

Review Article



Left Ventricular Assist Devices (LVADS): History, Clinical Application and Complications

Howard J. Eisen , MD, FACC, FACP, FAHA, FAST, FHFA, FESC

Heart and Vascular Institute, Pennsylvania State University, Milton S. Hershey Medical Center, Hershey, PA, USA



Received: May 30, 2019

Accepted: Jun 3, 2019

Correspondence to

Howard J. Eisen, MD, FACC, FACP, FAHA, FAST, FHFA, FESC

Heart and Vascular Institute, Pennsylvania State University, Milton S. Hershey Medical Center, 500 University Drive, Hershey, PA 17033, USA.

E-mail: heisen@pennstatehealth.psu.edu

Copyright © 2019. The Korean Society of Cardiology

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs

Howard J. Eisen 
<https://orcid.org/0000-0003-1149-4344>

Conflict of Interest

The author has no financial conflicts of interest.

ABSTRACT

Congestive heart failure is a major cause of morbidity and mortality as well as a major health care cost in the developed world. Despite the introduction of highly effective heart failure medical therapies and simple devices such as cardiac resynchronization therapy that reduce mortality, improve cardiac function and quality of life, there remains a large number of patients who do not respond to these therapies or whose heart failure progresses despite optimal therapy. For these patients, cardiac transplantation is an option but is limited by donor availability as well as co-morbidities which may limit survival post-transplant. For these patients, left ventricular assist devices (LVADs) offer an alternative that can improve survival as well as exercise tolerance and quality of life. These devices have continued to improve as technology has improved with substantially improved durability of the devices and fewer post-implant complications. Pump thrombosis, stroke, gastrointestinal bleeding and arrhythmias post-implant have become less common with the newest devices, making destination therapy where ventricular assist device are implanted permanently in patients with advanced heart failure, a reality and an appropriate option for many patients. This may offer an opportunity for long term survival in many patients. As the first of the totally implantable devices are introduced and go to clinical trials, LVADs may be introduced that may truly be alternatives to cardiac transplantation in selected patients. Post-implant right ventricular failure remains a significant complication and better ways to identify patients at risk as well as to manage this complication must be developed.

Keywords: Congestive heart failure; Circulatory shock; Ventricular assist device; Pumps, heartassist; Cardiac transplantation

HEART FAILURE: DEFINITIONS AND THE MAGNITUDE OF THE PROBLEM

Heart failure is the final common pathway of a number of disorders which result in myocardial dysfunction. These can be classified as either heart failure with reduced ejection fraction (HFrEF) defined as a left ventricular ejection fraction (LVEF) less than 40% or heart failure with preserved ejection fraction defined as a LVEF greater than 40%.¹⁾ The etiologies of these forms of heart failure are disparate and beyond the scope of this review article. LVAD therapy is reserved for patients with HFrEF who have failed Guideline Directed Therapies

including renin-angiotensin-aldosterone system (RAAS) antagonists, sympathetic nervous system antagonists and cardiac resynchronization therapy (CRT) with worsening symptoms and cardiac dysfunction. Patients with New York Heart Association (NYHA) class IV symptoms (dyspnea at rest) despite optimal Guideline Directed Medical Therapies (GDMT) have a poor prognosis at one year as well as a poor quality of life.²⁾ Patient with American College of Cardiology Foundation/American Heart Association Stage D heart failure have dyspnea at rest despite maximal GDMT, essentially failing these therapies and required more advanced therapies such as heart transplantation or LVADs. These patients are said to have advanced heart failure.

It is estimated that six million Americans have heart failure. Additionally, heart failure results in over 1,000,000 hospitalizations, 600,000 deaths and 600,000 new cases in the United States.³⁾ This makes it the leading cause of death and hospitalizations in the United States. It is estimated that 5% of patients with heart failure have NYHA class IV symptoms, meaning that there are 300,000 patients with advanced heart failure who may be candidates for advanced therapies.³⁾ These numbers will likely increase as the population ages and as patients survive diseases that damage the ventricles that they would have succumb from such as myocardial infarction, diabetes and valvular heart disease. It is estimated that within the next twenty years in the United States, the number of heart failure patients will double as will the number of patients with advanced heart failure. As the number of heart transplants in the United States has never exceeded 5,000 per year, there is a clear need for advanced therapies as alternatives to heart transplants. Similar increases in the number of patients with heart failure and advanced heart failure are anticipated in Europe, Latin America and much of Asia.

HISTORY OF MECHANICAL CIRCULATORY SUPPORT

The earliest effort to use external technology to support the cardiovascular system was by John Gibbons to provide cardiopulmonary bypass (CPB) during cardiac surgery in a patient undergoing atrial septal defect repair. Surgeons subsequently used CPB to support patients outside of the operating room for post-surgical recovery and to enable cardiac recovery. This led to interest in providing support of patients in cardiovascular shock.⁴⁾ The National Institutes of Health (NIH) convened panels to develop strategies for providing this support. The earliest efforts were directed at completely replacing the heart. In the 1950s, Kolff developed a total artificial heart (TAH) at the Cleveland Clinic. Liotta in Argentina also worked on an artificial heart.⁵⁾ This work was done mainly in animals. Liotta subsequently moved to Baylor where a concerted TAH program was being developed. Michael DeBakey received a grant from the NIH to develop a LVAD.⁶⁾ After cardiac transplantation was first performed in Cape Town, South Africa and elsewhere around the world, the intention of these early devices was to serve as a bridge in patients in cardiogenic shock until a donor heart became available. The earliest ventricular assist devices (VADs) were paracorporeal with external VADs providing blood flow to the patients. The first of these was implanted in the late 1960s.⁸⁾ At Penn State University fifty years ago, Dr. William Pierce developed a pneumatic heart assist device (**Figure 1**).⁷⁾ This device ultimately became the Thoratec pneumatic VAD which was one of the first VAD to be approved by the Food and Drug Administration (FDA) as a bridge-to-transplant (BTT). It has subsequently been used as a BTT in over 4,000 patients for ventricular support. This technology evolved further into the HeartMate I, a pulsatile device that was first used over 25 years as a BTT.⁷⁾



Figure 1. The prototype of the first left ventricular assist device which became the Thoratec XVE and the HeartMate (with appreciation to Gerson Rosenberg, PhD, Professor of Artificial Organs, Pennsylvania State University, Hershey, Pennsylvania).

Destination therapy (DT) was first investigated as an approach for using LVADs, in this case the HeartMate I, as mechanical circulatory support (MCS) for patients with advanced heart failure in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial.⁹⁾ In this randomized clinical trial, 129 patients with advanced heart failure were randomized to receiving an LVAD (n=68) or receiving optimal medical therapy (OMM; n=61), consisting mainly of intravenous inotropic therapy. Patients who received an LVAD had a 48% reduction in the risk of all cause mortality compared to the OMM group.⁹⁾ Quality of life was improved in the LVAD vs. the OMM group. However, despite the survival advantage in the LVAD group, survival was only 52% at one year in the LVAD group.⁹⁾ LVAD patients had many adverse events related to their LVADs including infection, bleeding and device malfunction. The one year survival for the LVAD patients was far inferior for what was reported for heart transplant recipients at the time. Thus despite an improvement in survival compared to OMM, the outcomes with the HeartMate I as a device for DT was not adequate for DT to be widely adopted. This was due to the LVAD technology available at the time, the HeartMate. For DT to flourish and benefit more newer LVADs would have to be available.

