



## Review

# Left Ventricular Assist Device as Destination Therapy

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## Abstract

Mechanical circulatory support is the most rapidly evolving strategy in heart failure management. The growing number of patients who need better results than medical therapy can offer, the limited pool of donors for cardiac transplantation, and several technological breakthroughs have all made the option of implanting a left ventricular assist device (LVAD) as destination therapy more important.

In this review, we outline the indications and decision making process of considering a patient for a destination therapy LVAD, as well as outcomes, complications, and issues related to management of patients on currently approved devices. The future direction of the field will be determined by progress in technology and by further improvement in size, durability, pump dynamics, and most importantly, by solving the problem of supplying energy to the pump without a percutaneous driveline.

## Keywords

Heart failure; Ventricular assist device; Mechanical circulatory support

## End Destination of Heart Failure Is LVAD

The population of patients with heart failure (HF) is growing at a rate approaching that of an epidemic. This means that although only a small fraction of patients with heart failure progress to the end-stages of the disease, there are probably between 100,000 and 250,000 patients in the United States who have exhausted traditional methods of treatment, including all evidence-based medications and pacemaker-based therapies (1).

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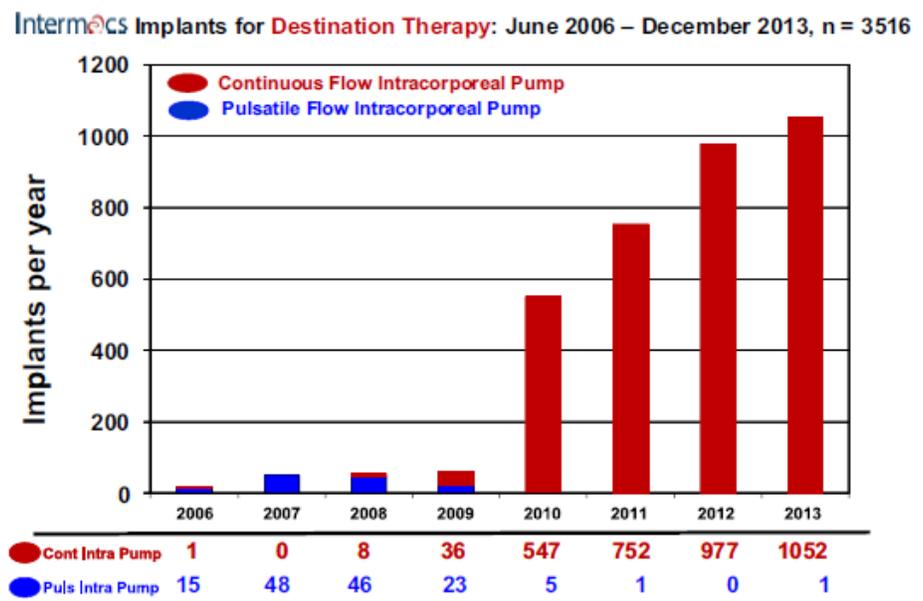
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Meanwhile, the number of heart transplants in the United States has remained at about 2,500 per year for several decades (2). Unless we learn how to make better artificial hearts, or learn how to patch failing ventricles using stem cells, the vast majority of advanced HF patients will have to be considered as potential candidates for mechanical circulatory support. At first, LVADs were thought of as a temporary intermediate step that can bridge patients to heart transplantation. However, LVADs have now been used as destination therapy (DT) for more than a decade and are quickly replacing transplants as the standard therapy.

This transition was made possible by technological breakthroughs including: (a) conversion from external to internal placement of the devices; (b) conversion from pneumatic to electrical power; and (c) transition from pulsatile to continuous-flow devices. The new continuous-flow LVADs that are currently used for DT are much smaller in size and weight and quieter in operation than the first pulsatile models. These characteristics improve patient satisfaction and allow the technology to support a greater variety of patients.

According to the sixth Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) annual report, more than a thousand LVADs were implanted for DT indication in 2013(3). This represents a doubling in volume since 2010 (Figure 1). This review builds on this clinical progress and discusses the most important aspects of LVADs as DT.



**Fig 1. Primary adult implants for destination therapy in the INTERMACS registry by year of implant (Kirklin et al. (3), with permission).**



## **Brief History**

In 2001, the REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial demonstrated for the first time that mechanical circulatory support as DT for advanced HF is superior to optimal medical management (4). This trial was performed using a pulsatile HeartMate I (HMI) (Thoratec Corporation, Pleasanton, California) device. This was later approved by the Food and Drug Administration (FDA) for DT and subsequently covered by Medicare in 2003.

Later, a continuous flow HeartMate II (HMII) (Thoratec) was proven to provide better survival, quality of life, and fewer adverse events, under conditions that included use as a DT (5, 6). Since the rotor is the pump's only moving part, the HeartMate II device is very durable with an estimated working life of 5 to 10 years. The pumps also have good hemocompatibility (that is, they do not cause adverse reactions with flowing blood) and can drive adequate cardiac output without inducing turbulence, stasis, or clinically significant hemolysis.

The FDA approved the HeartMate II LVAD for DT in January 2010. Currently, over 98% of all LVADs implanted in the United States are continuous flow devices (7), and the HMII has proven to be the "work horse" of LVAD centers across the United States. At present, it is essentially the only realistic option for large-scale implementation of LVAD DT. Heartware (Heartware, Framingham, MA), another durable pump with good outcome data, is not yet approved for DT.

## **Indications**

According to the most recent guidelines of the American College of Cardiology Foundation/American Heart Association (8), VADs are indicated for patients who have advanced systolic HF with a left ventricular ejection fraction (LVEF) less than 25% and who are in New York Heart Association (NYHA) class III-IV functional status. Patients must also have received guideline-directed medical therapy including (when indicated) cardiac resynchronization therapy and have a high predicted 1- to 2-year mortality (e.g., as suggested by markedly reduced peak oxygen consumption or clinical prognostic scores) or be dependent on continuous parenteral inotropic support.

The dependence on continuous intravenous inotropes can be shown for patients with low cardiac output by demonstrating that cardiac index improves by at least 20% after initiation of inotropes (9). Alternatively, patients exhibiting pulmonary congestion should show a  $\geq 20\%$  drop in pulmonary capillary wedge pressure after inotropes (9). Patients should also fail weaning attempts implemented by an experienced HF team.

In essence, LVAD as DT should be considered for patients who have advanced systolic HF and who are (a) otherwise functional, (b) ineligible for cardiac transplantation, and (c) have low-output syndrome and/or severe congestion. This means that all patients referred for mechanical circulatory support should already have had their transplant candidacy assessed (10). Of course, these



plans also assume that any potentially reversible causes of systolic HF, such as severe aortic stenosis, persistent tachyarrhythmias, ongoing ischemia, etc. have been corrected.

### **Candidate Selection: LVAD, Transplant, or Hospice?**

The steps for choosing treatments for patients who have advanced HF include:

- Evaluation for reversible causes of cardiomyopathy/HF.
- Evaluation for heart transplant eligibility.
- In patients who are ineligible for heart transplant, evaluation for mechanical circulatory support (Figure 1).

Many conditions that prevent a patient from being candidate for heart transplantation do not impact the option of LVAD DT.

