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# Left Ventricular Assist Devices

## An Evidence-Based Analysis

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Ontario

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## About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

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The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and input from practicing medical experts and industry add important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to optimize patient outcomes.

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# Abbreviations and Glossary

| | |
|---|---|
| BiVAD | Biventricular assist device |
| ECMO | Extracorporeal membrane oxygenation |
| LVAD | Left Ventricular Assist Device |
| RVAD | Right Ventricular Assist Device |
| Acute myocardial infarction (AMI) | Damage to the heart muscle as a result of insufficient oxygen and nutrients. Heart attacks are frequent consequences of coronary heart disease. |
| Cardiac Assist . | The use of medical devices to provide support to a failing heart. Mechanical cardiac assist devices help directly support the pumping function of the heart while pacemakers and defibrillators primarily help control the rhythm of the heart. |
| Bi-Ventricular | Pertaining to the two chambers within the heart that receive and circulate blood. |
| Cardiomyopathy | A general diagnostic term designating primary noninflammatory disease of the heart muscle, often of obscure or unknown etiology and not the result of ischemic, hypertension, congenital, valvular or pericardial disease. |
| Cardiotomy | Surgical incision of the heart for repair of cardiac defects. |
| Congestive Heart Failure (CHF) . | The heart's failure to maintain satisfactory circulation of the blood throughout the body, resulting in congestion or accumulation of fluid in various parts of the body such as the lungs, legs, abdomen, etc. It is generally progressive and accompanied by an enlargement in the size of the heart. CHF typically develops over a period of months or years. It is highly prevalent and represents the majority of heart failure patients. |
| Coronary Heart Disease (CHD) | An irregular thickening of the inner layer of the walls of the coronary arteries, resulting in the narrowing of the internal channel of the coronaries and a reduced blood supply to the heart muscle. CHD frequently leads to a heart attack (acute myocardial infarction). |
| Extracorporeal membrane oxygenation | A technique for providing respiratory support by circulating the blood through an artificial lung consisting of two compartments separated by a gas-permeable membrane, with the blood on one side and the ventilating gas on the other; used in newborns and occasionally in adults with acute respiratory distress syndrome. |
| Fully Implantable device | A medical device that is totally implanted in the body without any wires or tubes penetrating the skin. |
| Inotropic | Affecting the force or energy of muscular contraction |

| | |
|---|---|
| Intra-aortic balloon Pump | A device that provides circulatory support; a balloon is inserted into the thoracic aorta and inflated during diastole and deflated during systole, resulting in a decrease in afterload and improvement in cardiac function. |
| Left Ventricular Assist Device (LVAD) | A pumping device that can be attached to the weakened left ventricle of the heart to help increase blood flow to the body. LVADs, though subject to various inherent limitations, have a range of potential applications. LVADs can either reside partially external to a patient or be partially or fully implanted in a patient. |
| Myocarditis | Inflammation of the muscular walls of the heart. |
| Hemolysis | Disruption of the integrity of the red blood cell membrane causing release of hemoglobin; it may be caused by bacterial hemolysins or by antibodies. |
| Nosocomial infection | An infection not present or incubating prior to admittance to the hospital but generally occurring 72 hours after admittance. |
| Pocket infection | Infection in the area of the abdomen within which the ventricular assist device resides. |
| Sepsis | The presence in the blood or other tissue of pathogenic microorganisms or their toxins. |
| Thromboembolic event | Complications caused by obstruction of a blood vessel with thrombotic material carried by the blood stream from the site of origin to obstruct other vessel (e.g. stroke). |
| Uni-ventricular | Refers to either the left or the right ventricular chamber but not to both. |
| Ventricular Assist Device (VAD) | A device that assists the left and/or right chamber of the heart to receive and circulate blood. |

# Executive Summary

## Objective

The objective of this health technology policy assessment was to determine the effectiveness and cost-effectiveness of using implantable ventricular assist devices in the treatment of end-stage heart failure.

## Heart Failure

Heart failure is a complex syndrome that impairs the ability of the heart to maintain adequate blood circulation, resulting in multiorgan abnormalities and, eventually, death. In the period of 1994 to 1997, 38,702 individuals in Ontario had a first hospital admission for heart failure. Despite reported improvement in survival, the five-year mortality rate for heart failure is about 50%.

For patients with end-stage heart failure that does not respond to medical therapy, surgical treatment or traditional circulatory assist devices, heart transplantation (in appropriate patients) is the only treatment that provides significant patient benefit.

## Heart Transplant in Ontario

With a shortage in the supply of donor hearts, patients are waiting longer for a heart transplant and may die before a donor heart is available. From 1999 to 2003, 55 to 74 people received a heart transplant in Ontario each year. Another 12 to 21 people died while waiting for a suitable donor heart. Of these, 1 to 5 deaths occurred in people under 18 years old. The rate-limiting factor in heart transplant is the supply of donor hearts. Without an increase in available donor hearts, attempts at prolonging the life of some patients on the transplant wait list could have a harmful effect on other patients that are being pushed down the waiting list (knock on effect).

## LVAD Technology

Ventricular assist devices [VADs] have been developed to provide circulatory assistance to patients with end-stage heart failure. These are small pumps that usually assist the damaged left ventricle [LVADs] and may be situated within the body (intracorporeal] or outside the body [extracorporeal). Some of these devices were designed for use in the right ventricle [RVAD] or both ventricles (bi-ventricular).

LVADs have been mainly used as a "bridge-to-transplant" for patients on a transplant waiting list. As well, they have been used as a " bridge-to-recovery" in acute heart failure, but this experience is limited. There has been an increasing interest in using LVAD as a permanent (destination) therapy.

## Review of LVAD by the Medical Advisory Secretariat

The Medical Advisory Secretariat's review included a descriptive synthesis of findings from five systematic reviews and 60 reports published between January 2000 and December 2003. Additional information was obtained through consultation and by searching the websites of Health Canada, the United Network of Organ Sharing, Organ Donation Ontario, and LVAD manufacturers.

## Summary of Findings

*Safety and Effectiveness*

Previous HTAs and current Level 3 evidence from prospective non-randomized controlled studies showed that when compared to optimal medical therapy, LVAD support significantly improved the pre-transplant survival rates of heart transplant candidates waiting for a suitable donor heart (71% for LVAD and 36% for medical therapy). Pre-transplant survival rates reported ranged from 58% to 90% (median 74%). Improved transplant rates were also reported for people who received pre-transplant LVAD support (e.g. 67% for LVAD vs 33% for medical therapy). Reported transplant rates for LVAD patients ranged from 39% to 90% (median 71%).

Patient's age greater than 60 years and pre-existing conditions of respiratory failure associated with septicemia, ventilation, and right heart failure were independent risk factors for mortality after the LVAD implantation.

LVAD support was shown to improve the New York Heart Association [NYHA)] functional classification and quality of life of patients waiting for heart transplant. LVAD also enabled approximately 41% - 49% of patients to be discharged from hospitals and wait for a heart transplant at home. However, over 50% of the discharged patients required re-hospitalization due to adverse events.

Post-transplant survival rates for LVAD-bridged patients were similar to or better than the survival rates of patients bridged by medical therapy.

LVAD support has been associated with serious adverse events, including infection (median 53%, range 6%–72%), bleeding (8.6%–48%, median 35%), thromboembolism (5%–37%), neurologic disorders (7%–28%), right ventricular failure (11%–26%), organ dysfunction (5%–50%) and hemolysis (6%–20%). Bleeding tends to occur in the first few post-implant days and is rare thereafter. It is fatal in 2%–7% of patients. Infection and thromboembolism occurred throughout the duration of the implant, though their frequency tended to diminish with time. Device malfunction has been identified as one of the major complications. Fatalities directly attributable to the devices were about 1% in short-term LVAD use. However, mechanical failure was the second most frequent cause of death in patients on prolonged LVAD support. Malfunctions were mainly associated with the external components, and often could be replaced by backed up components.

LVAD has been used as a bridge-to-recovery in patients suffering from acute cardiogenic shock due to cardiomyopathy, myocarditis or cardiotomy. The survival rates were reported to be lower than in bridge-to-transplant (median 26%). Some of the bridge-to-recovery patients (14%–75%) required a heart transplant or remained on prolonged LVAD support. According to an expert in the field, experience with LVAD as a bridge-to-recovery technology has been more favourable in Germany than in North America, where it is not regarded as a major indication since evidence for its effectiveness in this setting is limited.

LVAD has also been explored as a destination therapy. A small, randomized, controlled trial (level 2 evidence) showed that LVAD significantly increased the 1-year survival rate of patients with end-stage heart failure but were not eligible for a heart transplant (51% LVAD vs 25% for medical therapy). However, improved survival was associated with adverse events 2.35 times higher than medically treated patients and a higher hospital re-admission rate. The 2-year survival rate on LVAD decreased to 23%, although it was still significantly better compared to patients on medical therapy (8%). The leading causes of deaths were sepsis (41%) and device failure (17%).

The FDA has given conditional approval for the permanent use of HeartMate SNAP VE LVAS in patients with end-stage heart failure who are not eligible for heart transplantation, although the long-term effect of this application is not known.

In Canada, four LVAD systems have been licensed for bridge-to-transplant only. The use of LVAD support raises ethical issues because of the implications of potential explantation that could be perceived as a withdrawal of life support.

*Potential Impact on the Transplant Waiting List*

With the shortage of donor hearts for adults, LVAD support probably would not increase the number of patients who receive a heart transplant. If LVAD supported candidates are prioritized for urgent heart transplant, there will be a knock on effect as other transplant candidates without LVAD support would be pushed down, resulting in longer wait, deterioration in health status and die before a suitable donor heart becomes available.

Under the current policy for allocating donor hearts in Ontario, patients on LVAD support would be downgraded to Status 3 with a lower priority to receive a transplant. This would likely result in an expansion of the transplant waiting list with an increasing number of patients on prolonged LVAD support, which is not consistent with the indication of LVAD use approved by Health Canada.

There is indication in the United Kingdom that LVAD support in conjunction with an urgent transplant listing in the pediatric population may decrease the number of deaths on the waiting list without a harmful knock-on effect on other transplant candidates.

## Conclusion

LVAD support as a bridge-to-transplant has been shown to improve the survival rate, functional status and quality of life of patients on the heart transplant waiting list. However, due to the shortage of donor hearts and the current heart transplant algorithm, LVAD support for transplant candidates of all age groups would likely result in an expansion of the waiting list and prolonged use of LVAD with significant budget implications but without increasing the number of heart transplants. Limited level 4 evidence showed that LVAD support in children yielded survival rates comparable to those in the adult population. The introduction of LVAD in the pediatric population would be more cost-effective and might not have a negative effect on the transplant waiting list.

# Objective

The objective of this health technology policy assessment was to determine the effectiveness and cost-effectiveness of using implantable ventricular assist devices in the treatment of end-stage heart failure.