CONTINUOUS FLOW LVADS: SECOND AND THIRD GENERATION LVADS

LVAD design evolved radically after the REMATCH trial with the development of continuous flow (CF) LVADs. These were no longer pulsatile. Instead, blood was propelled through a rotor. Flow was continuous and not pulsatile as in native hearts. These devices as opposed to the earlier HeartMate I required systemic anticoagulation. An initial study of 133 patients awaiting cardiac transplantation underwent implantation of the HeartMate II LVAD, a second generation VAD with an axial flow design.¹⁰⁾ Mean time of support was 126 days and the survival rate was 75% at six months and 68% at one year.¹⁰⁾ The latter represented an improvement from the 52% one year survival seen at one year in the REMATCH trial with the HeartMate.¹¹⁾ The functional status and Quality of Life improved three months after implantation of the CF LVADs. Major adverse events included right ventricular (RV) failure, postoperative bleeding, stroke, percutaneous lead infection and pump thrombosis.

A subsequent study in patients not eligible for cardiac transplantation compared the Heartmate II to the HeartMate I in a 2:1 randomization ratio.¹²⁾ The 134 patients received the HeartMate II and 66 received the HeartMate I. At two years, patients receiving the HeartMate II had a 58% survival compared to 24% for the HeartMate I recipients.¹²⁾ HeartMate II recipients had greater freedom from stroke or VAD replacement indicating that the HeartMate II was a more durable VAD than its predecessor. These results led to FDA approval of the HeartMate II for MCS for DT and the obsolescence of the HeartMate I which subsequently was no longer produced.

Third generation LVADs were CF devices which had centrifugal flow which meant that flow in the VAD was perpendicular to flow coming in from the left ventricle. These devices were smaller than the HeartMate II and had a moving impeller suspended by magnetic and hydrodynamic forces to reduce shear and prolong LVAD durability. The archetype LVAD in this group is the HeartWare ventricular assist device (HVAD) which was studied in the The HeartWare™ Ventricular Assist System as Destination Therapy of Advanced Heart Failure (ENDURANCE) study which was a comparison to of the HVAD centrifugal flow VAD to the HeartMate II axial flow device.¹³⁾ The 446 patients were randomized in a 2:1 manner to the HVAD (n=297) vs. the HeartMate II (n=148). The primary end point was survival at 2 years free from disabling stroke or device removal for malfunction or failure.¹³⁾ The primary endpoint was achieved in 554.1% of HVAD and 59.1% of HeartMate II patients (p=NS). More patients in the HeartMate II group had VAD malfunction or failure requiring replacement (16.2% vs. 8.8%) while the stroke rate was higher in the HVAD group compared to the HeartMate II group (29.7% vs. 12.1%).¹³⁾ Strokes were associated with higher blood pressures. Thus while the HVAD appeared to be more durable than the HeartMate II, it was associated with a higher stroke rate.¹³⁾

INDICATIONS: WHO SHOULD GET AN LVAD?

LVADs are reserved for those with poor cardiac function and are unlikely to live for more than a matter of a few months. There are two ways in which they can be utilized. The first is as a BTT to keep critically ill patients alive until a heart transplant becomes available. They will generally have MCS for shorter periods of time for patient receiving LVADs for DT. Consequently, potential VAD related complications are more significant in the latter group than in the former.¹⁴⁾¹⁵⁾ **Table 1** illustrates the predictors of poor survival in heart failure patients which should trigger consideration for LVAD therapy and an LVAD evaluation. **Table 2** shows the indications of LVADs.¹⁴⁾¹⁵⁾

There are several definitions for the strategy to be employed for LVAD implantation. These are shown on **Table 3**.¹⁵⁻¹⁷⁾ The Most common are BTT to support patients on the transplant

Table 1. Predictors of poor survival in heart failure patients

Predictors
“1 block or 1 year” (patient cannot walk more than one block and is likely not to survive for more than a year)
Beta blocker or ACE inhibitor intolerant (at significant “heart failure” doses)
Hospitalization for CHF on appropriate medications
In a six-month period, two or more hospitalizations for acute decompensated heart failure
Requirement for inotropes
LVEDD >75 mm
Non-responder to CRT

ACE = angiotensin-converting-enzyme; CHF = congestive heart failure; CRT = cardiac resynchronization therapy; LVEDD = left ventricular end-diastolic dimension.

Table 2. Indications and contraindications for MCS¹⁷⁾

Indications	Contraindications	Implantation site requirements
DT	Absolute	<ul style="list-style-type: none"> • Surgeons implanting at least 10 durable devices over last 36 months with activity in last 12 • Cardiologists trained in advanced heart failure and device-based management of VADs • VAD program coordinator • Social worker • Palliative care specialist
<ul style="list-style-type: none"> • Failed optimal medical management for at least 45 of the preceding 60 days (75% of time) • IABP dependency for 7 days • Inotrope dependency for 14 days • LVEF <25% • VO₂ ≤14 mL/kg/min in patients without balloon or inotrope dependency • NYHA functional class IV 	<ul style="list-style-type: none"> • Irreversible hepatic, renal, or neurological disease • Medical Non-adherence • Severe psychosocial limitations 	
	Relative	
	<ul style="list-style-type: none"> • Limited life expectancy (age >80 for DT, untreated malignancy) • Poor nutritional status (obesity or malnutrition) • Limitations to rehabilitation (musculoskeletal disease, severe peripheral vascular disease, active substance abuse, active infection, prolonged intubation) • Psychosocial barriers (unmanaged psychiatric disorders, lack of social support) 	

DT = destination therapy; MCS = mechanical circulatory support; IABP = intra-aortic balloon pumps; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; VAD = ventricular assist device.

Table 3. Goals of therapy in long-term MCS therapy candidates¹⁷⁾

Goal of therapy	Definition
BTT	Transplant-eligible patients who otherwise would not survive before a donor heart becomes available
DT	Patients who require lifelong MCS as an alternative to heart transplantation,
BTC	Patients who are not currently transplant-eligible but who do not have absolute contraindications and who may be reconsidered for transplant after a period of temporary circulatory support
BTR	Patients who require a temporary period of MCS for cardiac recovery from acute insults such as cardiogenic shock
BTD	Patients who are unassigned at device implantation

BTC = bridge-to-candidacy; BTD = bridge-to-decision; BTT = bridge-to-transplant; BTR = bridge-to-recovery; DT = destination therapy; MCS = mechanical circulatory support.

list until a donor heart becomes available and DT which is placement of an LVAD without a future heart transplant anticipated. Other scenarios include bridge-to-candidacy (BTC) in which LVADs are implanted in patients who are not at time of implant candidates for a heart transplant but may become a candidate in the future. An example of this would be a patient who is a few years out from treatment for a malignancy and develops severe heart failure requiring an LVAD. The patient would not at that point be a candidate for heart transplant because of the recent malignancy so the LVAD is implanted to save the patient's life and keep them alive until they are considered cured of the malignancy and could thus be listed for transplant. Bridge-to-decision (BTD) is similar to BTC. Bridge-to-Recovery (BTR) is where the LVAD is implanted in patients who are severely hemodynamically compromised but who with MCS may develop myocardial recovery to the point that the LVAD can be explanted. Identifying these patients before LVAD implantation may be challenging and recovery can usually only be identified after LVAD implantation and during the course of MCS.¹⁸⁻²⁰⁾

The severity of cardiac dysfunction and heart failure and the necessity and timeliness of LVAD intervention has been defined using the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles.²¹⁾ These are derived from INTERMACS, a US registry of all patients undergoing MCS. These are shown on **Table 4.**²¹⁾ The modifiers include additional clinical parameters that can affect outcomes. These include: Arrhythmias (modifier 1: A), Temporary Circulatory Support (modifier 2: TCS) and Frequent Flyer (modifier 3: FF).²¹⁾ The term "Frequent Flyer" denotes patients with frequent hospital admissions and visits. The INTERMACS profile score is predictive of outcomes without LVAD intervention. When INTERMACS data were first reported in 2009, 44% of patients receiving LVADs were in the INTERMACS 1 profile. However, it became clear that these