- **Age.** Age remains the most common reason that patients are ruled ineligible for transplant. Many programs consider patients aged 70 and over too old to transplant. Meanwhile, patients who are at least 70 years of age when they receive an LVAD typically perform well with one month, one year, -and two-year survival rates, as well as length of stay, not markedly different from data obtained from younger patients (11-13). Thus, age alone should not be viewed as a contraindication for LVAD.
- **Frailty.** One area that is becoming an increasingly important part of a DT evaluation is the assessment of frailty. Frailty is a biological syndrome that reflects a state of decreased physiologic reserve, and can be diagnosed if three or more of the following criteria are present: unintentional weight loss (10 pounds in the past year), self-reported exhaustion, weakness (typically measured as grip strength), slow gait, and low physical activity. Post-operative complications are adversely affected by frailty (14) and handgrip has been shown to be a particularly effective predictor of survival (15).
- **Obesity.** Traditionally, transplantation centers establish an arbitrary threshold for body mass index (BMI) which they use as a criteria for patient selection. This contrasts with data from LVAD procedures (16) which show that extremes of body mass index are not associated with poor survival in either univariate analysis, or in adjusted models (extremely obese: hazard ratio (HR) 1.29,  $p = 0.2$ ; obese: HR 0.94,  $p = 0.7$ ; underweight: HR 1.23,  $p = 0.4$ ). Extremely obese patients did however have higher rates of device-related infection and re-hospitalization (16). Butler et al.(17) also reported good outcomes on LVADs in patients with high BMI, with similar rates of infectious, neurological, respiratory, and bleeding complications as their leaner counterparts, but with



higher re-operation rates and more renal complications. Patients with lowest BMI (<22.9) had the worst prognosis (Table 1) (17).

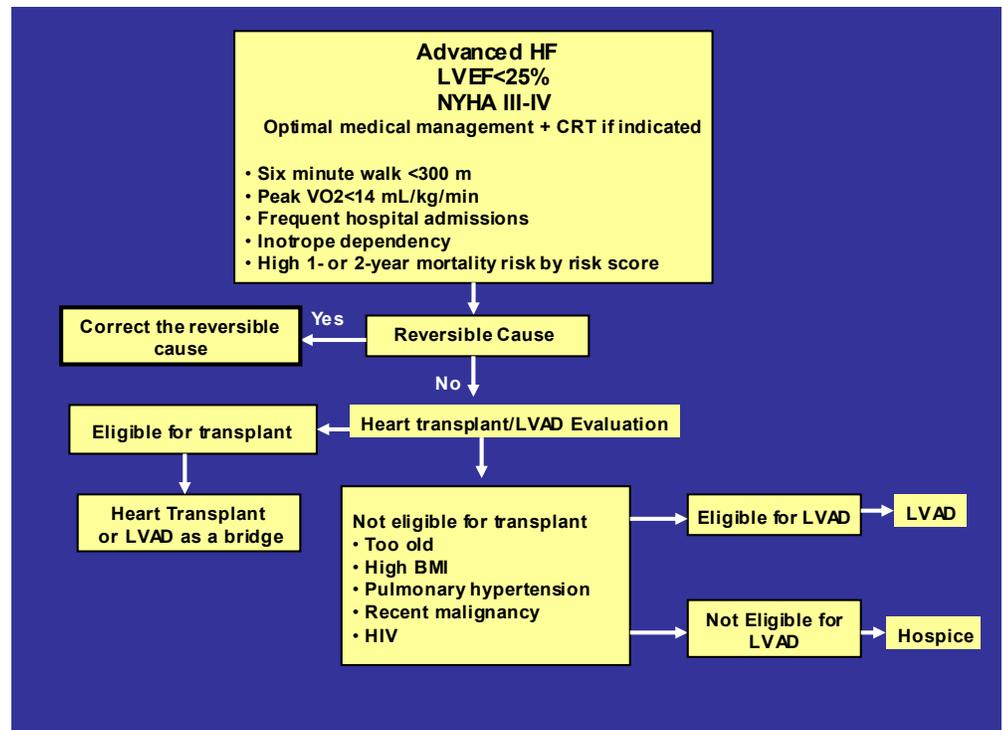
- **Pulmonary hypertension.** Patients who have severe fixed pulmonary hypertension (defined as pulmonary arterial systolic pressure greater than 60 mm Hg, transpulmonary gradient greater than 15 mm Hg, or pulmonary vascular resistance greater than 6 Wood units, while unresponsive to treatment with pulmonary vasodilators) are very high risk candidates for cardiac transplantation because of the high likelihood of post-operative right ventricular failure. These patients can however be treated with LVADs which may also reverse the pulmonary hypertension by unloading the left ventricle (18, 19).
- **Recent malignancy.** By convention, history of malignancy within 5 years is a contraindication for heart transplant, with rare exceptions. However, if the overall prognosis is good from an oncologic standpoint, there is no reason not to consider the patient for LVAD DT.
- **Human immunodeficiency virus.** While the fear of opportunistic infections typically precludes these patients from heart transplant, they can benefit from LVAD as DT (20).
- **Diabetes.** Caution is needed with this condition as outcomes for patients with LVADs and diabetes are typically as not as good as those for non-diabetics (Odds ratio (OR) 1.76, 95%CI 1.05-2.94) (21). Still, patients without severe end-organ damage due to diabetes, which would be a contraindication to transplant, can benefit from LVAD. Moreover, LVAD implantation with subsequent hemodynamic and metabolic optimization can improve the course of diabetes mellitus (22-26).

Congenital heart disease in adults produces more complex physiology than simple ischemic or non-ischemic cardiomyopathy. Congenital abnormalities can alter the chest anatomy as can prior surgeries performed for palliations and surgical repairs. Adhesions, conduits, shunts, patches, and anastomoses create multiple surgical challenges. Many centers avoid transplanting these patients because their outcomes are frequently worse than those patients who have “straightforward” advanced HF. Given the young age of many patients with adult congenital heart disease, it is especially important to find options to prolong their lives with mechanical circulatory support. The data on LVADs in adult congenital cases are limited but promising. A series of 6 cases with systemic right ventricle, including 2 patients with single-ventricle physiology, reports 2 deaths and long survival on LVADs for the four remaining patients (27).

Contraindications for LVAD (as well as heart transplantation) include: systemic illness with a life expectancy of less than two years, active malignancy with poor prognosis, severe aortic disease, severe obstructive pulmonary disease, and irreversible renal or hepatic dysfunction. The last condition does however require careful consideration as in many cases the dysfunction is secondary to



congestion/low output and may therefore be reversible on hemodynamic unloading (28, 29). Sometimes a liver biopsy is warranted to differentiate cirrhosis from potentially reversible fibrosis. If the team decides that the risk/benefit ratio for LVAD is unfavorable, a palliative care consult should be obtained to decide on the appropriateness of hospice. The decision making process is summarized in Figure 2.



**Fig 2. Decision making process on advanced HF management**

### Evaluation for LVAD as DT

The evaluation process is typically performed by a team of specialists that includes a HF cardiologist, a cardiothoracic surgeon, a dietitian, a pharmacist, a social worker, and a financial consultant. In most programs, the same team performs evaluations for heart transplant and LVAD implantation.

In order to benefit from the LVAD, the patient has to (a) survive the early post-operative period when most acute complications occur, and (b) maintain good functional status for several years in order to maintain a good quality of life after the implant.

To solve the first problem – getting the patient through post-operative period – their status has to be optimized before the surgery. This includes:

- Optimizing hemodynamics with maximal unloading (diuresis with or without inotropic support) and treating pulmonary hypertension



to decrease pulmonary vascular resistance and prevent post-operative failure of the right ventricle (RV).

- Minimizing renal and hepatic insufficiency.
- Improving nutritional status.
- Evaluating for potential bleeding and optimizing coagulation status.
- Treating infections and providing antibiotic coverage for prophylaxis.

