence B) for LVAD therapy among a selected subgroup of patients (LVEF <25%, NYHA Class III-IV functional status despite GDMT, including CRT when indicated ) with either high predicted 1-2 year mortality or dependence of continuous parenteral inotropic support) in whom definite management like cardiac transplantation or cardiac recovery is anticipated. It also suggests that the use of nondurable Mechanical Circulatory Support (MCS), including the use of percutaneous and extracorporeal ventricular assist devices (VADs), is reasonable as a “bridge to recovery” or “bridge to decision” for carefully selected patients with HFrEF with acute, profound hemodynamic compromise (Level of Evidence: B) while durable MCS is reasonable to prolong survival for carefully selected patients with stage D HFrEF (Level of Evidence: B) [6]. The focused update of the ACC/AHA guidelines from 2017 reflects no changes to these recommendations [7].

STAGE D HEART FAILURE AND TREATMENT: EMERGING ROLE OF LVADS

Various terminologies have been used to describe the group of patients who are classified with ACCF/AHA stage D HF, including “advanced HF,” “end-stage HF,” and “refractory HF.” In the 2009 ACCF/AHA HF guideline, stage D was defined as “patients with truly refractory HF who might be eligible for specialized, advanced treatment strategies, such as MCS, procedures to facilitate fluid removal, continuous inotropic infusions, or cardiac transplantation or other innovative or experimental surgical procedures, or for end-of-life care, such as hospice.” “The European Society of Cardiology” as developed a definition of advanced HF with objective criteria (Table 1) [8]. There are clinical clues that may assist clinicians in identifying patients who are progressing toward advanced HF (Table 2) [9]. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) has developed 7 profiles that further stratify patients with advanced HF (Table 3) [10].

Cardiac transplantation has been associated with excellent outcomes with a median survival of 10.7 years and survival, conditional on surviving to 1 year after transplant, reaching 13.6 years [11]. It also leads to significant improvement in the quality of life (QOL). In the United States, 117,755 patients are in need of a heart transplant and there are 75,982 patients active on the transplant list. Of these only 14,073 patients received heart transplant as of May of 2017 [12]. The major limiting factor to the growth of the cardiac transplant program has been the limited donor supply. With the results of the PROCEED II (Randomized Study of organ care System Cardiac for Preservation of Donated Hearts for Eventual Transplantation) trial which has shown non-inferiority of ex-vivo preservation to cold ischemia undergoing cardiac transplant with standard donors- the geographic limit with cold preservation techniques may be a thing of the past [13]. Nevertheless, despite the promise of more usable organs, with the donor supply remaining flat, cardiac transplantation is unfortunately not the solution for majority of the patients.

Fortunately, with the advent of MCS, transplant patients are able to receive mechanical support while they wait for an acceptable organ. LVADs are typically offered to transplant candidates who are developing end organ damage despite maximal medical therapy with an anticipated long waitlist time (large size and/or blood type O recipient) [14]. These categories correspond to INTERMACS Level 1-3. The INTERMACS scale assigns patients with advanced HF into 7 levels according to hemodynamic profile and functional capacity.

Initial use of pulsatile-flow LVADs and total artificial hearts demonstrated an improved survival among patients with advanced HF treated with Bridge to Transplant (BTT) (Table 4). The REMATCH study was the landmark study published in 2001 that demonstrated improved survival in advanced HF patients ineligible for transplantation treated with LVAD vs. optimal medical therapy [15]. More recent studies have shown continued improvement in survival and quality of life in patients implanted with CF LVADs compared with first-generation pulsatile devices (Table 4). The HM II was the first CF LVAD to receive US Food and Drug Administration approval for commercial use as BTT therapy for patients with advanced HF waiting for a heart transplant. CF devices are now predominantly used for BTT [16]. Recent registry data demonstrate that the use of the HM II as BTT has increased since 2008, and in 2011 about 30% of patients at time of listing were implanted with an HM II. The annual mortality of status IA and IB patients on the united network of Organ Sharing (UNOS) waiting list has decreased in recent years, which correlates with an increase in HM II use. With the recently published data from MOMENTUM 3, which was primarily designed to test the non-inferiority of the Heart Mate 3 LV assist system to the Heart Mate II LVAD, there were better outcomes at 6 months than was implantation of an axial-flow pump, primarily because of the lower rate of reoperation for pump malfunction [17].

INDICATIONS FOR MECHANICAL CIRCULATORY SUPPORT

There are three major indications for the use of LVADs

1. Bridge to Transplant: This indication is for heart transplant patients who are too sick to wait for donor to be identified because of severe acute or acute on chronic HF, or have contraindications that are deemed transient to transplantation.

2. Destination Therapy: LVADs are used as a lifelong support as an alternative for transplantation for patients deemed ineligible for heart transplantation.

3. Bridge to bridge: This is for patients who present with severe shock or following a cardiac arrest and are supported with a temporary support VAD to see if they become candidates for long-term support devices.