# Background

## Clinical Need

### Heart Failure

Heart failure is a complex syndrome that impairs the ability of the heart to function as a pump to maintain adequate circulation as a result of damage to the myocardium.[1] Etiologic factors for the damage may include ischemic insults (myocardial infarction), myocarditis, gene mutation with abnormal contractile function, valvular heart disease, and severe under-treated hypertension.[2]

Chronic systolic heart failure is often characterized by progressive enlargement of the left ventricle that becomes more spherical over months to years with a reduction in left ventricular ejection. The other three cardiac chambers are also frequently involved and can progressively dilate. The alterations in ventricular morphology, structure and function that occur with heart failure have been termed ventricular remodeling.[2]

Most of the clinical symptoms associated with heart failure result from secondary organ abnormalities in the lungs (dyspnea), the kidneys (salt and water retention that may result in peripheral edema), and skeletal muscle (chronic fatigue). Secondary organ involvement may also lead to severe right upper quadrant pain, abdominal fullness, nausea and vomiting. Arrhythmia, particularly atrial fibrillation, may contribute to the progression of heart failure.

The New York Heart Association [NYHA] functional classification has been widely used to stratify patients according to the severity of disease and guide therapeutic intervention [**Appendix 1A**]. The European Society of Cardiology[1] recommends an algorithm for the diagnosis of heart failure [**Appendix 2**].

Levy et al[3] assessed the temporal trends in the incidence of heart failure and survival after the onset of heart failure among subjects in the Framingham Heart Study. The study showed that the incidence of heart failure remained virtually unchanged among men but declined by 31-40% among women. The study also showed that survival after onset of heart failure has improved in both men and women (Table 1).

Table 1: Change in mortality rate following onset of Heart failure - Framingham Study

| | 30-day adjusted mortality rate | 1-year adjusted mortality rate | 5-year adjusted mortality rate |
|---|---|---|---|
| Men, 1950 -1969 (Framingham) | 12% | 30% | 70% |
| Men, 1990 - 1999 (Framingham) | 11% | 28% | 59% |
| Women, 1950 -1969 (Framingham) | 18% | 28% | 57% |
| Women, 1990 - 1999 (Framingham) | 10% | 24% | 45% |

Levy et al[3] stated that factors contributing to the improved survival need to be further clarified.

Despite the improvement in survival observed by Levy et al[3], the five-year mortality rates after the onset of heart failure remain remained high (45% for women and 59% for men). Sudden deaths from cardiac causes occurred among persons with heart failure at six to nine times the rate in the general population.[4]

## Prevalence of Heart Failure in Canada and Ontario

Congestive heart failure is the leading cause of hospitalization in elderly Canadians and a frequent cause of death.[5] In Canada, 2% (4,009) of all deaths were due to cardiac failure in 1992.[6]

Jong et al[7] studied 38,702 consecutive Ontario patients with first time hospital admissions for heart failure during the three-year period between April 1994 and March 1997. During this period, 12,900 Ontarians (1 in 853) were newly hospitalized each year on the average as a result of heart failure.

In the above study, 84.6% of the patients were 65 years or older and 57.9% were 75 years or older. The crude 30-day and one-year case-fatality rates were significantly lower for patients 20 to 49 years old with minimal comorbidity than the oldest (=/>75 years) comorbidity-laden subgroup. After adjustment for age, men showed a higher 30-day mortality rate compared to women (odds ratio 1.09, $[chi]^2$=10.3; p=0.001). This difference persisted at 1 year after discharge. The study suggests that age, sex, and comorbidity are independent prognostic indicators of heart failure, but their complex interaction with survival is not clear.[7]

Mortality rates of heart failure provided by Jong et al[7] and by the Institute for Clinical Evaluative Sciences [ICES][5] in 1999 using information from the Canadian Institute for Health Information [CIHI] are summarized in Table 2.

Table 2: Mortality rates of individuals with heart failure in Ontario

| | 30-day mortality rate | 1-year mortality rate |
|---|---|---|
| Men, overall, 1996/1997, (Ontario) , ICES | 10.6% (adjusted) | 32.9% (adjusted) |
| Men, overall, after 1st hosp. Admission, ON (Jong) | 11.4% | 34.0% |
| Men, age 20-49 yrs, low comorbidity, after 1st hosp admission , ON (Jong) | 4.5% | 12.9% |
| Men, age 65 - 74 yrs, low comorbidity, after 1st hosp admission , ON (Jong) | 5.8% | 21.1% |
| Men, age >/=75 yrs, high comorbidity, after 1st hosp admission , ON (Jong) | 23.8% | 60.7% |
| Women, overall, 1996/1997 (Ontario), ICES | 11.4% (adjusted) | 31.1% (adjusted) |
| Women, overall, after 1st hosp. Admission, ON (Jong) | 11.8% | 32.3% |
| Women, age 20-49 yrs, low comorbidity, after 1st hosp admission , ON (Jong) | 2.7% | 7.6% |
| Women, age 65 -74 yrs, low comorbidity, after 1st hosp admission , ON (Jong) | 4.3% | 16.3% |
| Women, age >/=75 yrs, high comorbidity, after 1st hosp admission , ON (Jong) | 22.7% | 55.8% |

## Treatment of heart failure

Heart failure is characterized by neurohormonal change that initially helps to maintain circulatory function but is ultimately harmful to the heart. Current treatment includes:

- Medical therapy
  Medical therapy is the cornerstone of therapy for patients with heart failure. Optimizing medical therapy has improved the survival rates of patients with chronic heart failure.[8] Angiotensin converting enzyme [ACE] inhibitors and beta blockers are the cornerstone of medical therapy, both having been shown to significantly improve symptoms, increase survival, and decrease hospitalization. Diuretics have also been shown to be helpful for the treatment of symptoms. While spironolactone has

improved survival and decreased hospitalization in patients with advanced heart failure, digoxin, the traditional therapy for the management of heart failure, has only been shown to improve symptoms and to decrease hospitalization in patients with moderate to severe heart failure. Lifestyle changes such as reducing salt intake, regular aerobic exercise, annual vaccination against influenza, abstinence from alcohol, and smoking cessation also have important impacts.

- Implantable pacemakers and defibrillators
  Current evidence shows that resynchronization therapy (bi-ventricular pacing) may be an effective treatment for a subset of patients who, despite optimized medical therapy, have moderate to severe chronic heart failure and significant intra-ventricular conduction delay characterized by a wide QRS complex. The therapeutic intent of bi-ventricular pacing is to activate both ventricles simultaneously in order to improve the mechanical efficiency of the ventricles.[9]

  Automatic implantable cardioverter defibrillators [ICDs] have been shown to decrease the risk of sudden cardiac death in patients with high risk of sudden death, including patients with previous cardiac arrest. It is not yet known whether all patients with significant left ventricular dysfunction regardless of etiology benefit from these devices.[1]

- Surgical interventions/therapy
  When heart failure results from damaged heart valves, surgical repair can improve cardiac function. However the timing of the repair is critical. Patients with heart failure as a result of coronary artery disease may benefit from revascularization by balloon dilatation or coronary artery bypass graft surgery [CABG].

  Partial ventriculectomy aims at improving myocardial function by decreasing the left ventricular wall tension. Lucchese FA et al[10] followed 44 patients who underwent partial left ventriculectomy and reported survival rates of 47.7% and 38.4% at 6 months and 18 months respectively. In spite of improvement of ventricular function and quality of life of the survivors, the high mortality rate is a limiting factor for this procedure.

- Mechanical circulatory assistance
  *Intra-aortic balloon counterpulsation pump* [IABP] is the most common cardiac assist device both to support patients as a bridge-to-recovery and as a bridge-to-transplantation. It functions by a combination of systolic unloading and diastolic augmentation, which enhances coronary flow. The most common complication is ischemia of the lower extremities.[6] IABP may not provide sufficient circulatory assistance to patients with severe heart failure. Furthermore, the evidence of its benefit for patients with non-ischemic cardiomyopathy is lacking.
  *Extracorporeal membrane oxygenation* (ECMO)

  ECMO is the most commonly used mechanical circulatory and pulmonary support system in newborns and young children, and can be used as a last resort for adults whose heart or lungs are failing.[11] ECMO has been used to support pediatric patients waiting for a heart transplant or during recovery in the post-transplantation period. This technology involves pumping a patient's blood through an external artificial membrane lung, where oxygen is added and carbon dioxide is removed. ECMO remains the most commonly used method of mechanical circulatory support in children because most programs are familiar with this technology, it can be initiated in the ICU, and it can be used in all forms of cardiopulmonary failure including bi-ventricular failure. The most significant disadvantages of ECMO are the requirements for immobilization, intubation, intensive care monitoring, and anticoagulation.[11]

- *Heart transplantation*
  Heart transplantation is the only treatment that provides substantial individual benefit for patients who do not respond to any of the above treatments. According to the registry of the International Society for Heart and Lung Transplantation, the overall one year survival rate following heart transplantation is 79% and the time to 50% post-transplant survival is 8.8 years.[12]

  Health Canada reported that 172 heart transplants and 4 heart-lung transplants were performed in the year 2000, with a one-year survival of 85% [http://hc-sc.gc/english/organand tissue/facts_faqs/]. However, the number of heart transplants is limited by the availability of donor hearts.

Circulatory assistance in the form of left ventricular assist devices [LVAD] has been studied as a means to support critically ill patients waiting for heart transplantation and is the subject of this review.

# Technology

Ventricular assist devices (VADs) are small mechanical pumps that assist the damaged left, right, or both ventricles. VADs do not replace the native heart, but rather assist it in pumping in order to provide adequate cardiac output and improve end-organ function. All ventricular assist devices consist of one or two pumps, a cannula connecting the pump to the patient's heart, a control console and a power source. The most common implantable VADs are the left ventricular assist devices [LVADs].

### Potential Application of LVADs

LVADs may be used in emergency situations where death would otherwise occur. They may also be used electively in the context of progressive heart failure.[13] There are three potential applications for LVADs:

- *Bridge-to-transplantation*: In this application, LVAD technology is used to prolong the life of potential transplant recipients until a suitable donor heart becomes available. In general, patients who may receive an LVAD for this purpose have end-stage heart failure without irreversible end-organ failure, and are candidates for heart transplantation.

- *Bridge-to-recovery*: In this context, an LVAD is used to provide circulatory assistance in order to allow the myocardium to recover from post-cardiotomy cardiogenic shock or other acute heart failures, to the extent that the native heart can function satisfactorily after the device is explanted.

- *Alternative to heart transplantation*: Due to the shortage of donor hearts, there is increasing interest in using LVAD as a permanent alternative to heart transplantation (destination therapy). It is believed that LVAD support has advantages over heart transplantation because it can be initiated earlier, its supply is not limited by the availability of donor hearts, and the recipients will be spared the ill effects of immunosuppression.

### Types and Regulatory Status of Ventricular Assist Devices

Many mechanical circulatory assist devices are being developed and can be characterized as follows: 1) pulsatile or continuous flow; 2) intracorporeal (implantable) or extracorporeal; 3) pneumatically or electrically powered; 4) for short-term or long-term support; and 5) uni-ventricular and/or bi-ventricular. Examples of these devices and their regulatory status are summarized in Table 3.

As of March 17, 2004, Health Canada has licensed Novacor LVAS®, HeartMate Implantable Pneumatic LVAD, HeartMate Vented Electric LVAS, and Thoratec® VAD as class 4 devices for bridge-to-transplant only. No devices have been approved for bridge-to-recovery or destination therapy and no pediatric LVADs have been approved.