Table 4. Interagency Registry for Mechanically Assisted Circulatory Support profile¹⁷⁾

Class	Descriptor	INTERMACS profile	Time frame for intervention	Modifier 1: A	Modifier 2: TCS	Modifier 3: FF
1	“Crash and burn”	Hemodynamic instability in spite of increasing doses of catecholamines and/ or critical hypoperfusion of target organs despite MCS; patients in critical cardiogenic shock	Necessary within hours	X	X	
2	“Sliding on inotropes”	Intravenous inotrope support with acceptable blood pressure but rapid deterioration of kidney function, nutritional state, or signs of congestion	Necessary within days	X	X	
3	“Dependent stability”	Hemodynamic stability with dependency on low or intermediate doses of inotropic agents due to hypotension, worsening symptoms, or progressive kidney failure	Elective within weeks to months	X	X	X
4	“Resting symptoms”	Temporary discontinuance of inotropic agents is possible, but patient presents to medical attention with frequent symptoms	Elective within weeks to months	X		X
5	“Exertion intolerant”	Stable at rest without inotropic agents but major limitation in any level of physical activity; clinical signs of moderate fluid retention and some level of kidney dysfunction	Variable, depending on nutrition, organ function, activity level	X		X
6	“Walking wounded”	Stable at rest without inotropic agents and minor limitation in physical activity; clinically without signs of fluid retention or kidney dysfunction	Variable, depending on nutrition, organ function, activity level	X		X
7	“Placeholder”	NYHA class II or III symptoms without current or recent fluid overload and hemodynamic instability	Transplantation or circulatory support may not currently be indicated	X		

INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; NYHA = New York Heart Association; Modifier 1: A = Arrhythmias; Modifier 2: TCS = Temporary Circulatory Support; Modifier 3: FF = Frequent Flyer.

patients had poor post-LVAD outcomes and were too sick for LVADs in general.²¹⁾ Consequently, the percentage of LVADs implanted for INTERMACS 1 “crash and burn” profile has declined more recently to 14%.²¹⁾ Most of the INTERMACS 1 patients would benefit from short term MCS (ECMO, Impella or Tandem Heart) as either a BTR, BTT or BTM (i.e., whether they have improved to the point that they could be candidates for durable LVAD implantation either as a BTT or DT). The majority of patients receiving LVADs now are INTERMACS profiles 2 and 3 and occasionally 4. INTERMACS profiles 5, 6 and 7 are generally considered to be too well for LVADs. Some of these patients may be listed for cardiac transplant and go on to transplantation.

Efforts have been made to determine if less ill patients (INTERMACS 4, 5 and 6 profiles) would benefit from LVAD implantation. One advantage of this strategy is that these profiles which consist of ambulatory heart failure patients, have better outcomes after LVAD implantation, specifically a lower incidence of RV failure at six months post-implant (2.3% for INTERMACS profiles 4–6, 3.9% for INTERMACS profiles 2–3 and 11.3% for INTERMACS profile 1).¹⁶⁾ MedaMACS was a medical arm registry for INTERMACS profile 5–6 patients who were ineligible for LVADs or transplants. The 144 such patients were studied and shown to have higher mortalities than similar profile patients who underwent LVAD implantation for DT.²²⁾ This was the rationale for the Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients (ROADMAP) trial, a prospective, multi-center study of 200 non-inotrope dependent INTERMACS 4–7 profile patients. Patients were randomized to receive either an LVAD or remain on OMM. Survival was improved in the LVAD patients compared to the OMM patients (80.4±4% vs. 63±% p=0.22). The primary composite endpoint included survival plus improvement in six-minute walk test >75 meters. More LVAD patients met the primary endpoint vs. OMM patients (39% vs. 21%, p=0.012). LVAD patients had more hospitalizations for VAD related complications but had a better quality of life.²³⁾²⁴⁾ The HeartMate II was used in this study. The LVAD patients had a higher rate of adverse events of which gastrointestinal

(GI) bleeding was the major event. One confounder in this study was the high crossover rate from the OMM to the LVAD group as patients became sicker in the OMM group (30%). Thus LVADs in this less ill population improved survival, exercise tolerance and quality of life at a cost of more hospitalizations and post-LVAD adverse events. It also appears that many of the INTERMACS profile 4–7 patients will progress clinically in terms of worsening heart failure to the point where LVAD implantation becomes more imperative.²³⁾²⁴⁾

In summary, patients should be referred for LVADs if they have NYHA class IV symptoms despite optimal GDMT and CRT (if they are candidates) or if they have recurrent hospitalizations for acute decompensated heart failure despite optimal medical GDMT. If they cannot tolerate optimal doses of angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), angiotensin receptor neprilysin inhibitors (ARNIs) or beta blockers due to side effects or hypotension, they should be considered for LVAD therapy. If patients require inotropic therapy such as milrinone or dobutamine to improve cardiac hemodynamics or end organ function, they should also be considered for LVAD therapy. Whether they are candidates for BTT, DT, BTC or BTD depends on noncardiac factors such as age and co-morbidities. It should be remembered that the sickest patients, the INTERMACS profile 1 “crash and burn” patients have generally poor outcomes after LVAD implantation with poor survivals, and higher frequencies of post-implant RV failure, infection and multi-organ failure. An alternative to immediate LVAD implantation in these patients is short-term nondurable MCS to improve end-organ function and optimize these patients for durable LVAD implantation. It should be remembered that some of these patients especially those who are post-myocardial infarction or who have myocarditis may improve to the point of recovery and not require a durable LVAD.

COMPLICATIONS OF LVADS

Right ventricular failure

RV failure is a feared post-LVAD implantation complication which heralds a 20% decrement in peri-operative survival.²⁵⁻²⁷⁾ It has been defined by INTERMACS as clinically and objectively having elevated central venous pressures. A recent meta-analysis of 36 studies reported an incidence of RV failure of 35% in 4,428 patients. The causes of post-LVAD implantation include the unloading of the left ventricular (LV) after LVAD implantation which results in septal shifts, increased RV preload and ultimately decreased RV contractility and function. Prediction of post-operative RV failure before LVAD implantation has been a challenge. Predictive scoring systems have been developed but have not been very successful and are not used often.

Echocardiography is often used to predict post-operative RV failure after LVAD implantation. One such measure which may offer predictive power for postoperative RV failure is right ventricular stroke work index (RVSWI). RVSWI is defined as:

$$\frac{(\text{Mean pulmonary artery pressure} - \text{Mean central venous pressure}) \times \text{Stroke volume}}{\text{Body surface area}}$$

Patients with preoperative RVSWI <300 mmHg/mL/m², indicative of intrinsic RV dysfunction indicates a greater than ten times likelihood of developing postoperative RV failure after LVAD implantation when compared to patients with preoperative RVSWI >900 mmHg/mL/m².²⁵⁻³⁰⁾

Often, RV failure will be manifested in the operating room during LVAD implantation. This may necessitate implantation of a right ventricular assist device (RVAD). Sometimes RV failure is diagnosed clinical in the intensive care unit after LVAD implantation. This is manifested clinically by decreased blood pressures, cardiac outputs and urine outputs. Management would include implantation of an RVAD. Often, RVADs can serve as bridges to RV recovery and after several days to weeks, can be explanted as RV function improves.