   The most common indication, which constitutes 40% of all LVAD implantation according to data from INTERMACS, is for bridge to destination therapy [17]. It is used when the best long-term option for a given patient is unclear at the time of LVAD implantation.

   Data from the ISHLT (International Society of Heart and Lung Transplantation) registry show more than 33% of all patients who underwent transplantation has a LVAD [18,19]. This percentage can vary according to countries and can be as high as 75% in programs where donor availability is low. Duration of mechanical support does not seem to have an adverse impact on mortality after cardiac transplant

INCLUSION/EXCLUSION CRITERIA AND PATIENT SELECTION FOR LVADS

Centers for Medicare and Medicaid Services have established criteria for implantation of LVAD which are derived from the REMATCH (Randomized Evaluation of mechanical Assistance for the Treatment of Congestive Heart Failure) and Heart Mate II DT trials [20].

2. Patients with NYHA functional Class IV symptoms who have failed to respond to optimal medical management, for at least 45 of the past 60 days, or have been intra-aortic balloon pump (IABP) dependent for 7 days or IV inotrope dependent for 14 days.
Table 1: ESC Definition of Advanced HF.

ESC Definition of Advanced HF

1. Severe symptoms of HF with dyspnea and/or fatigue at rest or with minimal exertion (NYHA class III or IV)
2. Episodes of fluid retention (pulmonary and/or systemic congestion, peripheral edema) and/or reduced cardiac output at rest (peripheral hypoperfusion)
3. Objective evidence of severe cardiac dysfunction shown by at least 1 of the following:
   a. LVEF <30%
   b. Pseudonormal or restrictive mitral inflow pattern
   c. Mean PCWP >16 mm Hg and/or RAP >12 mm Hg by PA catheterization
   d. High BNP or NT-proBNP plasma levels in the absence of noncardiac causes
4. Severe impairment of functional capacity shown by 1 of the following:
   a. Inability to exercise
   b. 6-Minute walk distance 300 m
   c. Peak VO₂ <12 to 14 mL/kg/min
5. History of HF hospitalization in past 6 months
6. Presence of all the previous features despite “attempts to optimize” therapy, including diuretics and GDMT, unless these are poorly tolerated or contraindicated, and CRT when indicated

Abbreviations: BNP: B-type Natriuretic Peptide; CRT: Cardiac Resynchronization Therapy; ESC: European Society of Cardiology; GDMT: Guideline-Directed Medical Therapy; HF: Heart Failure; LVEF: Left Ventricular Ejection Fraction; NT-proBNP: N-Terminal pro-B-type Natriuretic Peptide; NYHA: New York Heart Association; PA: Pulmonary Artery; PWCP: Pulmonary Capillary Wedge Pressure; RAP: Right Atrial Pressure.

Adapted from Metra et al, [100].

Table 2: Clinical Events and Findings Useful for Identifying Patients with Advanced HF.

Repeated hospitalizations or ED visits for HF in the past year
Progressive deterioration in renal function (eg, rise in BUN and creatinine)
Weight loss without other cause (eg, cardiac cachexia)
Intolerance to ACE inhibitors due to hypotension and/or worsening renal function
Intolerance to beta blockers due to worsening HF or hypotension
Frequent systolic blood pressure <90 mm Hg
Persistent dyspnea with dressing or bathing requiring rest
Inability to walk 1 block on the level ground due to dyspnea or fatigue
Recent need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose >160 mg/d and/or use of supplemental metolazone therapy
Progressive decline in serum sodium, usually to <133 mEq/L
Frequent ICD shocks

Abbreviations: ACE: Angiotensin-Converting Enzyme; BUN: Blood Urea Nitrogen; ED: Emergency Department; HF: Heart Failure; ICD: Implantable Cardioverter Defibrillator.

Adapted from Russell et al, [101].

3. Left ventricular ejection fraction of <25% and
4. Functional limitation with a peak oxygen consumption of <14 ml/kg/min, unless on an IABP, IV inotrope, or physically unable to perform the exercise test.

Absolute contraindications include systemic illness with a life expectancy of less than 2 years or malignancy within 5 years, irreversible renal and hepatic dysfunction, severe obstructive pulmonary disease or other systemic disease with multi-organ involvement [21]. However, LVADs may be an acceptable option for patients with recent cancer, which might theoretically be cured, but unlikely to have a 5-year disease free survival typically required for cardiac transplantation. Active infection with HIV or advanced end organ function such as serum creatinine of 3.0 mg/dL may not preclude patients from LVAD implantation [22].

Presence of bleeding diathesis may be a serious contraindication for LVAD unless coagulopathy is caused by reversible hepatic dysfunction. Low platelet counts before implantation also predicts poor outcomes and is an exclusion criterion in most recent studies.

Moreover, all VAD patients should undergo a psychosocial evaluation by a trained mental health professional and social workers to ensure that are able to receive adequate postoperative care and medications before any decision for VAD implantation. Psychosocial predictors of poor post-implant outcomes are mental retardation, noncompliance, chemical dependencies (drug or alcohol), lack of adequate support system, personality disorders, underlying mental illness and organic brain disorders [23].