Table 3: Mechanical Ventricular Assist Devices[1]

| LVAD | Health Canada Approval | Advantages | Disadvantages |
|---|---|---|---|
| Implantable (pulsatile LV support, pneumatically or electrically driven pumps) | | | |
| Novacor LVA System® (World Heart Incorporated) | • Licensed Class 4 medical device<br>• To be used as a bridge-to-transplantation in patients with end-stage heart failure | • Portable electric power & control, allows ambulation<br>• Discharge from ICU & hospital possible<br>• Excellent rehab potential<br>• Decreased coagulation requirements | • Univentricular support<br>• Abdominal placement - risk of pocket infection<br>• Requires body surface are of >/= 1.5 $m^2$ |
| -HeartMate IP Implantable Pneumatic ® OR Vented Electric LVA system® (Thoratec Corp.) | • Licensed Class 4 medical device<br>• To be used as a bridge-to-transplantation in cardiac transplant patients at risk of imminent death from nonreversible LV failure. | • Portable electric power & control, allows ambulation<br>• Discharge from ICU & hospital possible<br>• Excellent rehab potential<br>• Low incidence of thromboembolic events<br>• Less need for coagulation | • Univentricular support<br>• Abdominal placement - risk of pocket infection<br>• Requires body surface >/= 1.5 $m^2$ |
| External (Pneumatically driven, pulsatile devices) | | | |
| Thoratec VAD® (Thoratec Corp.)<br><br>Extracorporeal | • Licensed Class 4 medical device<br>• For L, R or bi-ventricular support for bridge-to-transplant patients<br><br>. | • Can be used on small patients with body surface >/=1.3 $m^2$<br>• L, R or both ventricles<br>• Implantation without cardiac pulmonary bypass<br>• Transfer out of ICU setting<br>• Patient may ambulate with new mobile units | • Systemic coagulation needed<br>• Some mobility limitation<br>• Cannot discharge from hospital with older non-mobile models |
| DeBakey VAD® Child Left Ventricular System (MicroMed Techologies, Tx) | • **Not** licensed in Canada<br>• Approved by FDA for bridge-to-transplant in pediatric patients (5–16 years old) | • Small, can be use in children 5–16 years old with body surface >/= 0.7$m^2$<br>• Reduced surgical time<br>• Allows mobility<br>• Lower cost (1/3 of marketed VADs) | • Cannot be used in people with surface area >1.5$m^2$<br>• Abdominal placement & percutaneous cable -risks of infection |
| ABIOMED BVS 500 Bi-ventricular system® (ABIOMED Inc., Danvers, MA) | **Not** licensed in Canada (FDA approved for bridge-to-recovery) | • Can be used on small patients with body surface >/=1.3 $m^2$<br>• L, R or both ventricles<br>• Implantation without cardiac pulmonary bypass<br>• Lower cost | • Systemic anticoagulation needed<br>• Patient usually bedridden, not ideal for bridging in end-stage chronic heart failure.<br>• Gravity-filled chambers<br>• High potential for body heat loss |

Other ventricular assist devices and total artificial hearts are being developed and clinically tested but have **not** yet been approved in Canada or the US. These devices were not included in this review. Examples include:

[1] Adapted from Stahl MA, 2002[14]

LionHeart™
The Arrow LionHeart™ Left Ventricular Assist System (LVAS, Arrow International Inc.), is a fully implantable system designed to be used as a long-term option for patients with progressive, irreversible, end stage (Class IV) congestive heart failure, for which heart transplantation is not an option. The Arrow LionHeart™ LVAS is not intended as a bridge in clinical trials in Europe and the US. (http://www.arrowintl.com/products/lion_heart/).

Jarvik-7 & CardioWest®
An air-driven replacement heart, the Jarvik-7 is supported by an external drive console. The Jarvik-7 was discontinued due to medical and device complications, including stroke and mechanical failure and anatomical fit issues. After undergoing manufacturing and quality control refinements, it has been renamed the CardioWest heart and is now being used experimentally in limited quantities as an investigational bridge-to-transplantation device. This device appears to offer an advantage for those few patients who may present in cardiogenic shock secondary to a large myocardial infarct and/or significant complication from a MI leading to shock. It is also being used in patients with acute bi-ventricular failure. Patients with this type of implant can be mobilized but cannot be discharged from hospital.

AbioCor™
A medical device developed by ABIOMED® to be a fully implantable replacement heart. The AbioCor™ Implantable Replacement Heart is being implanted in patients as part of an initial clinical trial conducted under an Investigational Device Exemption from the United States Food and Drug Administration. (http://www.abiomed.com)

HeartSaver VAD ™
This is a pulsatile VAD being developed by World Heart Corporation. It is designed to be totally implantable in the chest, and remotely powered, monitored and controlled. The device is being tested in pre-clinical trials.

Berlin Heart VAD systems®
Berlin Heart EXCOR is an extracorporeal VAD system intended primarily for a bridge to transplant function. It consists of a blood pump with tilting disc valves or polyurethane velum valves and percutaneous silicone cannules and two types of drive units (one for stationary application and one for mobile patients).
Berlin Heart INCOR is a small axial pump with a magnetically suspended and contact free rotor. All components that come into contact with blood are made of titanium or silicone. INCOR will initially be supplied with an external control unit and battery packs with the plan for all components to be fully implantable. Both INCOR and EXCOR are undergoing clinical trials in Europe. (www.berlinheart.com/products/)

## Implantation and Functioning of the Devices

- LVADs are implanted in the abdominal wall (Novacor®) or in the abdomen behind the rectus muscle (HeartMate®). The procedure usually requires standard cardiopulmonary bypass. An inflow cannula is connected to the left ventricle and an outflow graft is passed over the diaphragm and anastomosed to the root of the ascending aorta. These conduits drain blood from the left ventricle to the pump and return it to the ascending aorta. Power wires (driveline) connect the pump to a bedside console or a portable controller and a power pack worn by the patient (Appendix 3). The LVAD may be pneumatically or electrically driven. The implantation procedure takes approximately 4 hours of operating time.

A patient can be fully ambulatory and be discharged from hospital following successful implantation of Novacor® or HeartMate VE® LVAS.

- Occasionally, patients require short-term right ventricular support after transplant or as a short-term bridge-to-recovery from post-cardiotomy shock following heart surgery including LVAD implantation. This may require short-term implantation of an LVAD, RVAD or both. Short-term VADs are usually extracorporeal and can be connected to the left, right or both ventricles. Connection to a RVAD during LVAD implantation takes an additional 30 minutes, whereas a separate surgical procedure to insert a VAD requires approximately 2 hours.

  Thoratec® Ventricular Assist Device System is currently the only short-term VAD licensed by Health Canada. The bi-ventricular application of this device is illustrated in Appendix 4. Patients need to be hospitalized when they are supported by the Thoratec® VAD system.
  BIOMED BVS 500® may also be a suitable device for the above purposes; however, Health Canada has not yet been approved this device.

# Literature Review

### Objective

The objectives of the review were:

- To assess the safety, effectiveness and cost-effectiveness of LVAD as a bridge to cardiac transplant.
- To assess the safety, effectiveness and cost-effectiveness of VAD as a short-term bridge-to-recovery from cardiotomy surgery and a short-term right ventricular support following LVAD implantation.
- To assess the safety, effectiveness and cost-effectiveness of LVAD as an alternative to cardiac transplant.
- To identify issues relevant to policy decisions regarding the implementation of LVAD and VAD programs in Ontario.

### Methods

Studies Targeted

Patient*:*
(a) Human subjects accepted as transplant candidates who are refractory to aggressive medical treatment, have severe heart failure of NYHA class III/IV, and have a highly expected impending mortality.
(b) Patients with post-cardiotomy-shock or other cardiogenic shock, hibernating myocardium, acute cardiac failure or other conditions from which the patient is expected to recover sufficiently to be weaned off the implanted device.
(c) Patients with heart failure with NYHA functional class III/IV, refractory to medico-pharmacologic and surgical treatment and who received an LVAD as a destination therapy.

Intervention:
LVAD or BIVD implantation.

Comparator*
Optimal medical management, but no LVAD or VAD implantation.

Endpoint measures:
Primary end-point: Survival rates on LVAD support, survival rate to transplant or survival to recovery.
Secondary endpoints: impact on NYHA functional classification of patients, quality of life including ambulatory status, device-related adverse events, impact on transplant survival rates.
Economic analysis data.

* There are limited established alternative technologies because the potential candidates for LVAD support have already been shown to be refractory to medical management or contraindicated from other approaches yet still need additional ventricular support to be able to continue waiting for a donor heart. However, for comparison purposes, inotropic therapy was chosen because it is still the main therapy used and new inotropic drugs have been shown to be effective in managing heart failure.

Inclusion Criteria
The studies included in the review had to meet the following criteria:

- English language journal articles reporting primary data on the effectiveness or cost effectiveness of Health Canada-licensed ventricular assist devices obtained in a clinical setting, or analysis of primary data maintained in registries or institutional databases meeting the following criteria:
  - Study design and methods were clearly described.
  - Systematic reviews, randomized controlled studies, non-randomized controlled studies, or cohort studies with =/> 20 patients or cost-effectiveness studies (published within the last six years). Pediatric and Canadian studies regardless of sample size.
  - The study is not superseded by a publication with the same purpose, by the same group or a later publication that included the data from centres involved in the same multicenter study (unless the articles address different endpoints).

Exclusion criteria
- Non-systematic reviews, letters and editorials.
- Animal studies and in-vitro studies.
- Studies using unlicensed LVAD or VAD devices.
- Studies that do not focus on the identified outcomes.
- Studies dealing only with design of the device or implantation/treatment procedure.

## Search Strategy & Results

Search of Health Technology Assessment Databases
The Cochrane & International Agency for Health Technology Assessment [INAHTA] databases were searched and yielded five systematic reviews.

- The Oregon Commission, 1997[15]
  This review assessed all cardiac assist devices except intra-aortic balloon pumps and artificial hearts. It included RCTs, non-randomized controlled studies and cohort studies from 1993 - 1997. An expert panel reviewed the findings and accepted only level 2 evidence.
- Comite d'Evaluation et de Diffusion des Innovations Technologiques (CEDIT, 1998) of France[16] - only a summary was available.

- The Wessex Institute in the United Kingdom, 1999[17]
  This systematic review was based on 10 cohort studies of 619 patients on bridge-to-transplant, and 1 cohort study of 17 patients on bridge-to-recovery.
- The Agence d'Evaluation de Technologies et Mode de Intervention de Santé of Quebec [AETMIS], 2000[13] Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES, 2001) of France[18]
  This systematic review included 18 efficacy studies, five of which are non-randomized controlled studies.

The systematic reviews were summarized in Appendix 11. Findings of the five HTAs will be incorporated in the synthesis of findings.

Follow-up Literature Search

The most recent systematic review conducted by Agence Nationale d'Accréditation et d'Evaluation en Santé [ANAES] was published in April 2001. The review included studies published up to and including1999. The Medical Advisory Secretariat therefore conducted an initial search of MEDLINE and EMBASE for the period of January 2000 to October 2002 using key words "Ventricular assist device" and "mechanical circulatory support", limited to humans and English language reports. A search in January 2004 was conducted to update an earlier report. The two searches yielded a total of 535 citations.