Gastrointestinal bleeding

The most common source of bleeding in patients with CF LVADs is from the GI tract. This is in part facilitated by the fact that these patients are systemically anticoagulated with warfarin. In contrast, GI bleeding was very rare in patients with the old pulsatile LVADs as they did not need systemic anticoagulation. The threat of GI bleeding necessitates a careful evaluation of LVAD candidates for potential sources of GI bleeding such as colonic polyps and stomach ulcers. Colonoscopy and occasionally endoscopy should be performed preoperatively to identify any potential sources of bleeding and they should be treated when possible preoperatively. GI bleeding rates in LVAD patients ranges from 10–61%.³¹⁻³⁴⁾ A metaanalysis of 1,697 patients showed a GI bleeding rate of 23%.³⁵⁾ The most common etiology of GI bleeding in LVAD patients is arteriovenous malformations or angiodysplasia which occur in 29% of LVAD patients.³⁵⁾ It is thought that the CF in the second and third generation LVADs may contribute to the development of angiodysplasias. The most common location of GI bleeding in these patients is the upper GI tract (48%) of patients.³⁵⁾ The pathophysiology of GI angiodysplasia in CF LVAD patients is incompletely understood but there is evidence that the hypoxia-inducible factor (HIF)-1 α /angiopeptin pathway may be involved.³⁶⁾³⁷⁾ Often the angiodysplasias are difficult to find and the source of bleeding can remain occult in these patients. One medical option is to use octreotide an analogue of somatostatin. Both somatostatin and octreotide inhibit GI bleeding by increasing platelet aggregation, decreasing splanchnic blood flow, downregulating the formation of vascular endothelial growth factor and increasing GI vascular bed resistance.³⁸⁾ Thalidomide has also been used to treat angiodysplasias in LVAD patients because of its anti-angiogenic effects.³⁹⁾ Another option for medical therapy is digoxin which inhibits HIF-1 α synthesis.⁴⁰⁾ Although the incidence of GI bleeding is higher in recipients of second and third generation LVADs compare to the first generation pulsatile LVADs, mortality from GI bleeds is actually lower in recipients of the newer, CF LVADs compared to the pulsatile LVADs (20.9% vs. 43.7%, respectively).³⁵⁾ From the DT clinical trial comparing HeartMate II to HeartMate I, there was no difference in GI bleeding episodes that required transfusions or surgery. Increasing experience with managing the newer CF LVADs has resulted in a reduction in GI bleeding incidence. From the INTERMACS data, these were 1.21 times more likely to occur in 2008–2011 than in 2012–2014.²¹⁾ Mortality from GI bleeding has also declined. This has likely been the result of more judicious use of anticoagulation, not using heparin loading and the use of medical therapy mentioned above.

Another contributor to increased risk of bleeding is acquired Von Willebrand Syndrome which has been documented in patients with CF LVADs.⁴¹⁾ It is thought that the VAD rotors degrade Von Willebrand Factor. Running LVADs at lower revolutions per minutes (RPMs) may mitigate this. That is a reversible phenomenon has been shown in patients with LVADs as BTT. Once the LVAD is removed at the time of transplant, the Von Willebrand Factor levels and its activity which were decreased pre-transplant return to normal.

Pump thrombosis and strokes

Patients with second and third generation CF LVADs are at risk of the sequelae of thromboembolic events despite receiving systemic anticoagulation and having acquired Von Willebrand Syndrome. The incidence of strokes ranges from 2–42% to 2–5% for transient ischemic attacks.⁴²⁻⁴⁵⁾ A more ominous complication is pump thrombosis. The incidence of pump thrombosis increased from 2% in 2011 to 5% in 2015 at six months post implant in HeartMate II LVADs ($p < 0.0001$) in data from 6,251 patients from INTERMACS.⁴⁶⁾ In a review from three institutions of 837 patients in whom 895 HeartMate II devices were implanted between 2004 and 2011. The 72 pump thromboses were observed in 66 patients.⁴⁷⁾ From March 2011, the incidence of pump thrombosis increased from 2.2% at three months post-implant to 8.4% in March 2013.⁴⁷⁾ The median time post-implant to thrombosis declined from 18.6 months before March 1, 2011 to 2.7 months afterward.⁴⁷⁾ Clinical pump thrombosis was preceded by a doubling of serum lactate dehydrogenase (LDH) from 540 IU to 1,490 IU.⁴⁷⁾ Pump thrombosis in these patients was managed by cardiac transplantation in 11 patients and LVAD replacement in 21.⁴⁷⁾ Of the remaining 40 patients with pump thromboses but who did not get a cardiac transplant or pump exchange, mortality was high at 48.2% at six months after pump exchange was diagnosed.⁴⁷⁾ Of note, the centers in this study had recently reduced their target international normalized ratio (INR) for anticoagulation to reduce the incidence of GI bleeding. The lower INR targets were in effect at the time of the increase in pump thrombosis.⁴⁷⁾ The PREVENTION of HeartMate II Pump Thrombosis through Clinical Management (PREVENT) study of 300 patients who underwent HeartMate II implantation at 24 medical centers showed a pump thrombosis rate of 2.9% at three months and 4.8% at six months.⁴⁸⁾ Strict adherence to a regimen of careful pump implantation. Heparin bridging within 48 hours post-operatively, initiation of warfarin at 48 hours with a target INR of 2.0–2.5, and addition of aspirin (81–325 mg daily) 2–5 days post implantation if there was no bleeding and maintaining pump speeds $\geq 9,000$ RPMs reduced the incidence of pump thrombosis from 8.9% to 1.9% ($p < 0.01$) and the incidence of ischemic stroke from 17.7% to 5.7% ($p < 0.01$) at six months post implant.

Recent data from INTERMACS indicates that the incidence of HeartMate II pump thrombosis at six months peaked at 8% in 2013 but declined to 5% in 2014.⁴⁹⁾ HeartMate II pump thrombosis incidence has been reported to be 3.6%, 5.7% and 3.6% at here, six and twelve months post implant respectively. Results from the HVAD Evaluation of the HeartWare Left Ventricular Assist Device for the Treatment of Advanced Heart Failure (ADVANCE) study showed that this device had a 4% pump thrombosis incidence at six months.

Clinical manifestations of pump thrombosis include symptoms of heart failure such as dyspnea on exertion and hematuria, the latter reflecting hemolysis. Serum free hemoglobin increases as does serum LDH and the latter two laboratory abnormalities precede clinical evidence of pump thrombosis. The LVAD itself will demonstrate elevated pump power and decreased pulse index. The combination of recurrent heart failure signs and symptoms with LVAD dysfunction as described above, signs and lab tests indicating hemolysis points to pump thrombosis as the cause. Pump Thrombosis is also associated with thromboembolic events such as strokes and TIAs. The presence of the aortic valve (AV) opening with most or every cardiac systole as demonstrated echocardiographically is further evidence of pump thrombosis. A chest computed tomography angiogram can confirm, the presence of pump thrombosis. Management includes administration of intravenous heparin and intravenous inotropic therapy to improve cardiac function. Patients should then be upgraded on the heart transplant list to emergently get a heart transplant which would include explantation of the

thrombosed LVAD. For those patients who cannot get heart transplants rapidly or who are receiving LVADs as DT, a pump exchange with explantation of the old LVAD and replaced with a new LVAD are definitive treatments of this problem. Thrombolytic therapy should be avoided given the risk of intra-cranial hemorrhage with this therapy.

Pump thrombosis will likely become less common as the rate of pump thrombosis and the need for pump exchange are significantly less common in HeartMate 3 vs. HeartMate II patients as discussed later in this article.