To prepare the patients for living on LVAD support for a long time, several steps are usually undertaken before the decision to operate:

- Evaluating for serious co-morbidities which may limit longevity such as severe chronic obstructive pulmonary disease, severe vasculopathy, including atherosclerotic changes in carotis arteries or presence of peripheral vasculoar disease, impaired neurologid status, or coagulopathy.
- Evaluating psychological stability, compliance, absence of drug or alcohol addiction, social support, and financial reserves.

Selecting the best candidates for LVAD DT involves optimizing the balance between patients who are “too sick” and patients who are “too well”. Extensive prognostic data is available from INTERMACS, the unique registry of LVAD recipients in the USA which is sponsored by the National Heart, Lung, and Blood Institute, the Centers for Medicare and Medicaid Services, FDA, and industry. Patients who are entered into the registry are categorized into one of seven classes at the time of LVAD implantation. The highest INTERMACS profile (profile 1, “crash and burn”) corresponds to cardiogenic shock while profile 7 equates to stable NYHA III (30).

Unstable patients in cardiogenic shock (“crash and burn” INTERMACS profile 1) have the worst outcomes after they receive an LVAD but also have the most to gain if the treatment is successful (31). More stable patients in profiles 3 and 4 have much better outcomes but their gains in terms of longevity and quality of life are moderate. Presumably technical advances will mean that each new generation of pump will become better and smaller, and cause less discomfort to the patient. This will make LVADs a better option for patients with milder forms of HF. The ongoing MEDAMACS study is designed to address this idea and tests whether ambulatory patients who are in NYHA III with episodes of decompensation can benefit from current LVAD therapy. It’s also pertinent to note that some programs implement risk stratification and mortality prediction using well validated scores such as the Heart Failure Survival Score (32) and the Seattle Heart Failure Model (33).



## Outcomes

The field of mechanical circulation has been evolving so rapidly, and technological advances have been occurring so frequently, that the data on outcomes have been improving continuously. The results of yesterday are no longer valid today, and cannot be extrapolated into tomorrow. Outcomes obtained with pulsatile pumps are not applicable to continuous flow devices, and survival and other important outcomes have improved in each successive trial as clinicians gain experience.

Table 1 shows data on outcomes that we collated from the literature.. Many of the results were obtained from studies that included DT and Bridge to Transplant (BTT) and from different types of LVAD. Outcomes from trials that studied only BTT were not included. Most of the data in Table 1 are survival and length of stay values.

The historic starting point for LVAD DT outcome trials is the REMATCH trial. In this work, survival on the pulsatile HMI was 52% at one year and 29% at two years which greatly exceeded the survival rates on optimal medical therapy (one year, 23%; two year, 8%) (4). Since 2001, the survival of patients receiving optimal medical management has very modestly improved but the survival of patients receiving LVAD HT has continued to increase.

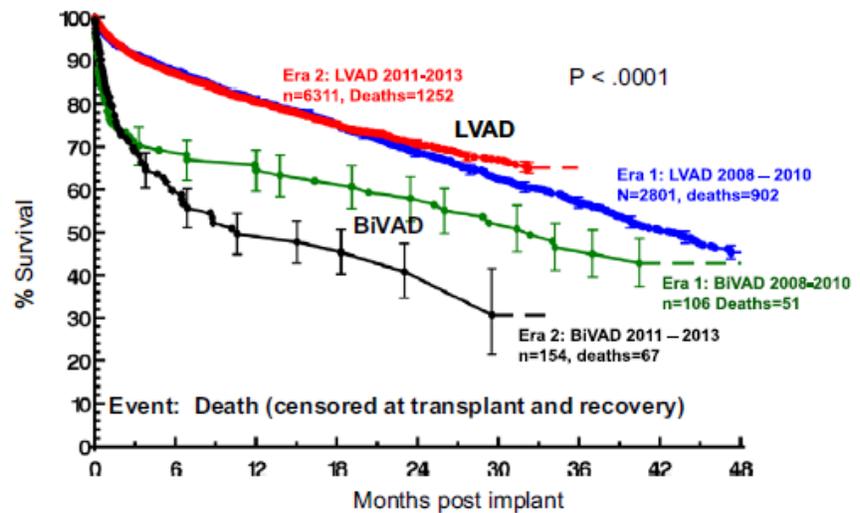
Several years later, in the HMII DT trial, patients ineligible for transplantation were randomized into continuous flow or pulsatile flow pumps (6). Patients who received HMII devices had better 2-year survival free from disabling stroke and/or re-operation to repair or replace the device than patients who were implanted with the pulsatile pump (46% versus 11%,  $p < 0.001$ ). Patients on HMII also had superior actuarial survival rates at 2 years (58% vs. 24%,  $p = 0.008$ ) and fewer complications.

Long term follow-up of HMII patients who were enrolled in the BTT trial showed an overall 18-month survival of 72% (5). Interestingly, patients who were enrolled later in the trial had better outcomes than patients who were enrolled near the beginning (34). The later cohort had better overall survival and fewer complications such as bleeding, device-related infections, and hemorrhagic stroke. This trend may reflect the growing skill and experience of the LVAD teams.

Heart transplantation is still regarded as the gold standard treatment for advanced HF and has an average 2-year survival of approximately 80% (2). However survival rates for LVAD DT are now approaching this level. Patients who receive a continuous flow LVAD and who do not have risk factors associated with high mortality (for example, history of cancer, high blood urea nitrogen, and/or cardiogenic shock at implant) have 1 and 2 year survival rates of 88% and 80% respectively (35). The sixth INTERMACS report shows that actuarial survival at 1 and 2 years is 80% and 70% respectively (3).



Intermacs Continuous Flow LVAD/BiVAD Implants: 2008 – 2013, n = 9372



**Fig 3. Actuarial survival for continuous flow LVADs (From Kirklin et al. (3), with permission)**

Some programs create a so-called “alternative” wait list for patients who have advanced age, diabetes, obesity, or renal dysfunction and transplant them with sub-optimal hearts that would otherwise be discarded. These hearts typically have left ventricular hypertrophy, mild systolic dysfunction, or some coronary artery disease. The survival rates for patients who receive these hearts, by a single center data, is similar to LVAD DT at one year (82.2% and 77.5%, respectively) and better than LVAD DT at three years (73% versus 50%). However, when patients who received pulsatile LVADs are excluded from the analysis, the outcomes for transplant and LVAD DT are similar at three years as well (36).

Predictably, when patients are unstable at the time of implantation, their outcomes are not as good as those of patients who were hemodynamically stable. An analysis of three groups of patients with different degrees of HF acuity showed that the patients who were most stable (ambulatory HF, INTERMACS profiles 4 to 7) had the best survival rate (96%), patients in the intermediate group (inotrope-dependent, INTERMACS profiles 2 or 3) had a moderate survival rate (69%), and patients in cardiogenic shock (INTERMACS profile 1) had the worst outcomes (51% survival) (31).

Table 1 (see page 10A-10F) shows that two year survival rates for continuous flow LVAD DT are generally in the 60~80% range. This is a substantial achievement given that the survival rate with optimal medical therapy was only 8% when the REMATCH trial was performed 15 years ago. Overall quality of life with LVAD DT is also good. In patients supported by predominantly HMII devices for at least a year, the average six minute walk distance was ~400 m while they



mean NYHA class was 1.4 +/- 0.6. These patients did however require about three hospital admissions per year and 77% had to undergo additional operations (37).