One researcher reviewed the abstract of each article and determined whether the article met the inclusion criteria. The full texts of eligible studies were reviewed to confirm eligibility.

Of the 535 citations, 61 articles met the inclusion criteria. 475 articles were excluded for the following reasons:

Animal, in-vitro or simulation studies

Less than 20 subjects

Case reports

Using devices not licensed in Canada

Not comparing LVAD with medical therapy

Focus on the procedure or design of the device

Internet search

The websites of Health Canada, FDA, Organ Donation Ontario, United Network for Organ Sharing, Agency of Healthcare Research and Quality (AHRQ) and LVAD manufacturers were also searched for statistical and regulatory information. Health Canada and Organ Donation Ontario were contacted and provided additional information.

## Level of Evidence /Data Extraction

Levels of evidence were assigned to the studies according to a scale based on the hierarchy by Goodman [1985] (Table 4). An additional designation “g” was added for unpublished reports of studies that have been presented to international scientific meetings.

With the exception of 1 randomized controlled trial and 5 non-randomized comparative studies, the evidence comes mainly from cohort studies. The level of evidence of the selected articles is summarized below.

Table 4: Levels of Evidence

| Type of Study (Design) | Level of Evidence | Number of Eligible Studies Analyzed |
|---|---|---|
| Large randomized controlled trial, Systematic reviews of RCTs | 1 | |
| Large randomized controlled trial unpublished but reported to an international scientific meeting | 1(g) | |
| Small randomized controlled trial | 2 | 1 |
| Small randomized controlled trial unpublished but reported to an international scientific meeting | 2(g) | |
| Nonrandomized trial with contemporaneous controls | 3 a | 6 |
| Nonrandomized trial with historical control | 3b | 1 |
| Nonrandomized controlled trial unpublished but reported to an international scientific meeting | 3g | |
| Surveillance (database or register) | 4a | 1 |
| Case series, multi-site | 4b | 2 |
| Case series, single-site | 4c | 50 |
| Case series unpublished but presented to an international scientific meeting | 4g | |
| TOTAL | | 60 |

In addition to the above articles, additional references were used for background information and were included in the bibliography list.

## Quality and Limitations of evidence on effectiveness

There is a paucity of data on Canadian experience and the Canadian studies identified had small sample sized. Almost all of the evidence is based on experience in the US and Europe.

There is only one randomized controlled study on the use of LVAD as a destination therapy. No randomized controlled trials were found on bridge-to-transplant or bridge to recovery. With the exception of seven non-randomized comparative studies on bridge to transplant, the remaining studies in this review are observational studies. They are either single centre experience or retrospective analysis of data from several centres. Hence, the evidence on effectiveness is not strong. There were also methodological flaws.

Inclusion and exclusion criteria were not always clearly articulated in the studies. Inter-study variations were evident. Finally, the type of inotropes used for the control groups was not identified in some reports, making it difficult to evaluate the aggressiveness of treatment.

All the studies were based on data accumulated over a period of many years, and different generations of devices were used. The outcomes reported may not, therefore, reflect those of the most current devices.

Other limitations included inconsistencies in the definition of end points (e.g. bleeding, survival), study protocols and inter/intra-study variability in devices used. The above limitations make inter-study comparisons difficult.

## Evidence on Bridge-to-Transplant

No randomized controlled studies were found on bridge-to-transplant. Ten comparative studies[2] and 33 case series were included in the assessment. Only three of the studies are prospective. Almost all of the comparative studies were conducted in the US. The patient selection criteria of the comparative studies are summarized in Appendix 6, and the studies are summarized in Appendix 7. The observational studies are summarized in Appendix 8 and Appendix 12.

Non-randomized comparative studies on the use of LVAD for bridge-to-transplant

- Frazier et al[19], 1995: A prospective multicenter cohort study comparing 75 patients on HeartMate IP LVAS® and 35 concurrent controls on inotropic therapy.
- Frazier et al[20], 2001: A prospective multicenter non-randomized evaluative study that compared 280 heart failure patients with HeartMate VE LVAS®, to 48 historical controls (from HeartMate IP LVAS® study) with similar characteristics who did not receive an LVAD.
- Baxter Corporation, 1998, Novacor® Trial[21] submitted to the FDA: A prospective non-randomized study that compared 129 core LVAD patients with 33 inotropic patients.
- Aronson K et al[22], 2002: A retrospective analysis of the outcome of 38 patients bridged to transplant by intravenous inotrope support versus that of 66 patients bridged by HeartMate LVAS®.
- Moffatt et al[23], 2003: A retrospective analysis that compared the post-transplant survival rate of 47 LVAD patients with 148 inotrope patients.
- Morgan et al, 2003[24]: A retrospective comparative analysis of post-transplant survival of 121 patients who received LVAD support and 145 patients who received inotropic support.
- Jaski et al[25], 2001 retrospectively analyzed prospectively collected data from the Cardiac Transplant Research database. The analysis compared the outcomes of heart transplants in patients treated with intravenous inotropes to those of 502 transplants that had LVAD bridging.
- Bank et al[26], 2000 retrospectively analyzed 40 consecutive patients who were listed as status 1 for heart transplantation. Twenty of these patients received HeartMate LVAS® support before transplant and the other twenty patients who received IV inotropic therapy.
- Sinha, 2000
- Massad et al[27], 1996 retrospectively analyzed the outcomes of 256 transplant recipients in a single institution. Of these 21% received Heartmate LVAS® support.

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## Synthesis of findings on Bridge-toTransplant

### Post-implant Survival

The ANAES HTA[18] found that post-implant survival for LVAD patients ranged from 52% to 89%. The Wessex HTA[17] reported that 3 of 4 studies suggested improved survival. The CEDIT review[16] concluded that, on average, 70% of patients who receive an LVAD implant would survive and proceed to transplantation.

In this review, the post-implant survival rates and transplant rates reported in comparative studies are summarized in Table 5. Post-implant survival rates of observational studies are summarized in Appendix 7.

[2] Including relevant comparative studies from earlier systematic reviews.

Table 5: Post-Implant (pre-transplant) Survival Rates (Comparative Studies)

| Author & year | No. of patients | Device | % Survived post LVAD Implant | % transplanted | Explanted % | Still on LVAD |
|---|---|---|---|---|---|---|
| Frazier, 2001[20] Prospective | 280 LVAD<br>48 inotrope (historical) | HeartMate ®VE | LVAD 71%<br>Inotrope 33% | LVAD 67%<br>Inotrope 33% | 4% (10) | 0 |
| Baxter, 1998[21] Prospective | 129 LVAD (core)<br>35 Inotrope (concurrent) | Novacor® | LVAD 81%<br>Inotrope 37% | LVAD 78%*<br>Inotrope 37%<br>(p<0.001) | No information | 19% |
| Frazier, 1995[19] Prospective | 75 LVAD<br>33 Inotrope (concurrent) | HeartMate® | LVAD 71%<br>Inotrope 36% | LVAD 71%<br>Inotrope 36% | 0 | 0 |
| Morgan 2003 Retrospective | 121 LVAD (Successful)<br>145 inotrope | HeartMate VE® | - | -LVAD 71% | | |
| Aaronson, 2002[22] Retrospective | 66 LVAD<br>38 inotrope | HeartMate® | LVAD 82%<br>IV Inotrope 74%<br>Not signific | LVAD 73%<br><br>Inotrope 74% | 0 | LVAD 9% |
| Bank 2000[26] Retrospective | 20 LVAD<br>20 inotrope | HeartMate® | LVAD 90%<br>Inotrope 95% (Similar) | LVAD 90%<br>Inotrope 95% | 0 | 0 |
| Sinha 2000 Retrospective | 86 LVAS<br>50 no LVAD | Heartmate VE® | LVAD 74% | LVAD 71% | 2% recovered | 1% |
| Massad, 1996[27] Retrospective | 53 LVA<br>203 Inotrope | HeartMate IP or VE® | No information | LVAD 80%<br>Inotrope 84% | No information | No information |

*Excluding patients still on LVAD (62% of total cohort)

Six comparative studies and 14 observational studies reported survival rates after LVAD implant. These ranged from 58% to 90% with a median of 74% and an average of 73% (Appendix 7).

The percentage of patients that received a transplant while on LVAD support ranged from 39% to 90% with a median of 71% and an average of 68.5% (Appendix 7). For example, Navia et al[28] conducted an analysis of a series of patients on LVADs that included 264 patients and 277 LVAD implantations. The analysis showed that a cohort of patients receiving an LVAD has a 68% chance of transplant and a 29% chance of dying before transplant within 1 year following LVAD implantation.[27]

Three prospective studies reported improved pre-tranplant survival rates (71% vs 33%, 81%vs37%, and 71% vs 36% respectively), and improved heart transplant rates for LVAD-bridged patients (67% vs 33%, 78% vs 37%, 71% vs 36%) compared to inotrope-bridged patients.[19-21]

In contrast to the above studies, Bank et al [26] and Aaronson[22] reported similar survival rates (90% vs 95%, 82% vs 74%) and similar heart transplant rates for LVAD and inotrope patients (90% vs 95%, 73% vs 74%) in retrospective studies. Massad et al[27] also reported similar transplant rates for the two groups (80% vs 84%) in a retrospective analysis. Despite a lack of survival benefit among the LVAD cohort, Bank et al[26] reported that patients treated with LVAD showed improved clinical and metabolic function at the time of transplant as indicated by significantly higher blood pressure and sodium with significantly lower blood urea nitrogen and creatinine.

Post-transplant Survival for Bridge- to-Transplant

Post-transplant survival rates of comparative studies are summarized in Table 6.