Infection

Infections can occur anywhere throughout the LVAD circuit including the LVAD pocket where the LVAD is implanted, the LVAD itself or the cannulae that go from the left ventricle to the VAD and from the LVAD to the aorta and the driveline which goes from the LVAD through the skin to the LVAD power source. The latter is the most common site of LVAD infections because it represents a pathway from the external environment to the LVAD interior. The most common organisms causing LVAD infections are skin flora such as *Staphylococcus aureus* and coagulase-negative staphylococci.⁵⁰⁾ These are particularly common in driveline infections. Infections of the LVAD and other internal components can be caused by other organisms as well such as *Serratia*, *Klebsiella*, and *Enterococcus* species, *Pseudomonas aeruginosa*.⁵⁰⁾ *Candida* can cause up to ten percent of infections.⁵⁰⁾ Bacteremia from another infection can seed the LVAD and infect it. Infections have declined from 38% of patients reported in the first year of INTERMACS to 17.6% reported in 2014 by INTERMACS. Mortality from sepsis has declined from 41% reported in the REMATCH study to 8.8% in recent INTERMACS reports.⁹⁾¹⁶⁾²¹⁾

The management of LVAD related infections includes debridement of infected tissue and administration of intravenous antibiotics. Often, the driveline site where the driveline traverses the skin can provide insight into the presence of infection as there may be erythema and purulent discharge. When the VAD or the cannulae are infection, the only cure is explantation. If the patient is on the transplant list, an LVAD related infection will raise the patient on the priority list allowing for earlier transplantation and removal of the infected LVAD. Antibiotics can be used to suppress the infection. For DT patients, the infected LVAD may need to be explanted. Temporary nondurable support with an Impella can be used to support the patient hemodynamically until the infection is eradicated at which point a new LVAD can be implanted.

Ventricular arrhythmias

Ventricular arrhythmias are common after LVAD implantation especially in the early postoperative period. In the first annual INTERMACS report, 14.8% of patients had ventricular arrhythmias within the first 30 days of implant whereas 5.2% had arrhythmias beyond 30 days after implant.¹⁶⁾ The presumptive mechanism includes establishment of reentrant circuits around the site of the inflow cannula in already damaged myocardium. Concomitant postoperative use of catecholamines in the postoperative period may exacerbate this. A more common cause is suction events. This occurs when the inflow cannula sucks too much blood, bringing the cannula to appose the septum. The left ventricle becomes markedly unloaded and may collapse upon itself. The remedy for this usually to decrease the LVAD flow rate which results in greater left ventricular filling. Although LVADs can provide hemodynamic support even in the setting of ventricular tachycardia or ventricular fibrillation, this hemodynamic situation is inherently unstable and must be treated. Many

of these patients will go to LVAD implantation already having an implantable cardioverter-defibrillator. This can help with management of these arrhythmias. Use of heart failure medications including RAAS inhibitors and beta blockers may mitigate the development of ventricular arrhythmias. As time goes on after MCS, the ventricle may remodel and this may make ventricular arrhythmias less likely to develop. Use of anti-arrhythmic agents such as lidocaine or amiodarone is rarely necessary.⁵¹⁾

Hypertension

Patients with CF LVAD generally do not have systolic or diastolic pressures if they have CF. Thus, the mean arterial pressures (MAP) have to be assessed using Doppler. Hypertension in CF LVAD patients is defined as a MAP greater than 90 mmHg. This is associated with a much higher risk of stroke. Hypertension in patients with continuous LVADs can impede LVAD function. Hypertension can be managed in these patients using conventional agents ranging from ACE inhibitors, ARBs, ARNIs to beta blockers. Hydralazine is often rapidly effective in these patients. The goal should be a MAP=60–70 mmHg.⁵²⁾

Pump optimization

Contemporary CF LVADs are complex devices as are their interactions with the heart and the cardiovascular system. Their speed can literally be dialed up but not enough RPMs may result in continued heart failure and end-organ dysfunction as well as pump thrombosis. Too many RPMs can exacerbate RV failure, ventricular arrhythmias and acquired Von Willebrand's Syndrome. Strategies have been developed to allow for optimization of LVAD flows to optimize their function in conjunction with the heart and to avoid the above mentioned problems. The goal is to identify the optimal speed of the LVAD for the patient. This can be done using echocardiography. This is usually deferred until after the early postoperative period once inotropic and vasoactive agents have been stopped and the patient's volume status has stabilized. Ramp studies are performed to accomplish optimization using echocardiography to visualize the heart at different pump speeds. Device speed optimization is defined as the speed in which the LV is adequately unloaded with a midline intraventricular septum with minimal mitral regurgitation (MR) and intermittent AV opening.³¹⁾ This can vary greatly from patient to patient.

The protocol as described by Uriel and colleagues is as shown below.⁵³⁾ This should be performed in patients with HeartMate II and HVAD. The RPMs differ with these two LVADs and so adjustments must be made accordingly.

1. Before performing a ramp test, appropriate anticoagulation must be confirmed with an INR greater than 1.8 or partial thromboplastin time greater than 60 seconds. Opening arterial pressure by Doppler during the study should be >65 mmHg at baseline to proceed.⁵³⁾
2. The parasternal long-axis view is then primarily used to assess LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), frequency of AV opening, degree of aortic insufficiency (AI), MR, and heart rate.⁵³⁾
3. Continuous-flow LVAD parameters, including power, pulsatility index (PI), and flow, are recorded at each stage. Baseline evaluation of these variables are also recorded at the given speed at presentation.⁵³⁾
4. For HeartMate II LVADs, the device speed is then lowered to 8,000 RPM and 2,300 RPM for the HVAD devices. After 2 minutes of washout time, LVEDD, LVESD, degree of MR, AI,

- assessment of AV opening, Doppler blood pressure, and heart rate are all recorded. Pump parameters (power, PI, and flow) are also recorded during each stage.⁵³⁾
5. Stepwise increase in speed at intervals of 400 RPM for HeartMate II and 100 RPM for HVAD are then made; other protocols have shown 130-RPM intervals in the HVAD physiologically correlates with 400-RPM intervals in the HeartMate II.⁵³⁾⁵⁴⁾
 6. The testing speed range for HeartMate II is 8,000 to 12,000 RPM and 2,200 to 3,200 RPM for the HVAD.⁵³⁾
 7. The protocol is complete once the upper limit speed is reached, LVEDD reaches less than 3.0 cm, suction event, or ventricular ectopic beats occur. The clinician must also pay attention to development of premature ventricular contractions, which may indicate contact of the inflow cannula with the septum.⁵³⁾
 8. From a medical optimization standpoint, the speed is adjusted to clinically achieve a midline intraventricular septum, minimal MR, and intermittent AV opening to prevent development of AI.⁵³⁾

An alternative to echocardiographically guided ramp studies is the hemodynamic ramp protocol to facilitate optimization of the LVAD in patients supported with these devices. This involves left and right heart catheterization to obtain continuous aortic and left ventricular pressures as well as right atrial, pulmonary arterial pressure (PAP) and pulmonary capillary wedge pressure (PCWP). LVAD flows are adjusted to obtain optimal right and left ventricular hemodynamics.⁵⁵⁾

A less invasive approach is to use right heart catheterization alone to adjust LVAD flows to optimize cardiac output, PAP and PCWP.⁵⁶⁾

THE HEARTMATE 3: FURTHER ADVANCES IN LVAD TECHNOLOGY

The Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM 3) study was a pivotal LVAD clinical trial involving the randomization of 294 patients to receive the HeartMate 3, a fully magnetically levitated centrifugal CF LVAD to the axial flow HeartMate II. The 152 patients received the HeartMate 3 while 142 received the axial flow HeartMate II.⁵⁷⁾ The primary end point was a composite of survival free of disabling stroke (with disabling stroke indicated by a modified Rankin score >3; scores range from 0 to 6, with higher scores indicating more severe disability) or survival free of reoperation to replace or remove the device at 6 months after implantation. The 131 (86.2%) patients in the HeartMate 3 group reached the primary endpoint vs. 109 (76.8%) patients in the HeartMate II study. There was no significant difference in rate of deaths or disabling strokes in the two groups. However, reoperation for pump malfunction was less common in the HeartMate 3 group vs. the HeartMate II group (1 [0.7%] vs. 11 [7.7%], $p=0.002$). No suspected or confirmed pump thromboses were seen in the HeartMate 3 group vs. 14 (10.1%) patients in the HeartMate II group.