Severe aortic regurgitation needs to be corrected simultaneously with LVAD placement to avoid a closed loop circulation between LV and the ascending aorta. In most cases a bioprosthetic valve is placed. In some cases, the aortic valve
is completely closed surgically which makes the patient very sensitive to any VAD malfunctioning [24]. Mitral surgery is only necessary in the presence of significant mitral stenosis compromising LV filling. Intra-cardiac shunts are typically closed at the time of VAD implantation. Pre-existing mechanical or biological mitral or aortic prosthetic valves usually do not cause complications during LVAD implantation [25,26].

Active infection is a contraindication for VADs. Bacterial infections are especially dangerous but on the other hand controlled infection like HIV may not be a contraindication to VADs [27].

Table 3: Intermacs Profiles for Advanced Heart Failure.

<table>
<thead>
<tr>
<th>INTERMACS 1</th>
<th>Critical cardiogenic shock describes a patient who is “crashing and burning with life threatening hypotension and critical organ hypoperfusion. This patient can have modifier A or TCS</th>
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<tbody>
<tr>
<td>INTERMACS 2</td>
<td>Progressive decline describes a patient who has been demonstrated “dependent” on inotropic support with signs of continued deterioration or patients where inotropic support cannot be maintained. This patient can have modifiers A or TCS.</td>
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<tr>
<td>INTERMACS 3</td>
<td>Stable but inotrope dependent Patient Profile 3 can have modifier A, TCS and/or FF.</td>
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<tr>
<td>INTERMACS 4</td>
<td>Patient on oral therapy who are symptomatic at rest or with activities of daily living (ADL). This patient can have modifiers A and/or FF.</td>
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<tr>
<td>INTERMACS 5</td>
<td>Exertion Intolerant but comfortable at rest. This patient can have modifiers A and/or FF.</td>
</tr>
<tr>
<td>INTERMACS 6</td>
<td>Exertion Limited – patient able to do mild activity with occasional episodes of worsening symptoms. This patient can have modifiers A and/or FF.</td>
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<tr>
<td>INTERMACS 7</td>
<td>Advanced NYHA Class 3 describes a patient who is clinically stable and is comfortable with reasonable activity.</td>
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Modifiers of the Intermacs Patient Profile

A-Arrhythmia: This modifier can modify any profile. Recurrent ventricular tachyarrhythmias contributing substantially to the overall clinical course. This includes frequent shocks from ICD or requirement for external defibrillator, usually more than twice weekly.

TCS-Temporary Circulatory Support: This modifier can modify only patients who are confined to the hospital, Patient Profiles 1, 2, and 3; support includes, but is not limited to, IABP, ECMO, Tandem Heart, Levitronix, BVS 5000 or AB5000, Impella.

FF-Frequent Flyer: This modifier is designed for Patient Profiles 4, 5, and 6. This modifier can modify Patient Profile 3 if usually at home (Frequent Flyer is designated for a patient requiring frequent emergency visits or hospitalizations for intravenous diuretics, ultra filtration, or brief inotropic therapy. Frequent would generally be at least two emergency visits/admissions in the past 3 months or 3 times in the past 6 months.

Table 4: Trials and major Studies of destination therapy.