Table 6: POST-TRANSPLANT SURVIVAL RATES IN COMPARATIVE STUDIES

| Author & year | No. of patients | Device | Study Design | % transplanted | Survival after transplant (%) |
|---|---|---|---|---|---|
| Frazier, 2001[20]<br><br>Prospective | 280 LVAD<br>48 control<br>(historical) | HeartMate VE® | MultiC, non-rand<br>48 historical control | LVAD 67%<br><br>Inotrope 33% | 1yr<br>LVAD 84%<br>Inotrope 63% (p=0.0197) |
| Baxter, 1998[21]<br>Prospective | 104 LVAD<br>35 Inotrope<br>(concurrent) | Novacor® | MultiC<br>Prospective non-rand | LVAD 78%<br>Inotrope 37% | 1 year (actuarial)<br>LVAD 78%<br>Inotrope 85% |
| Frazier , 1995[19]<br><br>Prospective | 75 LVAD<br>33 Inotrope<br>(concurrent) | HeartMate® | Prospective comparative analysis<br>MultiC | LVAD 71%<br>Inotrope 36% | 60 day 1 year<br>LVAD 92% 91%<br>Inotrope 83% 67% (p=0.0001) |
| Moffat, 2003[23]<br>Retrospective | 47 LVAD<br>148 inotrope | - | Retrospective comparative analysis | - | 1 yr (actuarial)<br>LVAD 92%<br>Inotrope 82% (p<0.05) |
| Morgan 2003<br>Retrospective | 121 LVAD<br>(Successful)<br>145 inotrope | HeartMate VE® | Single centre<br>Retrospective analysis | - | Actuarial 1 yr 3 yr 5 yr<br>LVAD % 92.4 83.6 74.4<br>Inotrope% 90.8 84.0 73.2 (p=.649) |
| Aaronson, 2002[22]<br>Retrospective | 66 LVAD<br>38 inotrope | HeartMate® | Retrospective comparative Analysis | LVAD 73%<br><br>Inotrope 74% | 3 year<br>LVAD 95%<br>Inotrope 65% (p=0.007) |
| Jaski 2001[25]<br><br>Retrospective | 502 LVAD<br>2,,514 IV<br>Inotrope | Mixed | Retrospective comparative analysis of transplant database | No information | 1 yr 5 yr<br>LVAD 82% 72%<br>Inotrope 85% 71% (not significant) |
| Bank 2000[26]<br><br>Retrospective | 20 LVAD<br>20 inotrope | HeartMate® | Retrospective comparative of transplant pts | LVAD 90%<br><br>Inotrope 95% | 6 month survival 6 months survival without major complication<br>LVAD 88.9%, 55.6%<br>Inotrope 73.7% Not signif 15.8% |
| Sinha 2000 | 86 LVAS<br>50 no LVAD Tx (matched) | Heartmate VE® (95+/-71 D) | Retrospective chart review | LVAD 71% | 3-year<br>LVAD 79%<br>Inotrope 87% (p=0.35) |
| Massad, 1996[27]<br><br>Retrospective | 54 LVA<br>203 Inotrope | HeartMate IP® or HeartMate VE® | MonoC, controlled | LVAD 80%<br>Inotrope 84% | 30 day 1 year<br>LVAD 96.2% 94%<br>Inotrope 95.6% 88% (Not significant) |

Conflicting results were reported regarding the impact of pre-transplant LVAD support on post-transplant survival.

The AETMIS review[13] concluded that LVAD support before transplant might improve the five-year transplant survival rate from 70% to approximately 90% in elective cases.

Two prospective studies by Frazier et al[19 20]showed significantly higher one-year post-transplant survival rates for the LVAD group compared to the inotrope group (91% vs 65% and 84% vs 63% respectively). In a retrospective study, Moffat et al[23] reported that the 5-year actuarial survival rate was 80% for the LVAD cohort (n=47) compared to 72% for an inotropic cohort of 148 patients (p<0.05). Similarly, Aaronson[22] reported a significantly higher 3-year post-transplant survival rate for LVAD patients compared to inotrope patients (95% vs 65%).[22]

The prospective Novacor® study reported similar one-year actuarial survival rates after transplant for LVAD and inotropic support (78% and 85% respectively).[21] Morgan et al[24] also reported similar actuarial post-transplant survival rates at 1, 3 and 5 years for the LVAD group (n=121) and inotrope patients (n=145) in a retrospective analysis (92.4% vs 90.8%, 83.6% vs 84.0%, and 74.4% vs 73.2% respectively).

Similar post-transplant survival rates for LVAD and inotrope patients were also reported by Bank[26] (88.9% and 73.7% respectively at 6 months), Jaskie[25] (82% and 85% respectively at 1 year) and Massad[27] (96.2% and 95.6% respectively at 30 days; 94% and 88% respectively at one year). Although Bank et al[26] reported similar post-transplant survival rates, the investigators indicated that the six-month survival rate without major complication is significantly lower in the inotropic group (15.8%) than in the LVAD group (55.6%).

The above evidence suggests that post-transplant survival rates for patients bridged to transplantation with LVAD are similar to or better than those of patients bridged with inotropes.

Improvement in cardiac function

Improvement in New York Heart Association classification was reported by some studies. In the 2001 HeartMate® study by Frazier et al[20], 96% (153) of the patients belonged to NYHA class IV and 4% (7) to class I-III at baseline. By the time these patients qualified for outpatient treatment, 57% (91) belonged to NYHA class II and 43% (69) to NYHA class I.

At the 2003 Heart Failure Society of America Scientific Sessions, Torre-Amione[29] of the LVAD Working Group presented the preliminary results of a prospective study on 46 patients who underwent LVAD implantation at 8 centers and were participants in a registry. These patients underwent monthly evaluation during LVAD support including, echocardiography at full and reduced (4l/min) LVAD flow, and cardiopulmonary exercise testing. The pre-and post-LVAD left ventricular functions are summarized in Table 7.

Table 7: Impact of LVAD Support on Cardiac Function

| Outcome | Pre-LVAD | 30 days LVAD | 60 days LVAD | 90 days LVAD | 120 days LVAD |
|---|---|---|---|---|---|
| LVAD end diastolic diameter in cm | 7.1+/-1.1 | 4.8+/-0.9 (p<0.0001) | 4.9 | 4.8 | 4.8 |
| LVEF (%) | 17.5+/-6.1 | 34+/-14.7 (p<0.0001) | 34.5 | 31.5 | 29.4 |
| LV mass (grams) | 247+/-49.2 | 200+/-89.9 (p<0.0001) | 181.9 | 187.3 | 169.9 |

The study demonstrated that LVAD support was associated with significant improvement in left ventricular ejection fraction, LV end diastolic diameter and LV mass. Left ventricular ejection fraction (LVEF) peaked at 60 days and then decreased over time, whereas LV mass decreased steadily with time. Three patients with acute heart failure were able to have the LVAD removed. However, the degree of recovery is not sufficient to enable patients with chronic heart failure to be weaned from the LVAD device.[29]

Ambulatory Status

Studies reported that 41 - 49% of patients on LVAD support were able to return home and resume work and recreational activities while waiting for heart transplant.

In the non-randomized comparative study by Frazier et al[20], a hospital release program was established for LVAD patients. The major eligibility criteria for participation in the release program were

- LVAD implantation for at least 14 days; achievement of NYHA class I or II;
- Sufficient left ventricular contractility to open the aortic valve;

- Residence within 2 hours travel from the hospital;
- Willingness and ability of patient and companion to participate and handle the equipment
- Free from conditions requiring hospitalization.

Of the 280 LVAD patients, 58% (160) enrolled in a stepwise hospital release program and 41% (115) reached full outpatient status. Forty-five patients only left the hospital for day trips, overnight trips or 3-day releases for a variety of reasons such as potential for transplantation, concerns on the part of the investigators, or patients' own choice. The median length of outpatient stay was 82 days (range 3-660 days), and the cumulative outpatient stay was 33.9 patient years.[30]

In a German series reported by El-Banayosy et al[31], 134 patients received LVAD implant with a mean duration of support of 143 days (range 1 - 1,000+ days). Of these patients, 66 (49%) were discharged from hospital with either Novacor® or HeartMate® support. The selection criteria for out-of-hospital discharge were: fully recovered and ambulatory, no end-stage organ failure, partial recovery of left ventricles, patient able to operate LVAD and NYHA class status I or II. The age range was 15 to 68 years. In addition to anti-coagulation therapy, depending on the device, these patients also received beta blockers, angiotensin converting enzyme inhibitors, and diuretics to achieve an optimal heart rate <90 beats per minute and to reduce diastolic blood pressure to <90 mm Hg. Amiodarone, started previously, was continued after implantation. During a mean out-of-hospital follow-up period of 162 days and a cumulative outpatient experience of 30 patient years, 56% of the patients (37) accounted for a total of 54 hospital re-admissions. The primary reasons for readmission during outpatient LVAD support included neurologic disorders, infection complications and shunt malfunction[32 33].

Holman et al[34] reported that 43% of a 46-patient series was discharged with an LVAD for a median of 83 outpatient days. Morales[35] reported that 49% of patients on HeartMate LVAS® were discharged from hospital.

Quality of Life

The HTAs conducted by ANAES[18], AETMIS[13] and the Wessex Institute[17] showed improved quality of life for LAVD patients. Overall, the quality of life for patients with LVAD implantation was considered superior to that of a patient with advanced heart failure without LVAD, but inferior to that of a transplant survivor.

Dew M et al[36] compared the quality of life (QOL) of 63 LVAD patients who received heart transplant with that of 90 non-LVAD transplant patients matched to the VAD group on cardiac-related and socio-demographic characteristics. Both groups underwent QOL evaluations of physical functioning, emotional and cognitive wellbeing and social functioning at 2, 7, and 12 months after transplant. Both groups showed similar levels of statistically significant improvement in physical functioning after transplant during the study period. Emotional wellbeing was stable and improved in both groups with the LVAD patients showing significantly lower anxiety rates. However, the LVAD patients showed significantly more post-transplant cognitive impairment and they were less likely to return to employment.[36]

In another study, Dew M et al[37] found that the patients' perception may have an impact on their quality of life while on LVAD support. These investigators interviewed 42 patients and their primary caregivers prior to and after LVAD implantation. The results showed that 22-52% of patients reported specific concerns. The most common concerns included worry about infection (52%), difficulty sleeping due to the position of the drive-line (40%), pain at the exit site (46%), worry about device malfunction (40%) and being bothered during the day by device noise (32%). These concerns increased with the duration of VAD support. Higher levels of device related concerns were correlated with more physical functional

limitations, more psychological distress and reduced quality of life. The caregivers' perceptions did not vary significantly from patient perceptions.[37]

## Adverse Events Related to LVAD Bridge to Transplant

The implantation of an LVAD requires thoracotomy and cardiotomy procedures. Even after a successful and uneventful implantation, the patient is still at risk for further complications.

Because of changing anti-thrombotic and anti-infection protocols, changes in pump design, absence of randomized studies and changing medical management, precise comparison of the rates of adverse events in patients supported by LVADs with those treated conservatively is not possible. In addition, many postoperative adverse events such as hepatic and renal failure vary in frequency with the severity of the illness in the patient selected.[38]

Based on bridge-to-transplant studies, the most commonly reported device-related adverse events were infection, thromboembolism, bleeding, right heart failure, neurologic events and multiorgan failure.

Infection

Nosocomial infection remains a major life-threatening complication despite new technology used in the implantable LVADs. Because the LVAD pump and cannulas are foreign to the body, the potential for infection is increased. Infection rates up to 78% have been reported and infection has been identified as the cause for up to 14% of all mortality after LVAD implants.[28] In a prospective study, Frazier[20] reported that the infection rate was 66% in LVAD patients and 46% in the control group.[21]

Analysis of 19 studies **(Table 8)** showed:

- Overall infection rate: median = 53%, average = 49%, range: 6% - 72%.
- LVAD - related infection rate: median = 20%, range: 17% - 40%
- Driveline/exit site infection: median 15%, range 3.8 - 33%
- Pocket infection: 2.6% - 21%, median 7%
- Blood stream infection: 5.8% - 38%, median 34%
- LVAD related sepsis: 4% - 18%
- LVAD endocarditis 1.8% - 14%
- Mortality from infection: 5% - 14% of patients, median 5.8%

Based on the above analysis, infection occurred most frequently in the drive line or exit site. Malani et al[39] reported that 46% of patients in a series of 36 developed surgical site nosocomial infection, 56% of which was deep tissue infection. Multivariate analysis showed that the need for hemodialysis was the only patient characteristic associated with an increased risk of deep surgical site infection. Tjan et al[40] reported that severe wound infection with necrosis following LVAD implant was related to multiple surgical interventions on the same site. Patients with this type of infection required hospitalization for treatment.