In a follow up study, 366 patients were enrolled, 190 of whom received the HeartMate 3 and 176 of whom received the HeartMate II.⁵⁸⁾ The primary end point was a composite of survival free of disabling stroke (with disabling stroke indicated by a modified Rankin score >3; scores range from 0 to 6, with higher scores indicating more severe disability) or survival free of reoperation to replace or remove the device at two years after implantation.⁵⁸⁾ The 151 (79.5%)

of HeartMate 3 patients reached the primary endpoint compared to 106 (60.2%) in the HeartMate II group. Reoperation for pump malfunction was less common in the HeartMate 3 group compared to the HeartMate II group (3 [1.6%] vs. 30 [17.0%], $p=0.01$). Death rates were similar between the two groups but rate of disabling strokes was less in the HeartMate 3 group compared to the HeartMate II group (10.1% vs. 19.2%, $p=0.02$).⁵⁸⁾

A final phase of the MOMENTUM 3 trial enrolled 1,028 patients, of which 516 received the HeartMate 3 and 512 received the HeartMate II.⁵⁹⁾ The composite primary end point was survival at 2 years free of disabling stroke or reoperation to replace or remove a malfunctioning device. The principal secondary end point was pump replacement at 2 years. The 397 (76.9%) patients in the HeartMate 3 group reached the primary endpoint compared to 332 (64.8%) in the HeartMate II group.⁵⁹⁾ Pump replacement for malfunction was less common in the HeartMate 3 group compared to the HeartMate II group (12 [2.3%] vs. 57 [11.3%], $p<0.001$).⁵⁹⁾ Patients in the HeartMate 3 group had fewer strokes, major bleeding, GI bleeding or ventricular arrhythmias than in the HeartMate II group. Thus, this newest LVAD has fewer pump thromboses and LVAD replacements for LVAD malfunction. There are unique aspects of this device which may account for its superior outcomes: It has wide blood flow conduits which reduces shear of the blood, it is frictionless without mechanical bearings and it has an intrinsic pulse which is designed to reduce stasis and prevent pump thrombosis. The intrinsic pulse may help to prevent GI angiodysplasia.

FULLY IMPLANTABLE PUMPS

At present, none of the LVADs that are commercially available are fully implantable. They still have drivelines that go from the LVAD to the external power source. This serves as a source of infection and limits the activities that LVAD supported patients can pursue; they cannot swim and have difficulties showering. To become fully implantable, there would need to be an internal power source and a way to charge it transdermally. This technology does exist and has been used in artificial hearts. The first was the AbioCor which was placed in 14 patients in the early 2000's.⁶⁰⁾ The longest time a patient lived with the device was 512 days. The patients who received the device were too sick for transplant. Another approach was the Penn State LionHeart which was a totally implantable VAD. These were implanted in small numbers in the early 2000s.⁶¹⁾⁶²⁾

There is now a totally implantable LVAD which uses the Jarvik VAD platform. It is produced by Leviticus and is called the Leviticus FiVAD. It has been implanted in two patients.⁶³⁾ Plans are underway for further development of this VAD and for clinical trial. Such devices could reduce or eliminate the threat of infection in these patients.

LVADS COMPARED TO CARDIAC TRANSPLANTATION

LVAD outcomes have improved consistently over the past twenty years since the results of the REMATCH trial. Outcomes for cardiac transplantation have also improved mainly due to improvements in the survival in the first six months to one year post-transplant as a result of a lower incidence of rejection and infection in this time period and better outcomes when these events occur. This is from the Registry on the International Society of Heart and Lung Transplantation (ISHLT).⁶⁴⁻⁶⁶⁾ Notably, the incidence of cardiac allograft vasculopathy (CAV)

and malignancy post-transplant have declined modestly in recent years with better outcomes. Despite this, survival beyond the first year post-transplant has not changed substantially with CAV and malignancy being the major causes of death in these patients.⁽⁶⁵⁾⁽⁶⁶⁾ Despite this, newer immunosuppressive agents, specifically the mTOR inhibitors everolimus and sirolimus, have been shown to reduce the incidence and severity of CAV.⁽⁶⁷⁾⁽⁶⁸⁾ Newer strategies have enabled initiation of the agents weeks or months after transplant, thus preventing the adverse events seen in *de novo* early initiation while preserving their salutary effects on CAV.⁽⁶⁸⁾ These agents also have anti-neoplastic effects and are used as adjuncts in the management of patients with certain malignancies. Data from the SRTR indicates that renal transplant recipients receiving either mTOR inhibitors alone or with calcineurin antagonists (tacrolimus, cyclosporine) have lower rates of malignancies than patients receiving calcineurin antagonists alone.⁽⁶⁹⁾

The ISHLT Registry reports survival at one year in excess of 90%. In contrast, the best one year survival reported for LVADs is in the high 80s, inferior to transplants although there has been no randomized comparison. Advantages of LVADs over transplant include the fact that they are readily available, essentially “off-the-shelf”. The post-transplant complications, CAV, malignancy, rejection, infection and nephrotoxicity (from immunosuppression) do not occur in LVAD patients. There is no limits in LVADs as there is in donor hearts and this explains why more LVADs are being performed than cardiac transplants. AS the heart failure population continues to age, this will further shift the numbers toward LVADs.

Who should get transplants instead of LVADs? Generally younger patients with few co-morbidities should get transplants as transplants have kept many patients alive for decades and longer than has been seen with LVADs. This will likely improve over time. LVAD survival will likely improve with improvements in technology. More durable, reliable VADs with lower stroke rates, GI bleeding and pump thrombosis rates that are totally implantable may give transplants competition in terms of outcomes. At presents, VADs should be used in older patients with co-morbidities including recent malignancies, and smoking should be considered for VADs.

CONCLUSIONS

Management of heart failure from medical therapy to devices to LVADs to transplants has improved dramatically over the past few decades. LVADs represent a significant advance in that they allow patients who were critically ill to survive to transplant and to function including becoming physically active. As the technology has improved and outcomes have improved, LVADs have become viable and realistic alternatives for patients who might not be optimal transplant candidates. As the technology continues to improve and disseminate worldwide, the number of patients who receive LVADs will continue to grow. Eventually with improved technology, LVADs may provide realistic competition to cardiac transplantation in most patients.

REFERENCES

1. Centers for Disease Control and Prevention. Heart failure fact sheet [Internet]. Atlanta: Centers for Disease Control and Prevention; 2019 [cited 2019 April 30]. Available from https://www.cdc.gov/dhdspl/data_statistics/fact_sheets/fs_heart_failure.htm.