### **Myocardial Recovery**

Although it is not common, myocardial recovery is a highly desirable outcome of LVAD implementation. Replacing a failing heart with a mechanical pump produces multiple beneficial effects. For example, LVAD implantation decreases left ventricular dimensions, increases left ventricular ejection, and induces regression of cardiomyocyte hypertrophy (41). Hemodynamically, LVADs increase cardiac output, decrease pulmonary capillary wedge pressure (42) and pulmonary vascular resistance (18, 19), and eventually improve right ventricular structure and function. Moreover, LVADs decrease plasma epinephrine, norepinephrine, arginine vasopressin, renin and angiotensin II (43) as well as circulating and myocardial inflammatory mediators such as interleukin 2 and tumor necrosis factor (44). The renal and hepatic dysfunction that is typical of end stage HF, improves as well (45, 46). Six months of LVAD treatment essentially normalizes liver enzymes, bilirubin, blood urea nitrogen, and serum creatinine in patients who had previous renal and hepatic dysfunction and also maintains values in patients who had normal pre-LVAD levels (29, 47).

Specifically, in patients with HMII, overall LVEF increased from 17% at the time of implantation to 25% 6 months later ( $p < 0.01$ ). LV mass decreased from 114  $\text{g m}^{-2}$  to 95  $\text{g m}^{-2}$  30 days after LVAD implantation and continued to fall progressively over the 1-year follow-up. Interestingly, LVEF improved to >40% in a significant proportion (19%) of patients. Most of the improvement in LVEF was achieved within 6 months with little if any improvement after this cutoff (48). Younger age and shorter duration of HF were the main predictors of recovery. Importantly, the patients who recovered LVEF received the same post-VAD cardiac medications and had the same incidence of non-ischemic cardiac disease as the patients who did not recover LVEF (48).

Ultimate success of LVAD-associated myocardial recovery implies successful explantation of the LVAD followed by sustained normal cardiac function. The typical rate of explantation in patients with non-ischemic cardiomyopathy is 10~20% (49) although there are also some outlying studies that have much higher recover rates (50, 51). Since the number of patients qualifying for LVAD DT is expanding rapidly, a considerable number of patients could potentially be explanted in the next few years. Recovering myocardium should be a goal in most LVAD implants, at least in non-ischemic patients.

Dandel et al. (52) have proposed a protocol to help ensure stable cardiac function after the explant, and to minimize the risk of having to re-implant the LVAD if the attempt to remove mechanical support fails. They suggest turning the LVAD to its minimum speed (6200 revolutions per minute for the HMII) and only proceeding with the VAD explantation if LVEF recovers to  $\geq 45\%$ . This test predicts cardiac stability that lasts for at least 5 years in 79% of cases. Increasing

**Table 1 Outcomes of patients on LVADs (Studies with BTT only are not included. Either mixed DT/BTT or DT only are included.)**

	<b>Setting</b>	<b>Patients population</b>	<b>Indication</b>	<b>Device</b>	<b>Measure</b>	<b>1 month</b>	<b>6 months</b>	<b>1 year</b>	<b>2 years</b>	<b>3 years</b>	<b>Actuarial survival</b>
<b>Pulsatile LVADs</b>											
Rose et al., 2001 (4)	REMATCH	68 patients	DT	HMI	Survival			52%	29%		
Butler et al., 2005 (17)	Multiple centers	222 patients	Mixed BTT and DT	Novacor	Survival	84.1%	57.5%	42.4%			
		1 <sup>st</sup> quartile BMI <22.9			Survival	81.3%	35%	26%			
		2 <sup>nd</sup> quartile BMI 22.9 to 26.3				81.3%	60%	34.9%			
		3 <sup>rd</sup> quartile BMI 26.4 to 29.4				92.1%	65%	50%			
		4 <sup>th</sup> quartile BMI >29.4				81.8%	73%	66%			

Butler et al., 2005 (21)	Multiple centers	222 patients	Mixed BTT and DT	Novacor	Survival						
		57 patients with diabetes				76.6%	45.6%	30.4%			
		165 patients without diabetes				86.7%	62.4%	47.1%			
Lietz et al., 2007 (38)		280	DT	HMI		86.1%		56%	30.9%		
Rogers et al., 2007 (39)	The INTrEPID (Investigation of Nontransplant- Eligible Patients Who Are Inotrope Dependent) trial	37	DT	Novacor			46%	27%			
Mixed pulsatile and continuous flow LVADs											
Long et al., 2008 (40)	Utah Artificial Heart Program	23	DT	HMI and HMII	Survival			77%	77%		

Daneshmand et al., 2010 (36)	Duke University	60 patients ineligible for standard list cardiac transplantation	DT	HMI and HMII	Survival	93%		78%		50%	
Kirklin et al., 2012 (35)	INTERMACS	1287	DT	HMI and HMII				75%	62%		
Randomized trial of pulsatile versus continuous flow LVADs											
Slaughter et al., 2009 (6)	Randomized controlled trial	66	DT	HMI	Survival			55%	24%		
					Survival free from disabling stroke and reoperation				11%		
		134		HMII	Survival			68%	58%		
					Survival survival free from disabling stroke and reoperation				46%		
Continuous flow LVADs											
Adamson et	Single center,	55	Mixed	HMII	Survival						

al., 2011 (11)	trials at a community hospital		BTT and DT								
		30 patients aged ≥70				97%		75%	70%		
		25 patients aged ≤70				96%		72%	65%		
Boyle et al., 2011 (31)	University of Minnesota, University of Pittsburgh and Columbia University	101 patients	Mixed BTT and DT	HMII or VentrAssist	Actuarial survival from the date of implant to death, transplantation, LVAD explantation, or if they remained LVAD on September 1, 2009						
		28 patients INTERMACS									51.1%

		profile 1 (cardiogenic shock)									
		49 patients INTERMACS profiles 2 or 3 (inotrope- dependent and hospitalized)									68.8%
		24 patients INTERMACS profiles 4 to 7 (outpatients with low functional capacity)									95.8%
Brewer et al., 2012 (16)	The HMII BTT and DT trials	896 patients	Mixed BTT and DT	HMII							
		48 underweight						73±7%,	59± 9%		

		patients (BMI<18.5)									
		596 normal weight patients (BMI 18.5-30)						71 ± 2%,	60± 2%		
		164 obese patients (BMI 30-35)						76 ±4%	66± 5%		
		88 extremely obese patients (BMI≥35)						79 ±5%	68± 6%		
Park et al., 2012 (34)	The HMII DT trial		DT	HMII							
		133 patients (early cohort)						68±4%	58±4%		
		281 patients (mid-trial cohort)						73±3%	63±3%		



the LVEF threshold to  $\geq 50\%$  increases the predictive value of the weaning test to 92%.