Blood stream infection is another common infection. Gordon et al[41] reported that up to 38% of all blood stream infections in a series of 214 patients were LVAD related and were significantly associated with mortality. Navia et al[28] reported 282 blood stream infections among 264 LVAD patients during a six-month period.

LVAD endocarditis occurred in 14% of LVAD patients in one series[42], often required re-operation[38], and resulted in a mortality rate of 50%.[42] Other common infections included pneumonia, urinary tract infection and infection in the pump and pump pocket.

HeartMate® devices, particularly Heartmate IP®, were shown to be significantly more prone to infection than Novacor® or Thoratec® devices[28;43].

Table 8: Infection with Mechanical Ventricular Assist Devices

| Study | Sample Size n | Device | Total Infection Rate | LVAD related infection rate | Sepsis | Infection mortality |
|---|---|---|---|---|---|---|
| Vitali 2003[44] | 53 | mixed | | LVAD related endocarditis 1.8%<br>Pocket infection 3.77%<br>Driveline exit site infection 3.77% | 5.6% | 0 |
| Granfeldt 2003[45] | 59 | Mainly Heartmate® | 44% | Driveline or exit site 15.2%<br>Valve endocarditis 5/59 | - | - |
| Malani 2002[39] | 35 | | | Surgical site infection 46% (16)<br>Deep tissue infection 9/16<br>Pneumonia (7), venous infection (6), blood stream (2), urinary tract (3), skin/soft tissue (2) | - | - |
| Navia 2002 | 264 | 6 months | | Cumulative infection rate = 1.88/patient @ 6 months<br>Blood stream infection 1.07 infections/patient<br>Driveline infection 0.94 infection/patient<br>Pocket infection 0.49 infection/patient | - | - |
| Gordon 2001[41] | 214 | | | Attack rate of blood stream infection 49%.<br>LVAD related BSI 38%<br>Coagulase negative staph 33<br>Staph. Aureus 19<br>Candida 19, Psuedomonas aeruginosa | - | - |
| Frazier 2001[20] | 280 | HeartMate® 1 year | 45% | LVAD related 40% | - | - |
| Grossi, 2001[46] | 43 | Novacor® | 72% (severe 52.6%) | Bacteremia 34% (26 episodes)<br>Urinary tract infection 18.4% (14 episodes0<br>Drive line exit 14.5% (11episodes)<br>Tracheobronchitis 9.2% (7 episodes)<br>Device pocket 2.6% (2episodes)<br>Pneumonia 1.3 episodes (1episode)<br>10 patients successful transplant during anti-infection treatment. No patient developed same infection after transplantation | 4% | - |
| Bank, 2000 | 20 | HeartMate® | 45% | | | |
| Helman, 2000[47] | 12 (< 21 yrs) | HeartMate® | | Systemic infection 33% of patients. | - | - |
| Sinha 2000 | 86 | HeartMate VE® | 66% had =/>1 | LVAD related infection 17%<br>LVAD endocarditis 8% (2 cases fatal)<br>A high incidence of infection during LVAD support did not have an impact on pre-transplant or post-transplant mortality, post-transplant infection rate or overall patient survival. | 5.8% | 5.8% |
| Sun, 1999 | 95 | HeartMate® | 54% | LVAD related infection = 27%<br>Drive line: 16%<br>Pocket: 2%<br>Endocarditis: 9% | - | 10% of infections,<br>5% of all patients |
| McCarthy [48]1999 | 97 | HeartMate® | 59% | Drive line infection: 28%<br>Pump infection: 11%<br>28+11 = 39% | - | - |
| Oz, 1997[42] | 58 | HeartMate® | 53% | Driveline: 14% (7 - 20%)<br>Endocarditis 14% | - | - |
| Griffith, 1996 | 162 | HeartMate® | | Driveline: 33% (54/162), major in 24 cases (44%)<br>Other infections: 45% (73/162) | - | - |
| El -Banayosy, 2001[49] | 144 | Novacor®<br>HeartMate®<br>Thoratec® | | Driveline Exit site:<br>Novacor: 24%, Heartmate: 30%, Thoratec: 9% (9-30%)<br>Pocket Infection:<br>N: 7%, H: 21% | 11 - 13% | 32% of infection (14% of all patients) |
| Meyns 2002[8] | 165 | Novacor®<br>ABIOMED® | 6% | | - | - |

| Study | Sample Size n | Device | Total Infection Rate | LVAD related infection rate | Sepsis | Infection mortality |
|---|---|---|---|---|---|---|
| Loisance, 2000[50] | 36 | Novacor®® | | Overall freedom from infection: 75% at 1 year, 67% at 1.5 yeas and 58% at 2 years. Most significant Staph. Aureus | - | - |
| Holman 2002[34] | 46 (53 devices) | Thoratec® HeartMate® | | Device infection 20% | 11% | 11% mortality due to sepsis |
| Novacor 1998 | | Novacor® | 66% | | | |
| Bentz 2004[43] | 90 | Thoratec ® HeartMat® | Overall device related 20% | Thoratec 10%, HeartMate 29% Staphlococcus found in 61.9% of device related infection; Driveline 52.1%(31% pocket, 15% VAD); 16/18 with LVAD related infection were successfully transplanted | | |

The most common cause of infection is staphlococci.[41] In addition to bacterial infection, the risk of opportunistic fungal infection is high among LVAD patients and the prophylactic use of antifungal therapy has been recommended.[51] Nurozler et al[51] reported that 22.4% of 165 patients on HeartMate LVAD developed fungal infection, and about 50% of the fungal infection was found to be device related. Five of the patients with fungal infection developed endocarditis that required replacement of the device or urgent transplantation.

Almost all infections could be treated. However, sepsis occurred in 3.8% to 14% of patients and was one of the main causes of mortality.

Despite the high infection rate, studies have reported that infection from the same organism after transplant was rare and that infection did not adversely affect the rate of heart transplantation or post-transplant survival rates.[27;43;46]

Bleeding

LVAD implantation is associated with bleeding that is more than 1.5 litres or severe enough to require operation. The Oregon HTA[15] reported rates of bleeding that ranged from 25% to 50%, and the ANAES review reported a bleeding rate of 3-31%. The AETMIS review[13] indicated that bleeding requiring re-operation may occur in 20-44% of patients

In this review, the rate of bleeding ranged from 8.6% to 48% with a median of about 35% (Appendix 8).

In a comparative study using HeartMate VE LVAS®, Frazier et al[20] reported that throughout the study, bleeding of any kind occurred in 48% (133) of the patients. Of these patients, 11% had bleeding arising directly from LVAD itself or from the abdominal implant site and 83% had bleeding in the perioperative period (within 5 days of implant, re-implant or explant).

With Novacor® that requires anticoagulation, late hemorrhaging has been reported.[21]

Thromboembolic Events

Reported rates of thromboembolic events such as stroke ranged from 5% to 37%. The rates appear to vary according to the definition, type of device and anticoagulant therapy. The AETMIS HTA[13] reported thromboembolism rates of 5-15% for HeartMate® and 12-37% for Novacor®. Of the 10-25% reported by the Oregon HTA[15], 2-7% were reported to be fatal.

Navia et al[28] reported that among 264 patients supported by LVAD, the number of cerebral bleedings per patient was 0.037, 0.072 and 0.154 after 30 days, 3 months and 6 months of LVAD support respectively.

The risk was found to be initially high, but fell rapidly, then peaked at 3 months followed by rapid decline. Cerebral infarction occurred 55 times with an overall cumulative events function of 0.154, 0.25, and 0.30 per patients after 30 days, 3 months and 6 months of support, respectively. While no significant differences in the risk of cerebral bleeding were detected between the different devices, the original Novacor® devices had a substantially higher risk of cerebral infarction than HeartMate® despite intense coagulation. The Vacutek conduits in current Novacor® devices have reduced the overall stroke rate, but overall, Novacor® Vacutek stroke rate is still higher than HeartMate® devices.[28]

The lower risk of thromboembolic complications in HeartMate® devices despite the sole use of aspirin without anticoagulant, has been attributed to the textured inner surface of the pump chamber that allows for covering by a neointimal layer, thus reducing the thrombogenity of the artificial surface.[52] Thromboembolism in patients supported by Novacor® or Thoratec® LVADs were managed by the use of Warfarin therapy to decrease coagulation risk.[53]

Risk factors identified for thromboembolic events are acute myocardial infarction, cannulation via left atrium, and the amount of blood units transfused after device implantation. The main sources of embolization are the pump itself and the concave surface of the valves.

Neurologic events

The Oregon HTA[15] reported neurologic events in 10% - 20% of LVAD patients. In the current literature review, neurologic disorders were reported in 7- 28%[54], 27%[20] [Frazier 2001] and 15%[34] [Holman 2002] of LVAD treated patients. However, Frazier reported that of the 27% neurologic complications, only 5% were deemed device related. Other neurologic complications included metabolic encephalopathy, confusion and syncope. These were attributed to other causes.

Right ventricular failure

Right heart failure occurred in 11% to 26% following LVAD implantation depending on the device used.[20;55] Right ventricular assistance was required in 7% to 11% post LVAD implant with no significant differences among Heartmate®, Novacor® and Thoratec® devices. Right heart failure was found to have a significant negative impact on LVAD bridging outcome. In one study, 35% of patients with right heart failure compared to 63% of patients without right heart failure were successfully bridged to transplantation.[56] Regression analysis showed that the need for circulatory support, female gender, and nonischemic etiology were the most significant predictors for RVAD use after LVAD insertion. Regarding hemodynamics, low pulmonary artery pressures, and low right ventricular stroke work, reflecting low right ventricular contractility were important parameters.[55]

Device Malfunction/Mechanical failure

In a comparative study on 280 patients supported by HeartMate®, Frazier[20] reported fatal mechanical failure in 3 patients (1%) as a result of disconnection of the outflow assembly from the pump body, and pump diaphragm failure. In addition, 435 confirmed device malfunctions occurred during the study. Most of these were malfunctions of external accessories. During the study, 9% of the LVAD patients needed to use the backup components because of controller or cable malfunction.[20]

Navia et al[28] reported that device failure occurred in 21 instances among 264 patients on LVAD support, with all except one occurring in HeartMate® devices. In this series, device failures were caused by late inflow valve assembly bleeding (11/21), driveline fracture (4/21), and one each of controller failure, inflow cannula dislodgment, outflow graft obstruction, aspiration of blood into driveline vent, and two

unexplained pump failures. Freedom from failure was 96%, 90%, 86% and 82% at 30 days and 3, 6 and 12 months, respectively.[28]

Other adverse events

Other adverse events reported included hemolysis (6-20%) and organic dysfunction (5-50%). Based on a pathology study, Heverly et al[57] concluded that the most common neuropathologic findings among patients with LVAD were related to ischemia and infarct. In a significant subset of patients, central nervous system [CNS] pathology, particularly hemorrhage with herniation, was the primary cause of death.