2. Patel CB, Rogers JG. Durable mechanical circulatory support devices. *Prog Cardiovasc Dis* 2011;54:132-43.
[PUBMED](#) | [CROSSREF](#)
3. Stewart GC, Givertz MM. Mechanical circulatory support for advanced heart failure: patients and technology in evolution. *Circulation* 2012;125:1304-15.
[PUBMED](#) | [CROSSREF](#)
4. Gibbon JH Jr. Application of a mechanical heart and lung apparatus to cardiac surgery. *Minn Med* 1954;37:171-85.
[PUBMED](#)
5. Frazier OH. Mechanical cardiac assistance: historical perspectives. *Semin Thorac Cardiovasc Surg* 2000;12:207-19.
[PUBMED](#) | [CROSSREF](#)
6. Hogness JR, VanAntwerp M, editors. *The artificial heart: prototypes, policies, and patients*. Washington, D.C.: National Academy Press (US); 1991.
7. Stewart GC, Mehra MR. A history of devices as an alternative to heart transplantation. *Heart Fail Clin* 2014;10:S1-12.
[PUBMED](#) | [CROSSREF](#)
8. Cooper DK. Christiaan Barnard-The surgeon who dared: the story of the first human-to-human heart transplant. *Glob Cardiol Sci Pract* 2018;2018:11.
[PUBMED](#) | [CROSSREF](#)
9. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med* 2001;345:1435-43.
[PUBMED](#) | [CROSSREF](#)
10. Miller LW, Pagani FD, Russell SD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med* 2007;357:885-96.
[PUBMED](#) | [CROSSREF](#)
11. Lok SI, Martina JR, Hesselink T, et al. Corrigendum to "Single-centre experience of 85 patients with a continuous-flow left ventricular assist device: clinical practice and outcome after extended support" [Eur J Cardiothorac Surg 2013;44:e233-8]. *Eur J Cardiothorac Surg* 2014;45:400.
[CROSSREF](#)
12. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med* 2009;361:2241-51.
[PUBMED](#) | [CROSSREF](#)
13. Pagani FD, Milano CA, Tatooles AJ, et al. HeartWare HVAD for the treatment of patients with advanced heart failure ineligible for cardiac transplantation: results of the ENDURANCE destination therapy trial. *J Heart Lung Transplant* 2015;34:S9.
[PUBMED](#) | [CROSSREF](#)
14. WRITING COMMITTEE MEMBERS, Yancy CW, Jessup M, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013;128:e240-327.
[PUBMED](#) | [CROSSREF](#)
15. Miller LW, Guglin M. Patient selection for ventricular assist devices: a moving target. *J Am Coll Cardiol* 2013;61:1209-21.
[PUBMED](#) | [CROSSREF](#)
16. Kirklin JK, Naftel DC, Stevenson LW, et al. INTERMACS database for durable devices for circulatory support: first annual report. *J Heart Lung Transplant* 2008;27:1065-72.
[PUBMED](#) | [CROSSREF](#)
17. Cai AW, Islam S, Hankins SR, Fischer W, Eisen HJ. Mechanical circulatory support in the treatment of advanced heart failure. *Am J Transplant* 2017;17:3020-32.
[PUBMED](#) | [CROSSREF](#)
18. Birks EJ, Tansley PD, Hardy J, et al. Left ventricular assist device and drug therapy for the reversal of heart failure. *N Engl J Med* 2006;355:1873-84.
[PUBMED](#) | [CROSSREF](#)
19. Drakos SG, Kfoury AG, Stehlik J, et al. Bridge to recovery: understanding the disconnect between clinical and biological outcomes. *Circulation* 2012;126:230-41.
[PUBMED](#) | [CROSSREF](#)
20. Drakos SG, Mehra MR. Clinical myocardial recovery during long-term mechanical support in advanced heart failure: insights into moving the field forward. *J Heart Lung Transplant* 2016;35:413-20.
[PUBMED](#) | [CROSSREF](#)
21. Kirklin JK, Naftel DC, Pagani FD, et al. Seventh INTERMACS annual report: 15,000 patients and counting. *J Heart Lung Transplant* 2015;34:1495-504.
[PUBMED](#) | [CROSSREF](#)

22. Ambardekar AV, Forde-McLean RC, Kittleson MM, et al. High early event rates in patients with questionable eligibility for advanced heart failure therapies: results from the Medical Arm of Mechanically Assisted Circulatory Support (Medamacs) Registry. *J Heart Lung Transplant* 2016;35:722-30.
[PUBMED](#) | [CROSSREF](#)
23. Estep JD, Starling RC, Horstmanshof DA, et al. Risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients: results from the ROADMAP study. *J Am Coll Cardiol* 2015;66:1747-61.
[PUBMED](#) | [CROSSREF](#)
24. Starling RC, Estep JD, Horstmanshof DA, et al. Risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients: the ROADMAP study 2-year results. *JACC Heart Fail* 2017;5:518-27.
[PUBMED](#) | [CROSSREF](#)
25. Hayek S, Sims DB, Markham DW, Butler J, Kalogeropoulos AP. Assessment of right ventricular function in left ventricular assist device candidates. 2014;7:379-89.
[PUBMED](#) | [CROSSREF](#)
26. Holman WL, Acharya D, Siric F, Loyaga-Rendon RY. Assessment and management of right ventricular failure in left ventricular assist device patients. *Circ J* 2015;79:478-86.
[PUBMED](#) | [CROSSREF](#)
27. Bellavia D, Iacovoni A, Scardulla CA, et al. Prediction of right ventricular failure after ventricular assist device implant: systematic review and meta-analysis of observational studies. *Eur J Heart Fail* 2017;19:926-46.
[PUBMED](#) | [CROSSREF](#)
28. Houston BA, Shah KB, Mehra MR, Tedford RJ. A new “twist” on right heart failure with left ventricular assist systems. *J Heart Lung Transplant* 2017;36:701-7.
[PUBMED](#) | [CROSSREF](#)
29. Aissaoui N, Salem JE, Paluszkiwicz L, et al. Assessment of right ventricular dysfunction predictors before the implantation of a left ventricular assist device in end-stage heart failure patients using echocardiographic measures (ARVADE): combination of left and right ventricular echocardiographic variables. 2015;108:300-9.
[PUBMED](#) | [CROSSREF](#)
30. Khazanie P, Rogers JG. Patient selection for left ventricular assist devices. *Congest Heart Fail* 2011;17:227-34.
[PUBMED](#) | [CROSSREF](#)
31. Aggarwal A, Pant R, Kumar S, et al. Incidence and management of gastrointestinal bleeding with continuous flow assist devices. *Ann Thorac Surg* 2012;93:1534-40.
[PUBMED](#) | [CROSSREF](#)
32. Marsano J, Desai J, Chang S, Chau M, Pochapin M, Gurvits GE. Characteristics of gastrointestinal bleeding after placement of continuous-flow left ventricular assist device: a case series. *Dig Dis Sci* 2015;60:1859-67.
[PUBMED](#) | [CROSSREF](#)
33. Draper K, Huang RJ, Gerson LB. Gastrointestinal bleeding in patients with continuous-flow left ventricular assist devices: a systematic review and meta-analysis. *Gastroenterology* 2014;146:S-558.
[CROSSREF](#)
34. Balcioglu O, Engin C, Yagdi T, et al. Effect of aortic valve movements on gastrointestinal bleeding that occurred in continuous flow left ventricular assist device patients. *Transplant Proc* 2013;45:1020-1.
[PUBMED](#) | [CROSSREF](#)
35. Kim JH, Brophy DF, Shah KB. Continuous-flow left ventricular assist device-related gastrointestinal bleeding. *Cardiol Clin* 2018;36:519-29.
[PUBMED](#) | [CROSSREF](#)
36. Pichiule P, Chavez JC, LaManna JC. Hypoxic regulation of angiopoietin-2 expression in endothelial cells. *J Biol Chem* 2004;279:12171-80.
[PUBMED](#) | [CROSSREF](#)
37. Yamakawa M, Liu LX, Date T, et al. Hypoxia-inducible factor-1 mediates activation of cultured vascular endothelial cells by inducing multiple angiogenic factors. *Circ Res* 2003;93:664-73.
[PUBMED](#) | [CROSSREF](#)
38. Hayes HM, Dembo LG, Larbalestier R, O'Driscoll G. Management options to treat gastrointestinal bleeding in patients supported on rotary left ventricular assist devices: a single-center experience. *Artif Organs* 2010;34:703-6.
[PUBMED](#) | [CROSSREF](#)
39. Seng BJ, Teo LL, Chan LL, et al. Novel use of low-dose thalidomide in refractory gastrointestinal bleeding in left ventricular assist device patients. *Int J Artif Organs* 2017;40:636-40.
[PUBMED](#) | [CROSSREF](#)