<table>
<thead>
<tr>
<th>Study (Ref #)</th>
<th>Number of patients</th>
<th>Device Tested</th>
<th>Comparison Group</th>
<th>Design</th>
<th>Patient characteristics</th>
<th>Exclusion Criteria</th>
<th>Primary Outcome</th>
<th>Freedom from Primary Outcome</th>
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<tr>
<td>REMATCH[15]</td>
<td>129</td>
<td>HMXVE</td>
<td>Medical Therapy</td>
<td>Prospective 1:1 HeartMate XVE vs. medical therapy</td>
<td>NYHA Functional Class IV for 60 days, LVEF &lt;25% and peak oxygen consumption &lt;14ml/min/kg (unless on balloon pump or physically unable to perform exercise test) or intra-aortic balloon pump or IV inotrope dependent for 14 days</td>
<td>Patient cannot be enrolled in a clinical trial with mortality as an end point. No investigational gent within 30 days of randomization. Must not have undergone cardiomyoplasty or ventricular reduction operation. Body surface area &lt;1.5m2. Contraindication for anticoagulation, Presence of mechanical aortic valve, CVA or TIA within 6 months of enrollment, &gt;70% carotid stenos or ulcerated carotid plaque, drug or alcohol dependency, systemic infection, serum Creatinine &gt;5.0mg/dl, mechanical ventilator support for &gt;48 hrs at time of enrollment. life expectancy &lt;2yrs</td>
<td>Death from any cause. 1 year HMXVE 52%, Medical therapy 25%, P=0.001</td>
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<tr>
<td>INTrEPID[96]</td>
<td>55</td>
<td>NovaCor</td>
<td>Medical Therapy</td>
<td>Prospective Non-randomized</td>
<td>LVEF &lt;25% for ≥ 6 months, NYHA Class IV symptoms for ≥ 3 months, two failed attempts at weaning from inotropic support by at least 7 days</td>
<td>All cause mortality at 6 months. 1 yr: Novocor 27%, Medical Therapy 11%, P=0.02</td>
<td>Death from any cause. 1 year HMXVE 52%, Medical therapy 25%, P=0.001</td>
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<tr>
<td>Study</td>
<td>Patients</td>
<td>Age</td>
<td>Functional limitations</td>
<td>LVEF</td>
<td>NYHA Class IIB or IV symptoms</td>
<td>Device Limitations</td>
<td>Interpretation</td>
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<tr>
<td>Heart Mate II DT Trial[72]</td>
<td>192</td>
<td>Heart Mate II</td>
<td>HMXVE</td>
<td>Prospective randomized 2:1 Heart Mate II vs. HMXVE</td>
<td>LVEF &lt;25%, NYHA Class IIB or IV symptoms</td>
<td>At least 45 days of the 60 days before enrollment, Dependent on IABP for a period of 7 days or inotropes for a period of at least 14 days before enrollment, peak oxygen consumption &lt;14ml/min/kg or less than 50% of predicted value</td>
<td>Irreversible severe renal, pulmonary or hepatic dysfunction or active infection</td>
<td>Survival at 2 years of disabling stroke and device replacement</td>
</tr>
<tr>
<td>Early vs Late HM II DT[97]</td>
<td>Midtrial n=281 vs. Early trial n=133</td>
<td>Heart Mate II</td>
<td>HMXVE</td>
<td>Retrospective analysis of patients enrolled in Heart Mate II DT Trial</td>
<td></td>
<td></td>
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<td>Survival at 2 years of disabling stroke and device replacement</td>
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<tr>
<td>HM II Post-approval[98]</td>
<td>247</td>
<td>Heart Mate II</td>
<td>HMXVE</td>
<td>Prospective evaluation of the first 247 patients who underwent HM II implantation after FDA approvals</td>
<td></td>
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<td>Survival at 2 years of disabling stroke and device replacement</td>
</tr>
<tr>
<td>ENDURANCE [99]</td>
<td>446</td>
<td>Heart Ware HVAD</td>
<td>HMII</td>
<td>Prospective 2:1 randomization</td>
<td>LVEF &lt;25%, NYHA Class IIB or IV symptoms</td>
<td>At least 45 days of the 60 days before enrollment, Dependent on IABP for a period of 7 days or inotropes for a period of at least 14 days before enrollment, Body surface area ≥1.2m2, BMI&gt;40 Prior cardiac transplant Eligible for cardiac transplant History of untreated abdominal/thoracic aneurysm &gt;5cm, Cardiotoracic surgery within 30 days, Acute Myocardial infarction within 14 days, Symptomatic cerebrovascular disease, or stroke, Severe RV failure, Active uncontrolled infection, Serum creatinine &gt;3.0 or requiring dialysis, Contraindications for anticoagulation, Cirrhosis of liver or AST/ALT &gt; 3 times upper limit</td>
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<tr>
<td>ROADMAP [90]</td>
<td>200</td>
<td>HMII Medical Therapy</td>
<td>Medical</td>
<td>Observational study of DT in INTERMACS profile 4-7</td>
<td>Age 18-85 yrs, NYHA Class IIB or IV functional limitations, and LVEF ≤ 25% on optimal medical therapy, Inability to tolerate neurohormonal antagonist, 6 min walk distance &lt;300 m within 45 days before enrollment, One unscheduled hospitalization for HF in last 12 months</td>
<td>Presence of mechanical aortic or mitral valve including planned conversion to bioprosthesis, Platelet count &lt;100,000/ml, Inability to perform 6 min walk test, IV inotrope within 45 days, Existence of any MCS Pregnancy, History of cardiac/other organ transplant, Psychiatric disease, active uncontrolled infection, intolerance to anticoagulation, Coronary revascularization within 3 months, GFR ≤25ml/min or need for renal replacement therapy, any condition that could that limit survival to less than 2 years</td>
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EVOLUTION OF LVAD TECHNOLOGY

First-generation volume displacement LVADs used a diaphragm and unidirectional valves to replicate the pulsatile cardiac cycle through diastolic filling and systolic emptying of the device. The results of the REMATCH trial led to FDA approval of the Heart Mate XVE for DT in 2002 [15]. With growing concerns regarding the large pump size, adverse events, and limited durability, with uniform failure after 18 to 30 months of support, Heart Mate XVE production was eventually discontinued.