**Summary Statements (Adverse Events Associated with LVAD Bridge-to-Transplant**

- The median post implant mortality rate is approximately 26% (range 58%–90%).
- A median of 71% of LVAD patients received a heart transplant (range 39%–90%)
- Serious adverse events included infection (median 53%, range 6–72%) with up to 40% mortality rate, bleeding (8.6%–48%, median 35%), thromboembolism (5-37%) with a 2-7% mortality rate, neurologic disorders (7- 28%), right ventricular failure (11-26%, with 7%-11% requiring right ventricular assistance) and hemolysis (6–20%).
- Among the common adverse events, bleeding tends to occur in the first few post-implant days and is rare thereafter, whereas infection and thromboembolism occurs throughout the duration of the implant, though their frequency tends to diminish with time.
- The malfunction rate of approved devices was about 1.55/patient in the first year requiring the use of back-up component in 9% of cases. Device failure rate of 8% had been reported. Most of the malfunctions appear to be associated with external components. Fatality directly attributable to the devices was about 1% in short-term LVAD-support.
- When evaluating the complication and mortality rates, it should be noted that the patients selected for LVAD implants tend to be in advanced heart failure, debilitated and are vulnerable to complications.

## Evidence on Bridge-to-Recovery

VADs have been used as short-term bridging in emergency cases of post cardiotomy failure and in cases of cardiogenic shock following various other myocardial insults such as myocardial infarction and fulminant myocarditis. Circulatory assistance could be provided to the left ventricle, the right ventricle or both ventricles.

Only small case series studies were found on bridge-to-recovery. These are summarized in Table 9.

**Table 9: Summary of Studies on Bridging with VAD in Acute Heart Failures**

| | Couper 1999[58] | McBride 1999[59] | Hendry 1999[60] | Makentso-Dessao 2002[61] | Hetzer 2001[62] | Farrar 2002[30] | Thoratec Corp 1998[63] | Samuels 2001[64] | Rodrigus 2001[65] |
|---|---|---|---|---|---|---|---|---|---|
| **Sample size** | 22 | 44 | 12 (VAD) | 39 | 95 | 22 weaned | 29 | 45 | 20 |
| **Cause of HF** | mixed | mixed | Cardiogenic shock, acute MI | Cardiomyo-pathy; myocarditis | Cardio-myopathy | Non-ischemic Cardiom-yopathy; myocarditis | Post cardiotomy shock | Pre or post cardiotomy shock | Post cardiotomy (15) or myocarditis (5) |
| **BiVAD** | 40% | 39% | | | | | 52% | | |
| **Overall survival on LVAD** | To discharge 59% | | | 64% | | | | | 33% |
| **Weaned & survived** | 36% Not sure how many survived to discharge | 27% | None weaned 25% died while on VAD support | 12.8% | 17% | -86% survived after weaning -Actuarial survival of native heart:86% @ 1 yr &77% @ 5 yr | 34% weaned to discharge<br><br>1-year survival 28% | 31% | Overall 25% Post cardiotomy 13% Non-cardiotomy 40% |
| **Received a Heart Transplant** | 23% (5) | - | 75% (50% of original cohort) survived transplant | 49% | | 14% after weaning | | | Cardiotomy =0 Non-cardiotomy 40% |

The sample size of the studies ranged from 12 (Canadian study) to 95 (German study) with only one study exceeding 45 patients. A high percentage of bridge-to-recovery patients required bi-ventricular support (up to 52%).

Analysis of the results showed that the percentage of patients actually bridged to recovery (weaned from LVAD and survived to discharge) ranged from 0% to 36% with a median of 26%. Instead of bridged-to-recovery, 14% to 50% of the patients in the studies were actually bridged-to-transplant or required a heart transplant after being weaned from LVAD.

The largest published series from the German Heart Institute included the outcomes of 95 patients who received LVAD implantation for end-stage heart failure from non-ischemic, idiopathic, dilated cardiomyopathy. Hetzer et al[62] reported that 28 patients (29.5%) fulfilled the criteria of improved cardiac performance and were weaned from the device. However, only 16 patients (17% of the original cohort) were weaned successfully, with normal heart functions after a follow-up period ranging from 1 month to 5.5 years. The other patients either died (4 patients) or required a heart transplant (8 patients). This study

showed that hearts that are less chronically altered have a better prospect for recovery. Long-term good outcomes were most likely in younger patients and in patients with a shorter history of heart failure.[62]

Based on a series of 20 patients, Rodrigues found that non-postcardiotomy shock patients had better survival (80%) compared to postcardiotomy patients (13%). Forty per cent of the non-cardiotomy patients received a heart transplant whereas none of the cardiotomy patients were transplanted.

It has been reported that bridge-to-recovery in the setting of dilated cardiomyopathy has been less widespread and overall makes up a small fraction of LVAD patients. Kumpati[66] reported that out of 250 patients who had LVAD placement, only two patients with dilated cardiomyopathy subsequently had device explantation after cardiac recovery. It was noted that among patients with dilated cardiomyopathy who had device explantation for recovery, a variable number (up to 30% - 50%) had recurrent failure after device removal requiring relisting for transplantation or repeat LVAD placement.[66]

There have been numerous reports of successful bridging to recovery for patients suffering from acute fulminant myocarditis; however, all of these studies were case reports or observational studies with less than 20 subjects.

Adverse Events Associated with Bridge-to-Recovery

The adverse events associated with the use of LVAD as a bridge-to-recovery were similar to those reported in bridge-to-transplant patients. These included:

Nosocomial infection: 20% to 79.5%, median 45% (most common: blood stream infection 26%, cannular infection 20.2%, urinary tract infection)
Bleeding 62-78%
Hepatic dysfunction 62%
Renal dysfunction 62%
Thromboembolism 38%
Hemolysis 31%[61;64;67].

Samuels et al[64] reported that the most common cause of death were cardiac events (40%), neurologic events (22%), sepsis (16%), multiorgan failure (16%) and technical problems (6%).

According to an expert in the field, experience with LVAD as a bridge-to-recovery technology has been more favourable in Germany than in North America where it is not regarded as a major indication since evidence for its effectiveness in this setting is limited.

**Summary Statements on Bridge to Recovery**

- Evidence on outcomes of bridge-to-recovery is limited, particularly in the long-term.
- Based on the results of a limited number of small case series, the rates of successful bridging to recovery ranged from 0 to 36% with a median of 26%.
- A high percentage (up to 50%) of the patients who received LVAD for bridge-to-recovery were actually bridged to transplant or required a transplant after being weaned from LVAD.
- A wide range of bridge-to-recovery rates was reported, probably because of inter-study heterogeneity in patient selection criteria. This partly reflects the difficulty in predicting which patients would likely recover cardiac functions.
- Adverse events in bridged-to-recovery patients were similar to those observed in bridge-to-transplant studies.

## Evidence on Destination Therapy

There is one randomized controlled trial on the use of LVADs as an alternative to heart transplantation.

Rose et al[68] reported on the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure [REMATCH]. This is the first prospective randomized controlled study that tested the hypothesis that mechanical cardiac support is an acceptable alternative to medical therapy. Due to ethical concerns relating to randomizing patients who are eligible for heart transplantation to an unproven therapy (permanent Heartmate VE LVAS® support), the study enrolled only patients who were ineligible for transplantation and were willing to be randomly assigned either to intensive medical therapy or LVAD implantation.

REMATCH[68] is a collaboration among the National Institutes of Health, Columbia University, and Thoratec Corporation, and was submitted to the FDA in support of an application to use HeartMate® as an alternative to heart transplantation in patients who were not candidates for transplant.
Inclusion criteria were:

- Ineligibility for heart transplant;
- NYHA class IV >/=90 days;
- Intensive medical therapy;
- LVEF <25% and VO2 max</=12ml/kg/min.

Exclusion criteria included:

- Correctable cause of heart failure;
- Body surface area</=1.5 square meters;
- Pulmonary hypertension;
- Creatinine>/=3.5ml/dl;
- Active infection or carotid stenosis;
- Impaired cognitive function; and
- History of stroke <90 days.

The primary end point was mortality at 2 years.

One hundred and twenty-nine patients were randomized to either receive LVAD (n = 68) or optimal medical management (n = 61). The mean age was 68+/-8.2 years for the optimal management group and 66+/-9.1 years for the LVAD group.

Long-term LVAD was associated with a 48% relative reduction and a 27% absolute reduction in the mortality rate at one year. The one-year Kaplan-Meier (KM) estimated survival was 52% for LVAD and 25% for medical therapy. However, this benefit diminished at two years with the KM survival for LVAD at 23% compared to 8% for medical treatment (p=0.09).[68]

Despite the one-year survival benefit, the morbidity associated with the use of LVADs was considerable. The frequency of adverse events in the LVAD group was 2.35 times that of the controls (6.45 per patient year for LVAD and 2.75 per patient year for medical treatment).[68] In particular, infection and mechanical failure of the device were major factors in the two-year survival rate of only 23%. LVAD support was associated with serious adverse events (bleeding requiring re-operation in 32% of patients, infection in 41%, and stroke in 10%) and hospitalization (a median of 88 days vs 24 days for the control group) throughout the course of the study. The rate of device failure was 35% and was the second leading cause of death.

In reviewing this study, the FDA noted that LVAD treatment resulted in decreased cardiac mortality rates and increased non-cardiac mortality rates and that survival past two years was poor in both the LVAD group and the control group. The FDA also noted that functional status favors LVAD but not consistently. (http://fda.gov/ohrms/dockets/ac/02/slides/3843s1_01_fda/tsld004.htm).

It should be noted that the subjects of the REMATCH trial were not eligible for a heart transplant mainly because of advanced age and presence of concomitant diseases that may partly explain the high morbidity rate.

PHADE

A non-randomized, single center study, Pneumatic HeartMate® Assist as Destination Evaluation (PHADE), was initiated at the Heart Institute of Spokane. As of September 2002, the web site of the Heart Institute of Spokane indicates that the PHADE Clinical Trial is temporarily on hold and is not evaluating or enrolling patients at the time. (http:\\www.this.org/phade/phys_intro.html).

Current Clinical Trial on Destination Therapy

Presently, a non-randomized trial INTrEPID (Investigation of Non-Transplant Eligible Patients who are Inotrope Dependent) is being conducted in Canada and the United States. The study aims to determine whether the Novacor® LVAS (World Heart Corp.) reduces the mortality rate and improves the quality of life in patients with end-stage heart failure 6 months after Novacor® implantation, compared to patients supported by the best available drug therapy. The trial in Canada is expected to have a total enrollment of up to 30 subjects at six medical centres [News release, http://www.worldheart.com/section3/sec3-1-100a.html]

**Summary Statements (LVAD for Destination Therapy)**

- LVAD used as an alternative therapy to transplant in patients who were not eligible for a heart transplant resulted in a 48% relative reduction in mortality at one-year. (Level 2)
- The 2-year survival rate on LVAD decreased to 28%; however it was still significantly higher than the survival rate of inotrope patients (8%).
- Permanent LVAD support was associated with more frequent adverse events (2.35 times) and more hospitalization compared to inotrope patients.
- Sepsis was the leading cause of death (41%) followed by LVAD failure (17%).
- The quality of life was significantly better for LVAD patients compared to inotrope patients.
- The patients in this study were elderly with more comorbidity compared to bridge-to-transplant studies.
- Long-term outcomes (beyond two years) are lacking.