**Table 2. Recovery of left ventricular function as defined by successful explantation of the device (from Guglin et al. (53))**

Study, year	Total number of patients	Number (%) of recovered overall	Number of nonischemic patients	Number (%) of nonischemic patients recovered	Outcomes
Mancini et al., 1998 (54)	111	5 (4.5%)	51	4 (7.8%)	20% survival with no recurrence of HF at 15 months
Farrar et al., 2002 (55)	271	22 (8.1%)	271	22 (8.1%)	86% and 77% transplantation-free survival at 1 year and 5 years
Gorscan et al., 2003 (56)	18	6 (33.3%)	13	5 (38.5%)	No HF recurrence in 67% at 1 year
Simon et al., 2005 (57)	154	10 (6.4%)	74	8 (11%)	80% alive and free from transplant at $1.6 \pm 1.1$ years
Matsumiya et al., 2005 (58)	11	5 (45.5%)	11	5 (45.5%)	No HF recurrence during follow-up ranging 8 to 29 months
Dandel et al., 2005 (49)	131	32 (24%)	131	32 (24%)	68.8% had no recurrence at three years
Birks et al., 2006 (51)	15	11 (73.3)	15 (100)	11 (73.3)	Long term survival 91%, rate of freedom from recurrent HF among the surviving patients 100% at 1 year and 88.9% at 4 years
Maybaum et	67	6 (9%)	37	5 (13.5%)	No death or transplants at 6



Study, year	Total number of patients	Number (%) of recovered overall	Number of nonischemic patients	Number (%) of nonischemic patients recovered	Outcomes
al., 2007 (59)					months
Dandel et al., 2008 (60)	188	35 (18.5%)	188	35 (18.5%)	Transplant-free survival $76.2 \pm 8.1\%$ and $70.7 \pm 9.2\%$ at 5 years and 10 years
Birks et al., 2011 (50)	19	12 (63.2)	19 (100)	12 (63.2)	83.3% survival without HF recurrence at 1 and 3 years
Lamarche et al., 2011 (61)	17	4 (23.5%)		3	Number of patients with ischemic/nonischemic cardiomyopathy and long-term follow-up is not reported

## Complications

### 1. Right ventricular failure

A downside of LVAD DT is frequent re-admissions related to complications. These can occur soon and long after the operation. Right ventricle (RV) failure is one of the most important problems.

Augmenting the failing LV with an LVAD improves hemodynamics immediately in patients with isolated LV failure. The situation is more challenging for patients (for example, most patients with ischemic cardiomyopathy) who have biventricular failure. Since no devices are yet approved for DT for right or bi-ventricular failure, the risk of RV failure post-LVAD needs to be assessed before every potential implantation. We have recently published a detailed discussion of risk predictors and risk scores that are relevant to candidate selection (62).

Increased blood flow in the postoperative period after LVAD implantation raises the workload of the RV. The septum is also shifted to the left which increases the RV's end-diastolic volume and compromises its contractility. If the RV was



already compromised before LVAD implantation, it may recover slowly, or not at all, after the surgery (48). The most favorable scenario is a gradual reduction of RV volume, ventricular mass, diameter of cardiomyocytes, and normalization of myocardial collagen content and chamber stiffness (63, 64).

Specific data obtained from DT HMII patients 1 month after surgery are as follows (65).. Central venous pressure decreased from  $12.4 \pm 5.9$  to  $8.7 \pm 4.5$  mm Hg ( $p < 0.001$ ). Systemic pulmonary arterial pressure decreased from  $52.3 \pm 14.1$  to  $36.8 \pm 11.3$  mm Hg ( $p < 0.001$ ). RV ejection fraction increased from  $33.1 \pm 4.9\%$  to  $40.4 \pm 6.2\%$  ( $p < 0.001$ ). In addition, RV end diastolic dimension decreased, RV stroke work index improved, and qualitative RV function on echocardiography improved from 57.1% moderately or severely reduced preoperatively to 38.1% after 1 month ( $p = 0.008$ ).

RV failure occurs when a patient exhibits at least two weeks of inotrope dependency, or if the patient develops late onset inotrope dependency within two weeks of the LVAD implantation, or if they need an RVAD. This happens in 5-13% of patients after LVAD implantation, and results in prolonged intensive care stay, higher mortality, greater risk of bleeding, and more renal insufficiency (66, 67).

Measurements that indicate potential postoperative RV failure include: low fractional area change and stroke-work index estimated by echocardiology, high central venous pressure (even with normal or near normal pulmonary capillary wedge pressure), elevated liver enzymes and creatinine (as signs of congestion), and low or normal pulmonary artery systolic pressure. The Berlin group uses the RV-to-LV end-diastolic diameter ratio of  $>0.72$  to identify patients with high risk for postoperative RV failure (68).

Several scores have been proposed for calculating the risk of RV failure post LVAD. One of them emphasizes requirements for vasopressors, liver function, and creatinine (69) while another other score highlights hemodynamic parameters (70). Focusing specifically on RV failure after HMII, Kormos et al. (71) identified a central venous pressure/pulmonary capillary wedge pressure ratio of greater than 0.63, need for preoperative ventilator support, and blood urea nitrogen level of greater than  $39 \text{ mg dL}^{-1}$  as independent predictors of RV failure after LVAD. In practice, despite all of these studies, it remains challenging to predict the post-LVAD performance of the RV for an individual patient.

Deswarte et al. (72) gave dobutamine (maximal dose  $15 \text{ mcg kg}^{-1} \text{ min}^{-1}$ ) to patients before they received an LVAD. The authors showed that if dobutamine increased the tricuspid annular plane systolic excursion by at least 40% and/or pulmonary artery systolic pressure by at least 30%, this ruled out post-LVAD RV failure with 100% specificity and sensitivity.

Treatment strategies for post-LVAD RV failure include decreasing RV afterload with intravenous vasodilator agents (especially phosphodiesterase-inhibitors such as Sildenafil) and increasing contractility with inotropes such as milrinone or dobutamine. Milrinone has been show to be the most effective inotrope for



reducing pulmonary vascular resistance and increasing LVAD flow (73). Some surgeons initiate inhaled nitric oxide in the operating room but this policy often requires simultaneous use of vasopressor agents to offset the associated vasodilation and resultant hypotension.

It has also been shown that repairing the tricuspid valve in patients with moderate-to-severe or severe tricuspid regurgitation at the time of LVAD implant can prevent RV failure in post-operative period (74, 75).

In general, RV failure that develops early in the postoperative phase can be overcome using inotropes and short-term or intermediate-term devices for RV mechanical support. RV failure that develops late, or which persists for months after LVAD implantation, is more difficult to manage. Sometimes patients are discharged on inotropes, or their transplant status is reconsidered, and they are put on the waiting list.

## *2. Gastrointestinal bleeding*

Managing complications is critical if patients receiving LVAD DT are to maintain a good quality of life. Bleeding in general is the most common complication in patients on LVADs, with major bleeding observed in about 20% -45% of cases (76, 77). Patients on continuous flow support require anticoagulation and have transfusion requirements which are double those of patients on pulsatile pumps (77). In the HMII DT trial, as many as 81% patients required a blood transfusion, and 30% required re-exploration for bleeding (6).

Gastrointestinal (GI) bleeding in particular is the most serious problem associated with LVAD DT. It significantly reduces the quality of life of many patients, leading to multiple admissions, unpleasant diagnostic tests, repeated blood transfusions, and generally unsatisfactory solutions.

GI bleeding affects 18 to 40% of patients with LVADs (77-81). Counting only episodes requiring transfusions of  $\geq 2$  units of packed red blood cells within 24 hours, Boyle et al. (82) reported GI bleeding in 9.4% of outpatients who were supported by a HMII device. These events formed 50% of all recorded bleeding incidents and were occurring a rate of 0.23 events/patient-year.

The proportion of patients who bleed repeatedly is 44% (78). The majority of these individuals (60%) bleed from the same site. The distribution of bleeding sites is as follows: upper GI tract, 89% (including 54% bleeding from gastric erosions, 15% from gastric ulcers, and 15% from angiodysplasias), lower GI tract, 35% (equally distributed between cecal/rectal ulcers and small bowel angiodysplasias) (78). The mean time to bleeding the LVAD implantation was  $128 \pm 155$  days.

Additional data suggest that 31% of GI tract bleeding events are caused by arterio-venous malformations (79). Since malformations in the proximal jejunum cannot be detected by routine upper endoscopy and are highly prevalent in patients receiving LVAD DT, many centers now perform capsule endoscopy as



part of the early evaluation of GI bleeding. Risk factors for GI bleeding include advanced age, prior GI bleed, a high international normalized ratio (INR), and low platelets (78). Fortunately, the death rate (even in recurrent GI bleeding) remains only 1% (78).