With improved durability and pump size, CF-LVAD technology has quickly developed in the last two decades. Contemporary second- and third-generation LVADs are valve-less pumps that utilize a permanent magnetic field designed to rapidly spin a single impeller supported by mechanical, hydrodynamic or magnetic bearings. Second-generation axial pumps have the impeller outflow directed parallel to the axis of rotation. The rotor spins on mechanical [Heart Mate II, Jarvik-2000, and Heart Assist] 5 or contact-free bearings (Incor, Berlin Heart, Berlin, Germany). Third-generation centrifugal pumps have the impeller outflow directed perpendicular from the axis of rotation (HeartWare Ventricular Assist Device [HVAD] and Heart Mate III). Mixed designs, pumps where blood flow follows the axis of rotation but exit perpendicular to the inflow (miniature ventricular assist device [MVAD] [HeartWare]) are also in use. Most recent pumps are contact-free, with no mechanical bearings (to avoid thrombus formation) and an impeller suspended using magnetic and/or hydrodynamic systems. Hydrodynamic levitation, in contact-free systems, uses a layer of blood (pumping) to lift the rotor (Incor, HVAD, and MVAD). Full magnetic levitation utilizes magnetic bearings only to levitate the rotor (Heart Mate III). Avoiding hydrodynamic bearings may reduce the risk that small pieces of foreign matter, such as a thrombus, disrupting the operation of the rotor, leading to additional thrombus formation and pump dysfunction.

In CF-LVADs, pump blood flow is directly proportional to rotor speed and inversely proportional to the pressure differential between the left ventricle and aorta. However, axial and centrifugal pumps differ in their hydrodynamic performance [28,29]. Axial flow pumps show a steep and inverse linear relationship between flow and head pressure. In contrast, this relationship is flatter and more susceptible to head pressure changes (i.e., more sensitive to re-load and after load) in centrifugal pumps. With the same change in pressure, centrifugal pumps generate larger changes in flow, ranging from 0 to 10 l/min, whereas the axial flow pump flow ranges from 3 to 7 l/min. These hydrodynamic characteristics of centrifugal pumps leads to a more pulsatile waveform; better flow estimation; and a lower risk of suction events (e.g., in a setting of dehydration, arrhythmias, or right ventricular failure [28-30].

ADVERSE OUTCOMES AND CHALLENGES WITH VADS

There is no doubt that LVADs have improved survival, functional capacity and QOL with advanced HF. However, only 30% of the recipients are free of any adverse effects within the first year [31]. The high burden of adverse effects associated with this therapy has been a limiting factor in offering it to patients without advanced HF. According to INTERMACS, the most common adverse effects (AE) (in declining frequency) include bleeding, infection, ventricular arrhythmias, respiratory failure and stroke [32].

AE of LVADs can be classified into three broad categories

1. AE intrinsic to the pump and its constituents (pump malfunction, controller faults, driveline faults and short -to- shield malfunction)
2. Patient related AE (ventricular arrhythmias, valvular insufficiency and RV failure)
3. AE resulting from pump patient interface (acquired von Willebrand disease, infection, stroke and pump thrombosis)

**RV DYSFUNCTION**

Most patients with advanced HF have some degree of RV dysfunction. However, severe RV dysfunction is often a contraindication for lifelong VAD therapy. RV failure, with the need for prolonged inotropic support or the temporary use of a RV assist device, occurs in 10-40% of LVAD implants and can lead to longer hospital stay and a higher risk of perioperative death [33]. Late onset RV failure has emerged as a new clinical challenge and it is associated with poor survival and decreased QOL [34]. Development of right ventricular (RV) failure is associated with worse outcome if it develops after LVAD implantation. It is associated with higher mortality, greater risk of bleeding and/or re-operation, longer hospitalization and a higher rate of renal insufficiency [35-37]. RV failure occurs in up to 20% of patients especially in the setting of biventricular dysfunction in non-ischemic cardiomyopathy.

**INFECTIONS**

Infection is now recognized as the leading cause of late mortality with estimated prevalence of 8% and 18% at 6 months and 12 months, respectively, after diagnosis of driveline infection [32,38]. Most infections start as superficial driveline infections but can progress over months to deep tissue infections [39,40]. The obligatory use of long-term antimicrobial therapy has led to the emergence of drug resistant organisms such as Pseudomonas and Staphylococcus aureus.

**LVADS AND VENTRICULAR ARRHYTHMIAS**

Ventricular arrhythmias are common and frequently associated with increased mortality in patients with LVADs [41]. However, it is often suggested that sudden cardiac death is an uncommon mode of death in these patients. In some studies, patients with LVADs have been reported to survive for days to months despite being in ventricular arrhythmias [42-45] and the postulated mode of death in these patients is primarily related to right heart failure and renal dysfunction.

The benefit of implantable cardioverter-defibrillators (ICDs) in patients with LVADs has remained unclear. Data for the effect of ICD on survival of patients with LVADs have been conflicting and limited to observational studies with smaller number of patients [12-17]. However, in a recent meta-analysis of 6 observational studies [46], including 931 patients with LVADs, presence of an ICD was associated with a 39% relative risk reduction in all-cause mortality (RR: 0.61; 95% confidence interval [CI]: 0.46 to 0.82; p <0.01). Among subgroup of patients with CF-LVAD (n=361), ICD use was associated with a statistically no significant trend toward improved survival (RR: 0.76; 95% CI: 0.51 to 1.12; p = 0.17).