40. Vukelic S, Vlismas PP, Patel SR, et al. Digoxin is associated with a decreased incidence of angiodysplasia-related gastrointestinal bleeding in patients with continuous-flow left ventricular assist devices. *Circ Heart Fail* 2018;11:e004899.
[PUBMED](#) | [CROSSREF](#)
41. Uriel N, Pak SW, Jorde UP, et al. Acquired von Willebrand syndrome after continuous-flow mechanical device support contributes to a high prevalence of bleeding during long-term support and at the time of transplantation. *J Am Coll Cardiol* 2010;56:1207-13.
[PUBMED](#) | [CROSSREF](#)
42. McIlvennan CK, Magid KH, Ambardekar AV, Thompson JS, Matlock DD, Allen LA. Clinical outcomes after continuous-flow left ventricular assist device: a systematic review. *Circ Heart Fail* 2014;7:1003-13.
[PUBMED](#) | [CROSSREF](#)
43. Tsiouris A, Paone G, Nemeš HW, et al. Short and long term outcomes of 200 patients supported by continuous-flow left ventricular assist devices. *World J Cardiol* 2015;7:792-800.
[PUBMED](#) | [CROSSREF](#)
44. Harvey L, Holley C, Roy SS, et al. Stroke after left ventricular assist device implantation: outcomes in the continuous-flow era. *Ann Thorac Surg* 2015;100:535-41.
[PUBMED](#) | [CROSSREF](#)
45. Kimura M, Kinoshita O, Nawata K, et al. Midterm outcome of implantable left ventricular assist devices as a bridge to transplantation: single-center experience in Japan. *J Cardiol* 2015;65:383-9.
[PUBMED](#) | [CROSSREF](#)
46. INTERMACS. Initial analyses of suspected pump thrombosis [Internet]. Birmingham: University of Alabama at Birmingham (UAB) School of Medicine; 2013 [cited 2016 February 1]. Available from https://www.uab.edu/medicine/intermacs/images/INTERMACS_PI_and_Website_Notice_9-6-2013_2.pdf.
47. Schmitto JD, Avsar M, Haverich A. Increase in left ventricular assist device thrombosis. *N Engl J Med* 2014;370:1463-4.
[PUBMED](#) | [CROSSREF](#)
48. Maltais S, Kilic A, Nathan S, et al. PREVENTion of HeartMate II Pump Thrombosis Through Clinical Management: The PREVENT multi-center study. *J Heart Lung Transplant* 2017;36:1-12.
[PUBMED](#) | [CROSSREF](#)
49. Klodell CT, Massey HT, Adamson RM, et al. Factors related to pump thrombosis with the HeartMate II left ventricular assist device. *J Card Surg* 2015;30:775-80.
[PUBMED](#) | [CROSSREF](#)
50. Martin SI. Infectious complications of mechanical circulatory support (MCS) devices. *Curr Infect Dis Rep* 2013;15:472-7.
[PUBMED](#) | [CROSSREF](#)
51. Pedrotty DM, Rame JE, Margulies KB. Management of ventricular arrhythmias in patients with ventricular assist devices. *Curr Opin Cardiol* 2013;28:360-8.
[PUBMED](#) | [CROSSREF](#)
52. Bennett MK, Adatya S. Blood pressure management in mechanical circulatory support. *J Thorac Dis* 2015;7:2125-8.
[PUBMED](#)
53. Uriel N, Morrison KA, Garan AR, et al. Development of a novel echocardiography ramp test for speed optimization and diagnosis of device thrombosis in continuous-flow left ventricular assist devices: the Columbia ramp study. *J Am Coll Cardiol* 2012;60:1764-75.
[PUBMED](#) | [CROSSREF](#)
54. Narang N, Raikhelkar J, Sayer G, Uriel N. Hemodynamic pump-patient interactions and left ventricular assist device imaging. *Cardiol Clin* 2018;36:561-9.
[PUBMED](#) | [CROSSREF](#)
55. Rosenbaum AN, Frantz RP, Kushwaha SS, Stulak JM, Maltais S, Behfar A. Novel left heart catheterization ramp protocol to guide hemodynamic optimization in patients supported with left ventricular assist device therapy. *J Am Heart Assoc* 2019;8:e010232.
[PUBMED](#) | [CROSSREF](#)
56. Uriel N, Sayer G, Addetia K, et al. Hemodynamic ramp tests in patients with left ventricular assist devices. *JACC Heart Fail* 2016;4:208-17.
[PUBMED](#) | [CROSSREF](#)
57. Mehra MR, Naka Y, Uriel N, et al. A fully magnetically levitated circulatory pump for advanced heart failure. *N Engl J Med* 2017;376:440-50.
[PUBMED](#) | [CROSSREF](#)

58. Mehra MR, Goldstein DJ, Uriel N, et al. Two-year outcomes with a magnetically levitated cardiac pump in heart failure. *N Engl J Med* 2018;378:1386-95.
[PUBMED](#) | [CROSSREF](#)
59. Mehra MR, Uriel N, Naka Y, et al.; MOMENTUM 3 Investigators. A fully magnetically levitated left ventricular assist device - final report. *N Engl J Med* 2019;380:1618-27.
[PUBMED](#) | [CROSSREF](#)
60. Dowling RD, Etoch SW, Stevens K, et al. Initial experience with the AbioCor implantable replacement heart at the University of Louisville. *ASAIO J* 2000;46:579-81.
[PUBMED](#) | [CROSSREF](#)
61. Mehta SM, Silber D, Boehmer JP, Christensen D, Pae WE Jr. Report of the first U.S. patient successfully supported long term with the LionHeart completely implantable left ventricular assist device system. *ASAIO J* 2006;52:e31-2.
[PUBMED](#) | [CROSSREF](#)
62. Pae WE, Connell JM, Adelowo A, et al.. Does total implantability reduce infection with the use of a left ventricular assist device? The LionHeart experience in Europe. *J Heart Lung Transplant* 2007;26:219-29.
[PUBMED](#) | [CROSSREF](#)
63. Michael Zilbershlag. CEO Leviticus Cardio, Personal communication.
64. Kransdorf EP, Mehta HS, Shah KB, et al.. ISHLT transplant registry: youthful investment-the path to progress. *J Heart Lung Transplant* 2017;36:1027-36.
[PUBMED](#) | [CROSSREF](#)
65. Yusen RD, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-first adult lung and heart-lung transplant report--2014; focus theme: retransplantation. *J Heart Lung Transplant* 2014;33:1009-24.
[PUBMED](#) | [CROSSREF](#)
66. Stehlik J, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: 29th official adult heart transplant report--2012. *J Heart Lung Transplant* 2012;31:1052-64.
[PUBMED](#) | [CROSSREF](#)
67. Eisen HJ, Tuzcu EM, Dorent R, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. *N Engl J Med* 2003;349:847-58.
[PUBMED](#) | [CROSSREF](#)
68. Eisen HJ, Hasni SF, Wang D. The return of the mTOR Inhibitors: getting it right in patients after cardiac transplantation. *J Am Coll Cardiol* 2018;71:651-3.
[PUBMED](#) | [CROSSREF](#)
69. Kauffman HM, Cherikh WS, Cheng Y, Hanto DW, Kahan BD. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of *de novo* malignancies. *Transplantation* 2005;80:883-9.
[PUBMED](#) | [CROSSREF](#)