Aggarwal et al. (78) analyzed echocardiograms and showed that the aortic valve opened in 17% of patients who had GI bleeds and 30% of non-bleeders. This suggests a potential link between pulsatility and GI bleeding. However the inter-group difference was not statistically significant, potentially due to the relatively small sample size.

Factors that may contribute to the high incidence of GI bleeds in patients who are supported by HMII devices include:

- **Narrow pulse pressure with limited pulsatility.** As in the case of tight aortic stenosis (Heyde's syndrome) (83), low pulse pressure causes hypoperfusion and hypoxia of the gut, resulting in vascular dilatation and angiodysplasia (78)
- **Acquired von Willebrand syndrome.** This condition is also associated with severe aortic stenosis (84) and is probably caused by mechanical depletion of high-molecular-weight von Willebrand factor multimeres. Multimeres are lost within days of the LVAD implant (85), possibly due to the effects of shear stress on the structure of von Willebrand factor (76, 77, 86).
- **Neoangiogenesis.** Some fragments of von Willebrand factor may be proangiogenic and actually promote angiodysplasia (76, 87).
- **Impaired platelet function.** Platelet numbers, function, and activation are reduced in patients who are supported with continuous flow LVADs (76, 88).

Unfortunately, none of these factors fully explain why some patients develop chronic recurrent GI bleeds and others do not. Many centers have therefore used their clinical experience to develop protocols that they follow in the event of GI bleeding. One of the typical protocols (78) includes:

- holding of all anticoagulation and antiplatelets agents.
- decreasing the VAD speed to create pulsatility
- administering proton pump inhibitors.
- administering octreotide (either as a continuous infusion or by subcutaneous injection).
- resuming anticoagulation at a lower INR goal of 1.5-2.0.

Although it seems physiologically advantageous to have some pulsatility, LVAD speed and pulse index are not consistent predictors of GI bleeding. In one study, reduced pulsatility index was associated with an increased risk of bleeding



(hazard ratio, 0.60; 95% confidence interval, 0.40-0.92;  $P=0.02$ ) (89), while in another study, VAD speed and PI were not significant predictors of GI bleeding (78).

Octreotide is a synthetic somatostatin analogue which inhibits gastric acid secretion and reduces portal and splanchnic circulation. There is some evidence that it is helpful. Nardone et al. (90) showed that subcutaneous injections for 6 months produced full or partial control of bleeding in 14 of 17 patients with angiodysplasias. On the other hand, Barbara et al. (91) reported no favorable effect. Similarly, a study showed that octreotide did not impact the amount of packed red blood cells used, rebleeding rates, length of hospital stay, or all-cause mortality (78).

There are some anecdotal reports of patients being off all anticoagulants for months after a major bleed. However, these practices may raise the incidence of pump thrombosis. There is also a report of successful use of danazol, a synthetic steroid that has weak androgenic and anti-estrogenic effects (92).

### 3. Pump thrombosis

Pump thrombosis is a serious and potentially fatal complication of LVAD therapy. If thrombosis is not treated with a heart transplant or LVAD replacement, the mortality approaches 50%. In clinical trials, the rate of thrombosis was low, but between 2011 and 2013 several high volume centers documented a sharp rise (from 2.2% to 8.4%) of pump thrombosis in the first three months after the implantation. The time from implant to pump thrombosis also shortened from 18.6 to 2.7 months (93). This increase was also apparent in an analysis of INTERMACs data (94).

Preexisting LV thrombi that are dislodged during the surgery can be pulled into the LVAD device. This problem becomes less frequent as surgeons gain experience. A more important problem is formation of new thrombi after the LVAD has been implanted. The heat generated by the LVAD can cause new clots to form and grow on the inflow bearing or on the rotor itself (95). Prothrombotic conditions can facilitate this process (96). These include: significant infection, sub-therapeutic anticoagulation, low flow state, hereditary thrombophilias such as protein S, protein C, or factor V Leiden deficiency, and antiphospholipid syndrome (95).

The surgical technique also seems to influence pump thrombosis and malposition of the inflow cannula and deformed outflow grafts have been linked to post-LVAD clots (97). Decreasing the LVAD flow to facilitate intermittent opening of the aortic valve increases the rate of thromboembolic events (98). This may be because high flow rates dissipate heat from the LVAD more effectively than low flow conditions. Clinically, it is thus important to achieve a balance between a high flow rate (which reduces thrombosis) and a low flow rate (which increases the incidence of bleeding).



Pump thrombosis typically presents with evidence of hemolysis clinically manifest as very dark cola colored urine, and a plasma free hemoglobin  $>30 \text{ mg dL}^{-1}$ , elevated lactate dehydrogenase, decreased haptoglobin, increased pump power, new palpable pulse, new opening of the aortic valve, worsening of mitral regurgitation on echocardiography (99), and sometimes symptoms of HF. Data suggest that increased lactate dehydrogenase ( $>600 \text{ U/mL}$  for HMII and  $>400 \text{ U/mL}$  for Heartware) is the most reliable predictor of pump thrombosis (100), and some centers have adopted the policy of immediate hospitalization based on elevated LDH alone. The best way to treat patients who have elevated LDH but no clinical signs of pump thrombosis is still unclear.

Some cases may be diagnosed with CT angiography (101) but while both cannulae can be visualized, the pump itself is not radiolucent. Recently, specially designed ramp protocols were suggested as a way to determine the presence of thrombi inside the LVAD device (102, 103). In addition to increasing the standard antithrombotic and anticoagulation drugs, thrombolytics and IIB/IIIA antagonists have been used empirically with intermittent success but multiple complications. Frequently, the only realistic option is pump exchange. This procedure is relatively safe for HMII devices with postoperative deaths within 30 days of 6.5% (104) (Table 3).

**Table 3. Outcomes of pump thrombosis with different therapeutic interventions**

Source	N	LVAD	Intervention	Outcome
Thenappan et al. (105), 2013	2	HMII	Alteplase (after heparin and eptifibatide failed)	Alteplase – 100% success Eptifibatide 100% failure No complication reported, but long term outcome not specified
Al-Quthami et al. (106), 2012	2	HMII	Eptifibatide	100% success, GI bleed in both
Tellor et al. (107), 2013	17 patients, total of 22 attempts	16 HMII, 1 Heartware	Eptifibatide	3 (17.6%) – success 14 (22.4%) – failure, including 7 (41.2% deaths) Complications: bleeding



				11 pts (64.7%) including SAH in 2 Conclusion: Risk of using eptifibatide outweighs the proposed benefit of salvaging the existing LVAD. No correlation between the dose and the outcome.
Hasin et al. (108), 2013	8	HMII	6 Heparin+clopidogrel  1 Heparin+clopidogrel+eptifibatide  1 Heparin+alteplase	All survived acute episode but had recurrent hemolysis, stroke in 1 (100% failure)  100% success (resolved but GI bleed with 12 units transfused)  100% failure  In 4 pumps which were eventually explanted, the clot was present in all.
Schlendorf et al. (109), 2014	8	HMII	Alteplase	3 (37.5%) success 5 death or exchange or transplant
Muthiah et al.	5	Heartware	1 tirofiban	100% success, with massive