**BLEEDING**

Bleeding has been one of the most common complications since the introduction of LVAD therapy, with a 4-fold increased risk of reoperation for bleeding over standard open heart surgery [47]. This is caused by multiple factors including abnormal coagulation at time of surgery, often because of preoperative use of warfarin and/or anti-platelet agents or hepatic congestion, poor nutrition, high venous pressures, and adhesions frequently occurring in patients with previous sternotomy. There is now an important second phase of the risk of bleeding that develops beginning 1 month after implant, which may occur in up to 25% of patients. Increasing age seems to be most correlated with increased risk of bleeding. The most common site of bleeding is in the upper gastrointestinal tract [48-50] and is typically caused by or associated with development of arterial-venous malformations, primarily located in the stomach or early portions of the small bowel. This seems to be a unique sequela of continuous flow physiology, as it was not seen with the first generation of pulsatile flow devices. Patients with prior history of gastrointestinal bleeding should have upper and lower endoscopy before LVAD. Recent attention has been directed at the uniform reduction in multimers of von Willebrand factor in the serum in response to nonpulsatile flow as one possible explanation for the increased bleeding associated with continuous flow VADs [51,52].

**STROKE**

With incidence being reported anywhere between 12.1-28.7% in various studies [53-57], strokes remain one of the leading complications noted among patients. Strokes can be both thrombotic and hemorrhagic. It is not only a major cause of mortality; it is also a contraindication for future cardiac transplantation in most centers [58]. Risk factors for the development include uncontrolled blood pressure, infection, pump thrombosis, gastrointestinal bleeding and insufficient antithrombotic therapy [59-61]. Willey et al. has reported a worse outcome with large hemorrhagic strokes compared to ischemic strokes in their study population even though subdural and extradural hemorrhage was excluded from the analysis [62].

**EMERGING ROLE OF IMAGING IN LVAD**

Echocardiography remains the cornerstone of imaging in LVAD and the role of computed tomography (CT) is rapidly emerging among patients that have poor echocardiographic windows. Recent guidelines endorse the important role of echocardiography in various stages in the clinical care of LVAD patients ranging from preoperative patient selection, perioperative imaging, postoperative surveillance, optimization of LVAD function, trouble shooting of LVAD alarms and evaluation of native myocardial recovery. There are recommendations and protocols for the timing and performance of echocardiography during LVAD patient selection, device implantation and postoperative management [63]. Discussion regarding this is beyond the scope of the article and the readers can refer to the document from the American Society of Echocardiography for details regarding that [64].

Periodic LVAD surveillance transesophageal echocardiographic (TEE) exams are recommended to establish patient-specific baseline parameters for both LVAD and native heart function. It should be considered at approximately 2 weeks after device implantation or before index hospitalization discharge followed by surveillance TEE at 1, 3, 6 and 12 months post implantation and every 6 to 12 months thereafter.
Cardiac CT is rapidly emerging as an important modality of imaging in this group of patients and is usually a problem-solving tool when echocardiographic images are difficult or poor (Figure 1-3). There have been reports on the utility of MDCT (Multi-detector CT) for detection of complications where echocardiography has been unyielding [65]. There are also reports of the use of FDG-PET/CT imaging for LVAD related infections [66].

INNOVATIONS IN SURGICAL TECHNIQUES

LVAD implantation was perhaps one of the most morbid operations in cardiac surgery. The hospital mortality rate in the REMATCH Trial was as high as 29% with the perioperative bleeding complication of 46% [15]. With advances in surgical techniques, a recent study has shown the operative mortality as low as 1% and median hospital stay of 17 days [67]. Implantation of LVADs through small incisions instead of the traditional median sternotomy has been developed to reduce the invasiveness and morbidity in LVAD surgery. Even though more technically challenging, they result in the same positioning and functioning of the LVAD and trend is towards lesser AE like RV failure, bleeding and respiratory failure [68,69]. These techniques are not without disadvantages. Besides being more technically challenging and requiring more skills and time consuming, they are potentially more prone to technical complications and surgeons are left with very little scope of dealing with intraoperative complications. These approaches are more likely to applied more frequently with advancements in techniques and likely to become standard in the near future [70].

It is standard to repair certain cardiac defects at the time of the LVAD implantation for optimal functioning of the device. Moderate to severe aortic insufficiency (AI) needs to be treated and mitral stenosis needs to be eliminated. A significant atrial septal defect needs to be closed to prevent right to left shunt.
With devices lasting longer, moderate AI has been reported as high as 30% within 2 years of surgery [71]. Dealing with the late complications is associated with higher mortality and morbidity.

STATUSES OF PRESENT DAY LVAD- ARE WE FAR FROM PERFECT?