(110), 2013			<p>1 alteplase and tenecteplase success</p> <p>1 tenecteplase died</p> <p>1 alteplase died</p> <p>1 alteplase+ tirofiban</p> <p>Clopidogrel used in 4 of 5</p>	<p>hemithorax</p> <p>100% success, with epistaxic</p> <p>100% failure</p> <p>100% failure</p> <p>100% success but transplant in 8 days therefore no long term f/u</p> <p>No intracranial bleeds</p>
Aissaoui et al. (111), 2012	7 episodes in 6 patients	Heartware	<p>5 pump exchanges (1 after failed tenecteplase)</p> <p>2 tenecteplase</p>	<p>Pump exchange 100% successful</p> <p>Tenecteplase 50% successful</p>
Najjar et al. (112), 2013	34 episodes in 31 patients	Heartware	<p>30 medical therapy</p> <p>4 heparin</p> <p>19 alteplase</p>	<p>15 (50%) success, with 5 bleeding events, including 2 hemorrhagic strokes.</p> <p>15 (50%) failure, with 1 death, 2 urgent transplants, 12 pump exchanges</p> <p>No success with heparin alone</p>



			6 epitifibatide  16 pump exchanges	Alteplase 12 of 19 (63.2%) success  3 (50%) success  12 (75%) success 4(25%) deaths  No statistical difference in survival at 6 months between those patients treated medically compared to patients that underwent device exchange (91.7% vs. 68.8%)
Starling et al. (93), 2014	38  19	HMII	Medical management, no details  Pump exchange	18 (50% success)  18 (95.5% success)
Ota et al. (113), 2013	19 with pump thrombosis, out of 30 total	HMII	Pump exchange	27 (90%) success, 3 death (10%) for the whole cohort, without subanalysis by the cause
Pagani et al. (114), 2009	4	HMII	Pump exchange	2 (50%) success, 2 died
Stulak et al.	14 with pump	HMII	Pump	Overall excellent results, not



(115), 2013	thrombosis, out of 57 total episodes		exchange	stratified by type of the device or the reason for exchange
Ravichandran et al. (116), 2013	9	HMII	Pump exchange	3 (33%) success
Kirklin et al. (94), 2014	383 (all pump exchanges due to thrombosis)	HMII	Pump exchange	<p>Freedom from pump thrombosis, 97% at 6 months, 95% at 1 year, and 92% at 2 years</p> <p>The survival after pump exchange for thrombosis was 56% at two years compared to 69% (p&lt;.0001) following primary implant.</p> <p>Although pump exchange can be performed with a relatively low hospital mortality, survival during the subsequent 6 months is adversely affected with each pump exchange.</p>
Moazami et al. (104), 2013	25 patients with pump thrombosis	HMII	Pump exchange	Outcomes are provided for all pump exchanges, not for thrombosis only.



	<p>s out of 72 patients exchanged for all causes</p> <p>77 exchange procedures total</p>			<p>The 30-day operative 6.5% (5 of 77)</p> <p>For the 66 patients with HMII to HMII exchange procedures, at 1 year, mortality was 30% + transplant 5%, 65% alive on LVAD</p> <p>The freedom from major device failure at 12 months was 93% ± 2%.</p>
Badiye et al. (117), 214	4	HMII	Argotroban	3(75%) success with tamponade due to hemopericardium, subdural hematoma, and GI bleed

Note that in Table 4, the data reported for pump exchange include only studies where the exchange was performed specifically for pump thrombosis. This excludes results from Ota et al (113), Moazami et al (104), and Stulak et al (115). Data from Kirklin et al (94) were also excluded because the medical strategies preceding pump exchanges were not reported. If these data had been included, the success rate for pump exchange would have increased substantially.

**Table 4. Outcomes of pump thrombosis grouped by interventions (derived from Table 3)**

	<b>Pump exchange</b>	<b>Thrombolytics</b>	<b>IIB/IIIA antagonists</b>
N	53	35	33
Success	40	19	13
Success, %	75.5	54.3	39.3



## Stroke

There are two forms of stroke in LVAD patients, ischemic and hemorrhagic. The annual ischemic stroke rate with optimal medical treatment is 5.2% (4). Boyle et al. (82) reported ischemic and hemorrhagic stroke rates per patient-year at 4.1% and 3.2%, respectively.

A factor that seems to influence the incidence of stroke is the level of anticoagulation. About 40% of ischemic strokes occurred at INR < 1.5, and 33% of hemorrhagic strokes occurred at INR > 3.0 (82). Routine aspirin therapy (81 mg daily) and maintaining INR in the 1.5 to 2.5 range may balance the risks of thrombosis and hemorrhage (82). The risk of ischemic stroke is increased if mean arterial pressure is above 90 mmHg and if there is a history of stroke. The odds almost double in the presence of systemic infection (118).

Table 5 summarizes the incidence of strokes in LVAD studies.

**Table 5. Hemorrhagic stroke, and ischemic stroke rates in patients with HMII implanted for DT or BTT indications (modified from Eckman et al. (76), with permission)**

	<b>Hemorrhagic CVA per Patient-Year</b>	<b>Ischemic CVA per Patient-Year</b>
HMI/HMII (119)	0.05	0.13
HMII (5)	0.05	0.09
HMII (6)	0.07	0.06
HMII(120)	0.01	0.06
HMII (121)	0.04-0.07	0.04-0.09
Heartware (122)	0.08	0.05
HMII (82)	0.032	0.041

## Infection

Drivelines that pass through the patient's skin to the implanted device are an "Achilles heel" of prosthetic pumps because it makes driveline infections a permanent threat. In the HMII DT trial, the rate of LVAD-related infections was 0.90 and 0.50 events/patient-year for HMI and HMII respectively (6).



In patients supported primarily by HMII devices for at least a year, infectious complications led to 43% of re-admissions and occurred in the driveline (47%), blood (37%), and LVAD pocket (20%) (37). In a prospective multicenter study of VAD infections, where 57% of patients had HMII devices, 22% of patients developed VAD-related infections with an incidence rate of 0.10 per 100 person-days. The driveline was the most commonly infected site, with *Staphylococcus* being the most common pathogen, followed by *Pseudomonas* or other Gram-negative bacteria. Importantly, there was no difference between HMI and HMII, but regardless of the device, infection increased one-year mortality (adjusted hazard ratio=5.6;  $P<0.0001$ ) (123).

In the Mayo clinic cohort, driveline infections were also the most common (47%), followed by bloodstream infections (24% VAD-related, 22% non-VAD related). The most common causative pathogens include gram-positive cocci (45%) and gram-negative bacilli (27%). Only 42% of the patients were managed by antibiotics while others had to undergo surgical procedures. A small number of patients had to have their LVAD removed (124). Importantly for DT patients, the odds of having a driveline infection increase by 4% for every month of support (125).

Prevention of the infection is achieved by surgical techniques, stabilizing the driveline to minimize motion, and meticulous attention to hygiene. Aseptic rules should be followed and patients and their caregivers should wear sterile gloves and a mask as they clean the exit site daily with antimicrobial soap. After cleaning, the site should be rinsed with sterile saline and covered with a sterile gauze.

### **Aortic Regurgitation**

Aortic regurgitation may create problems in LVAD patients. If regurgitant flow persists throughout systole and diastole, this can limit forward flow to the periphery. This can compromise end-organ perfusion even when the LVAD flow readings are abnormally high (7 to 10 L min<sup>-1</sup>) (126). While minimal symptoms can be addressed with diuretics and afterload reduction, surgical repair or replacement of the aortic valve may be needed in more serious cases (126). Because aortic regurgitation tends to worsen over time, some advocate prophylactic aortic valve repair at the time of LVAD implant in patients with more than trivial aortic regurgitation (126).

Few patients (~3%) develop more than mild AR after LVAD (65). There are also anecdotal reports of percutaneous transcatheter aortic valve closure in VAD patients (127).

### **Arrhythmias**

The frequency of ventricular tachycardia /fibrillation (VT/VF) has increased significantly with the change from pulsatile to continuous flow VADs. VT/VF now occurs in about one third of patients who have a continuous flow LVAD (128-130). This problem is due in part to the new ability to adjust pump speed and



instantaneously adjust preload. As a result, the LV chamber size can be reduced until the septum touches the VAD drainage cannula. This causes a suction event and triggers VT. Reducing the LVAD speed to expand the LV cavity may resolve the issue. Other causes of VT/VF include a pre-existing post-MI myocardial scar, as well as a new scar which can develop in a small percentage of patients at the apical device cannulation site. VT/VF in this case can sometimes be treated successfully by catheter ablation (131).

Because cardiac output in patients who have continuous flow LVADs is not dependent on systole and diastole, ventricular arrhythmias are relatively well tolerated. A continuous flow LVAD successfully provided hemodynamic support to a patient in sustained ventricular fibrillation for over 12 hours (132). The effect of automated implanted defibrillators on mortality in LVAD patients is controversial. Some data show that the defibrillators still reduce mortality (129) but other data show no impact (130, 133).

Although LVADs protect from hemodynamic compromise in arrhythmias, they can initiate symptoms including right heart failure and recurrent syncope. Persistent atrial fibrillation may be associated with increased mortality and HF hospitalization, as well as with thromboembolism at higher levels of anticoagulation (134). In persistent atrial flutter, radiofrequency ablation can resolve symptoms (135).

### **Non-cardiac Surgery**

As survival rates increase, patients with LVADs are developing additional health problems that require treatment. This sometimes includes surgery. Non-cardiac surgery in patients on continuous flow devices is a relatively new problem, and there are very few studies addressing this issue.

In one cohort of 36 LVAD patients who underwent 63 non-cardiac surgeries, 30-day mortality was 16% (136). Most of the surgeries were abdominal but urological operations and craniotomies were also performed. None of the patients who died were undergoing elective surgeries. All the deaths occurred in patients who had to have emergent operations and half of these were neurosurgeries for intracranial hemorrhage. Two-thirds of the surgeries did not use Swan-Ganz catheters or arterial lines for monitoring. Mean blood pressure was maintained above 70 mm Hg. LVAD parameters were monitored and adjusted as required either by an LVAD coordinator or perfusionist experienced with LVAD management (136).

In another series, 33 patients with LVADs underwent general anesthesia for 67 non-cardiac operations (91). Postoperative bleeding was the only complication and this occurred in 12 patients. 3 patients died within 30 days of their operation for reasons unrelated to the LVAD (91). A further study by Morgan et al. (137) reports no peri-operative deaths, thromboembolic complications, or device malfunction in 20 non-cardiac operations.



Recommendations for patients on LVAD support undergoing a non-cardiac operation include stopping warfarin and aspirin prior to the surgery and resuming these drugs two weeks after the procedure. Vancomycin and cefazolin can be administered before the surgery for antibiotic prophylaxis and continued for 24 to 48 hours postoperatively (136). Blood products can be used as needed, including fresh frozen plasma and platelets.

### **LVAD Maintenance**

Optimal outpatient management is the key to good outcomes in LVAD DT. Although each LVAD center develops its own protocols, some principles have become universal. The HF cardiologist and the VAD coordinator typically work together and meet with the patient at each visit. It is helpful if the cardiothoracic surgeon is available if needed.

Mean arterial pressure should be maintained in the 60 ~ 90 mm Hg range. Conventional evidence-based medications for HF (angiotensin inhibitors and receptor blockers,  $\beta$ -blockers, and aldosterone antagonists) should be continued and increased if appropriate to achieve guideline targets.

Parameters of LVAD function including speed, power, and pulsatility index are measured at each visit. Blood flow is estimated automatically from the power and speed parameters. The only device parameter that can be manually adjusted is the speed of the LVAD. For HMII devices, this is typically in the 8,600 ~ 9,800 revolutions per minute range. The pulsatility index is averaged over a defined time interval and reflects the flow pulses created by LV contractions.

A recent paper by Topilsky et al. states that there are three goals for optimal LVAD therapy: improved cardiac output, LV unloading and preserved pulsatility (138). So-called “ramp” protocols are widely utilized to achieve these aims and are normally performed under echocardiography guidance. The following parameters are measured initially at baseline and then 3~5 minutes after each change of LVAD speed: left ventricular dimension, frequency of the aortic valve opening, and position of the interventricular septum. LVAD speed is usually incremented in steps that are at least 400 revolutions per minute for HMII devices and 60 revolutions per minute for Heartware systems. Once the protocol has been completed, the cardiologist chooses the single device setting (revolutions per minute) that optimizes a middle position of the septum, intermittent valve opening, and adequate unloading of the LV.

Setting the pump speed too low may result in an LV that appears dilated. A recent publication suggests two novel parameters that may indicate insufficient unloading of the LV. These are a rightward deflection of the atrial septum due to high left atrial pressure and a mitral deceleration index (the ratio of deceleration time to E-wave velocity) that is less than  $2 \text{ ms} / (\text{cm s}^{-1})$  (138).

Setting the pump speed too high can cause suction events where the ventricle becomes decompressed and the septum shifts so far to the left that it gets



sucked into the inflow cannula of the LVAD. This will reduce the power and speed of the LVAD and can also initiate clinical episodes of VT.

Ramp protocols currently vary between institutions. Uriel et al. (102) have recently proposed standardizing the approach and provide a detailed step by step description of a protocol that can be used to optimize LVAD settings. They also note that pump thrombosis is more likely if the LV end diastolic dimension is relatively insensitive to the LVAD speed setting.

### **Cost of LVAD DT**

LVAD DT using continuous flow devices is expensive but substantially cheaper than support using pulsatile pumps (\$193,812 versus \$384,260 for initial hospitalization, respectively,  $p < 0.001$ ) (6). Although the cost of the actual devices has not changed, the switch from pulsatile LVADs to continuous flow devices is associated with a 50% reduction in the cost of implant hospitalization over the last decade.

Taking into account hospital stays, re-hospitalizations, and Medicare payments for professional services, the cost of LVAD therapy provides more quality-adjusted life years (QALY) (1.87 vs. 0.37), and life years (2.42 vs. 0.64), than medical therapy. The downside is that the five-year costs of LVAD DT are much higher (\$360,407 vs. \$62,856). The incremental cost-effectiveness ratio of the continuous flow LVAD is estimated at \$198,184 per QALY and \$167,208 per life year. This is a 75% reduction in incremental cost-effectiveness ratio from \$802,700 per QALY in 2004 (139). We conclude that although the cost of LVAD therapy remains above the defined level of cost-effectiveness in the USA (\$100,000 / incremental cost-effectiveness ratio) the trajectory is encouraging.

The most realistic way to reduce future costs is to prevent complications because hospital readmissions are very expensive. Shifting the indications for LVAD therapy towards “less sick” patients will also save costs because these individuals will recover faster and develop fewer complications.

### **Conclusions**

LVAD as a destination therapy prolongs life and improves its quality in thousands of patients with end stage heart failure. In the future, smaller devices, freedom from external driveline, better design and durability may further improve the outcomes and make prosthetic pumps a more attractive option for patients with less severe disease. Partial hemodynamic support, devices for short term right ventricular support, and other innovations can potentially reduce complications of current LVADs and result in even wider adoption of mechanical circulatory support by both physicians’ community and general public.



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