While we seem to have been able to achieve the goal of improved survival in the subgroup of patients with advanced heart failure, who otherwise would have a dismal long term outcome, the long term complications associated with CF-LVAD continue to plague our effort towards reaching the ultimate goal of survival without significant adverse effects with these devices. The post-approval Heart- Mate II DT study [72] reported a high probability of device- related adverse events in patients at 2-year follow-up: driveline infections (19%), sepsis (19%), strokes (11.7%), thrombus formation (3.6%), bleeding (54%), mechanical failures requiring replacement (4%), and right HF (18%). In addition, acquired von Willebrand disease rapidly develops in virtually all patients post-CF-LVAD implant. Aortic insufficiency is also frequent, with an incidence of >30% at 3 years.

THROMBOSIS AND BLEEDING WITH LVAD

The approval of CF LVADs created great enthusiasm, especially in the heart failure community, as these devices appeared to provide the much need solution some of the major problems of pulsatile flow (PF) LVADs, including frequent mechanical failure within 12 to 18 months of implantation, the loud noise generated, and the inability to implant the larger PF pumps in smaller patients, most of whom were women [72,73]. The CF LVADs also appeared to have superior rates of thrombosis and infection than PF LVADs [72,73]. There was a major setback to this enthusiasm in January 2014, when Starling et al. [74,75] reported that the rate of thrombosis of the Heart Mate II device (Thoratec Corp., Pleasanton, California) at 3 months post-implantation had increased from 2.2% before March 2011 to 8.4% by January 1, 2013—a finding confirmed in the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) registry [74,75]. LVAD thrombosis is a devastating complication, usually culminating with the need for urgent transplantation, LVAD replacement or death [74,76,77]. We now have the understanding that thrombotic and bleeding complications in LVAD patients are not solely dependent on the level of anticoagulation within the desired limits. Multiple factors influence the hemostatic homeostasis in CF-LVAD recipients. A testimony to our understanding that multiple factors seems to influence the hemostatic homeostasis in CF-LVAD recipients, are, patients who develop pump thrombosis on stable therapeutic INR or patients with recalcitrant gastrointestinal bleeding despite reduction or withholding of anticoagulation/antiplatelet therapy. A number of causes of LVAD thrombosis have been postulated and are the result of dynamic and complex interactions between the patient and the pump. Failure of maintenance of therapeutic anticoagulation, inadequate antiplatelet therapy, platelet activation by device materials or shear stress, decreased
flow rates with bearing heating and denaturation of coagulation proteins, abnormal angulation of the inflow cannula, new materials in the device, infection, overestimation of the level of anticoagulation using the activated partial thromboplastin time, and right ventricular failure are the important factors that are being thought to play a role in this important complication [78,79]. Systemic anticoagulation is recommended in all CF-LVADs currently approved for clinical use. Prospective investigations are therefore needed to determine the ideal approach to the monitoring of anticoagulation efficacy in this patient population. The balance of bleeding and thrombosis remains a constant and often perplexing challenge. Indeed, thrombotic and bleeding complications are a major source of morbidity and serve as a bottleneck for the intended goals of LVAD therapy- improved survival and better quality of life. Approaches that will decrease both bleeding and thrombotic complications are needed and unless we make significant strides towards this goal, we will continue to struggle to achieve ultimate goal of the perfect device.

COST-EFFECTIVENESS OF LVAD

VAD therapy has undeniably altered the prognosis of end-stage heart failure and restored patients to more normal functionality. But it is not without cost to the patient, their families, and the healthcare delivery system. First generation VADs were not found to be cost effective compared to medical therapy [80-84]. Currently nearly all implants used are second or third generation durable implantable continuous flow devices (HeartWare HLAD, Thoratec Heart Mate II, Jarvik 2000 Flow Maker, and Micromed Heart Assist) which are widely perceived to have superior performance compared to earlier devices. Aileen Clarke et al. investigated the cost-effectiveness of second and third generation ventricular assist devices (LVADs) as a bridge to transplant (BTT), compared to medical management with inotrope support in the British National Health Service (NHS ) bridge to heart transplant program [85]. Model outputs adapted by the authors included mean life years gained (LYG), mean quality- adjusted life years (QALYs) gained, mean costs, and mean incremental cost-effectiveness ratios (ICERs as (£($)/LYG and (£($)/QALY gained). Findings of the study suggested that in comparison to medical management, with inotropic support, individuals implanted with a LVAD had higher mean costs and higher survival benefit, delivering a probabilistic ICER of £53,527 (£84,963)/QALY (95% CI: £31,802 to £94,853; £50,479–£150,560) and a similar deterministic ICER of £55,173 (£87,576)/QALY for a lifetime.

In a similar study in the US patients, Shreibati et al. compared cost of care among Medicare beneficiaries before and after LVAD implantation [86]. They concluded that patients with advanced HF who are not dependent on intravenous inotropes would live 0.61 years longer, with improved quality of life (1.74 QALYs added), and incur an additional $3,644,400 in lifetime costs, if treated with DT-LVAD rather than medical management. These estimates imply that LVAD has an ICER of $209,400 per QALY gained for low-risk patients. In higher risk, potentially LVAD-ineligible patients, LVAD had an ICER of $171,000 per QALY gained.

LVADs in patients with non-inotrope-dependent HF appear to provide comparable value as LVADs in patients with inotrope-dependent HF. Using INTERMACS data, Long et al. [87], estimated an ICER of $212,100 (2016 U.S. dollars) for DT-LVADs in patients taking inotropes. In an older study, Rogers et al. [88], also evaluated LVADs in patients taking inotropes, with substantially higher mortality (92%) at 2 years for medical management and 42% for LVAD) and reported an ICER at 5 years of $220,000 (2016 U.S. dollars).

Currently, <1% of patients with advanced HF will receive an adult heart transplants in the United States [89]. If all of these patients were to receive a DT-LVAD, an estimated 100,000 new patients annually, the additional cost would be roughly $36 billion per year, nearly 6% of the entire Medicare budget. However, in the absence of any other viable alternative of therapy, unless we develop better devices with reduced adverse effects, this might be the only acceptable solution of this select subgroup of patients.

EARLY VS LATE INTRODUCTION OF LVAD

The ROADMAP Study (Risk Assessment and Comparative Effectiveness of left Ventricular Assist Device and Medical management) introduced the concept of extending the benefits of LVAD to the patient who are “less sick” with INTERMACS profiles 4 to 7 [90]. This moves away from the concept of reserving the therapy for the “sickest of the sick” where the benefits have already been demonstrated. While the study showed enhanced QOL and functional capabilities with early introduction of LVAD compared to optimal medical management (OMM), the results need to be interpreted cautiously. Key findings that need to be understood was that the survival rates were similar between the LVAD and OMM group and adverse effects were more common in LVAD versus OMM. While the ROADMAP study encourages the LVAD community to consider earlier introduction of LVADs, the challenges associated with such a decision also needs to be taken into consideration. In his editorial comment by Courtney R Bruce and Jennifer Barby [91], following the publication of the ROADMAP study, several commendations were made including collaborative discussion between referring and LVAD center cardiologist, tracking LVAD declination rates post ROADMAP, revisiting patient’s declination decisions and creating center specific decision regarding patient selection evaluation and candidacy determinations.

CONCEPT OF MYOCARDIAL RECOVERY WITH MECHANICAL CIRCULATORY SUPPORT

This concept arises from the fact that the heart has a ability to recover after significant injury, as exemplified by the reverse cardiac remodeling seen in a variety of clinical scenarios: the spontaneous recovery of the myocardium after acute lymphocytic myocarditis and improvement of left ventricular function after interventions (tachycardia induced cardiomyopathy and after cardiac resynchronization therapy) [92,93]. It is well known that there is pressure and volume overload in chronic HF with leads to progressive myocardial dysfunction and cardiac remodeling. There is clinical evidence that chronic mechanical unloading of the heart can achieve variable degrees of improvement in the structure and function of the native heart along with reversal of the systemic HF phenotype. Patients placed on long term MCS demonstrate reverse cardiac remodeling with restoration of cardiac function. The early results of the RESTAGE-HF (Remission
from Stage D Heart Failure) are extremely promising [94]. Even though the study population was relatively young (mean age of 35 years), with optimal medical therapy, and unloading of the heart with MCS, the primary endpoint (freedom of MCS or heart transplantation 1 year post VAD explant) was achieved in 33% of the studied population. The science of cardiac recovery in the setting of MCS is perhaps the most groundbreaking event in the era of LVADs. To advance this agenda, the National Heart, lung, and Blood Institute (NHLBI) convened a working group of experts in Bethesda, Maryland, to develop NHLBI recommendations aimed at advancing the science of cardiac recovery [95-101]. The biggest question to the clinicians will be, whether, exploring the mechanistic approaches of cardiac recovery at the genetic, molecular or physiological levels will improve the understanding of myocardial recovery and help develop novel interventions be extrapolated to the broader HF population. It seems that even though we have ways to go, we are starting to finally see some light at the end of the tunnel.

CONCLUSIONS AND FUTURE DIRECTIONS

LVADs may prove to be a viable alternative to cardiac transplantation by providing long-term support without the major disabling AEs. With the ability to improve patient survival that is competitive with heart transplantation up to approximately 2 years, there has been dramatic improvement and progress of this therapeutic modality. However, there is need for more improvement. The focus should be on developing a more compatible device with improved durability and fewer AEs. The future of fully implantable devices without need of external driveline while reducing infection risk will also significantly improve QOL. The concept of myocardial recovery holds the most promise in the future. The gaps in our basic science, as well as clinical knowledge of facilitated myocardial recovery, must be overcome by multidisciplinary and multicenter approaches that include combination of the cellular, structural, functional, and clinical attributes of myocardial recovery to develop a device that will be free of the shortcomings of the present generation of devices.

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