### LVAD in Children and Adolescents

Studies on the use of LVAD in children and adolescents are summarized in Table 10.

**Table 10: Summary of Pediatric VAD Support**

| Study | Helma, 2000 | Reinhartz, 2002 | Levi, 2002 | Goldman, 2003 | Price, 2003 | Hendry, 2003 (Canadian) |
|---|---|---|---|---|---|---|
| Cases (n) | 12 | 96 (Thoratec registry) | 28 (19ECMO, 9 VAD) | 22 (ECMO 13 BiVAD 9) | 21 | 7 |
| Time frame | ? | 20 years (1982-2001) | | 5 years (1998-2002) | 15 years (1987-2003) | 10 years (1992-2001) |
| Mean age (years) | 16 | 13.7 | ECMO 2<br>VAD 14.5 | ECMO 10<br>BiVAD 4.9 | 9.8 | 14.9+/-0.9 |
| Successful bridge to transplant | 62% | 58.3% | Transplant or weaned<br>ECMO 58%<br>VAD 89%<br>P=0.1 | ECMO 92%<br>BiVAD 66% | 57% | 100% |
| Successful bridge to recovery (explanted) | 15% | 10.4% | | - | 38% | 0 |
| Survival to transplant or recovery | 77% | 68.7% | VAD 89% | 66% | 95% | 100% |
| Survival after explantation | Not reported | Not reported | Not reported | - | 50% | NA |
| Survival after transplant | 73% survived 8-43 months | | Extubation while on support<br>ECMO 0%<br>VAD 67%<br>P<0.0001 | Survival to discharge<br>ECMO 92%<br>BiVAD 55% | 67% | 86% (1 mos - 3yrs)<br>1 died after 8 years |
| Overall survival | 58% discharged alive | 65.6% survived to disch | | Long Term<br>ECMO 85%<br>BiVAD 45% | 51% alive at the time of the review | 86% |

Evidence on the use of LVAD or BiVAD in the pediatric population is limited. Six studies were included. With the exception of a study based on the Thoratec registry, most of the studies had less than 30 patients.

The studies showed that the devices licensed in Canada were designed for use in adults. Due to their size, these devices are not used in infants. The mean age of the children who received VAD support was close to 10 years or older. Thoratec®, the device usually used for children in Canada, is not recommended for patients with body surface area less than 1.5 square meters.

The bridge to transplant rates ranged from 58.3% to 66% with survival after transplant ranging from 45% to 65.6%. A very small Canadian study (n=7) by Hendry et al[69] reported a bridge to transplant rate of 100% with a post-transplant survival rate of 86%. Bridge to recovery ranged from 10.4% to 38%.

The largest study is an analysis, by Reinhartz et al[70], of existing clinical data on the use of pulsatile VADs in 197 children in the United States and Europe. The three VAD systems studied were Thoratec® VAD, Berlin Heart®, and Medos® VAD. Of the three systems, Berlin Heart and MedosVAD are pediatric devices but they have not been licensed in Canada. The analysis showed that pulsatile VAD support of the failing heart in children can be performed with similar morbidity and mortality as in adults, but the survival rates were lower in neonates and infants. The survival rates were higher for Thoratec® than Berlin Heart® or Medos® VAD. Of the 96 patients on Thoratec® VAD, 58.3% survived to transplant, 10.4% survived to recovery and 65.6% survived to discharge. For all devices, support for

cardiomyopathies and myocarditis was associated with much higher survival rates as compared to support for congenital defects and postcardiotomy (83–84% vs 43%). ECMO or centrifugal pumps remain the methods of choice for postcardiotomy patients that cannot be weaned from extracorporeal circulation but have potential for early myocardial recovery.

Two small studies compared the outcome of ventricular support with ECMO and with LVAD/BiVAD. A study by Levi[71] (n=28) showed that pulsatile VAD support yielded a better survival to transplant or recovery than ECMO support (89% vs 58%). In contrast, a study by Goldman et al[72] (n=21) showed a better bridge to transplant rate with ECMO than with BiVAD (92% vs 66%). Goldman et al[72] used VAD in younger children (median age of 4.9 years vs mean age of 10 years for ECMO), whereas Levi et al[71] used VAD in older children (median age 14.5 years vs median age of 2 years for ECMO).

A 1998 audit of the United Kingdom pediatric transplant data showed that during the previous 2 years, 20 children died on the heart transplant waiting list while 59 donor hearts available for transplantation were not used because no suitable recipients were matched. Following the audit, a pediatric mechanical assist program was initiated in the UK in 1998 at 2 pediatric transplant centres, using the Medos HIV VAD (Medos, Stolberg, Germany) or ECMO to bridge children older than 1 year with end-stage cardiomyopathy to heart transplantation. A policy was simultaneously implemented to list as urgent most pediatric patients on mechanical support for the next available matched heart.[72] Goldman et al reported that a total of 22 children were supported in 5 years with 55% survival to discharge. During the study period, there was a progressive decline in the number of pediatric patients dying while on the waiting list. The total number of deaths was 59 in the 2 years before the study and was 51 during the 5-year study period. No child with cardiomyopathy died on the waiting list in the United Kingdom during 2002, except one patient who was taken off the ECMO at the patient's request. The policy to bridge and list the bridged patients as urgent for heart transplantation did not result in a harmful knock-on effect on patients who were pushed down the waiting list. The mean waiting time for all patients that received a heart transplant ranged from 7 days to 51 days (Those on mechanical circulatory support ranged from 6 to 10 days).[72]

Serious complication events included intrathoracic bleeding requiring re-exploration, cerebrovascular accident, sepsis, and life-threatening thrombus or hemorrhage.[73]

**Summary Statements (Pediatric LVAD Support)**

- The experience relating to the use of VAD support in children and adolescents is limited at present. The largest series comprised of 96 patients supported by Thoratec® VAD at 27 centres worldwide over a period of 20 years (1982-2002).
- ECMO and VADs are complementary technologies in supporting pediatric patients with end-stage heart failure.
- ECMO remains the most commonly used method of mechanical circulatory support in children because most programs are familiar with this technology, it can be initiated in the ICU, and it can be used in all forms of cardiopulmonary failure including bi-ventricular failure
- Small VADs designed for adults have been used successful to bridge pediatric patients to transplantation. Although bi-ventricular VAD support is possible, space considerations make it problematic in very small children.
- The survival rates of VAD support in children were comparable to those reported for adults (68.9% survived to transplant or recovery).
- Goldman reported better survival rates with ECMO support compared to VAD support, whereas Levi reported comparable survival outcomes for the two technologies in children with higher rates of extubation and oral feeding in the VAD group. It should be noted that VAD was used in older children with larger body size in the Levi group but not in the Goldman group.

- LVAD support provides better results in patients with cardiomyopathies and myocarditis than in patients with congenital heart defects and postcardiotomy.
- A study in the UK showed that with a surplus supply of donor hearts, bridging to transplantation (with ECMO or VAD) together with a policy of urgent transplantation reduced pediatric deaths on the transplant waiting list without negative impacts on other patients on the list. This applies only when there is no shortage of donor hearts.
- The studies are too small to draw any conclusions. No Kaplan Meier survival analysis was performed which makes it difficult to compare the survival rates.

### Effect of Patient Selection on Outcome

Deng et al[74] conducted a retrospective review and analysis of 366 LVAD recipients from the Novacor® European Registry. Multivariate showed that the following pre-implant conditions were independent risk factors for increased mortality after LVAD implantation:

- Respiratory failure associated with septicemia (odds ratio 11.2)
- Right heart failure (odds ratio 3.2)
- Age >65 years (odds ratio 3.01)
- Acute postcardiotomy (odds ratio 1.8)
- Acute myocardial infarction (odds ratio 1.7)

The analysis further showed that patients without any of these factors had an average 1 year survival of 60% after LVAD implantation including the post transplantation period; for the combined group with at least one of the above risk factors, the 1 year survival was 24%.

El Banayosy et al[56] conducted multivariate analysis of 25 parameters with regard to their effect on survival for 51 LVAD patients and 50 BVAD patients. The average duration of support was 57.4 days for the LVAD group and 55.4 days for the BVAD group. The BVAD group had greater co-morbidities and tended to have worse outcomes than the LVAD patients. The analysis found no significant predictors of survival in either sub-group. However, in the total collective, the following pre-implant conditions were independent risk factors for increased mortality after LVAD implantation:

- Patient age > 60 years (Odds ratio 3.87, CI 1.39-10.76))
- Pre-implant ventilation (Odds ratio 6.76, CI 2.42-18.84)
- Increased pre-implant total bilirubin (Odds ratio 1.42, CI 1.19-1.69)

Deng et al[75] also evaluated the impact of the timing of LVAD support on survival. Forty-one patients who underwent LVAD implantation at the Muenster Hospital were classified into elective, urgent, emergent and chronic categories. The elective patients experienced deterioration on the transplant waiting list and received LVAD support to prevent heart-induced end-organ dysfunction. Urgent patients experienced rapid deterioration of chronic heart failure and end-organ dysfunction that required immediate measures such as ventilator and VAD implantation within 48 hours. Emergency VAD patients included those who developed cardiogenic shock in the setting of cardiac surgery, myocardial infarction or myocarditis. Chronic VAD consisted of patients with chronic heart failure who were not candidates for heart transplantation. The survival to transplantation was 77% for the overall study group, 56% for the urgent group and 33% for the emergent group. The investigators indicated that if hemodynamic and clinical deterioration were complicated by multiorgan dysfunction, as occurred in emergency and urgency VAD groups, the associated immunological alterations aggravated by the trauma of VAD insertion would decrease the likelihood of a favorable outcome. Survival of patients who electively underwent LVAD implantation was better than that of patients who were stable on the waiting list and did not undergo heart transplantation during follow-up.[75]

The wide variability in the outcomes of LVAD implant may be partly explained by differences in patient selection criteria. Moreover, Deng concluded that early implantation of VAD may facilitate resolution of organ dysfunction before heart transplantation and may improve the survival of severely ill patients up to and following the transplant.

## Canadian Experience

Ontario

From 1986 to 2001, the Ottawa Hospital Heart Institute has provided circulatory support to 70 patients, using either CardioWest total artificial heart, the Thoratec® VAD or Novacor® LVAD.[69] For the pediatric population, CardioWest or Thoratec® VAD was used. Hendry et al reported the Ottawa experience in a 1999 and a 2003 report. These reports were described in previous sections.

Quebec

Cecere et al[76] presented the LVAD experience of the McGill University Health Centre Heart Failure and Heart Transplant Centre at the 2001 Canadian Cardiovascular Congress. A total of 8 patients (7 male, 1 female) with age 13-58 years received LVAD implantation for ischemic cardiomyopathy (5/8) and idiopathic cardiomyopathy (3/8). All patients were deemed suitable transplant candidates prior to VAD implant. Equal numbers received Novacor® and Thoratec® devices. Seven out of the eight patients survived the implantation. Two of these seven patients were discharged on VAD support. All seven received a heart transplant and five out of the seven were discharged post transplant [Abstract, website: www.ccs.ca/society/congress2001/abstracts/abs/a273.htm].

## Recommendations of Previous Systematic Reviews

*Use of LVAD as bridge-to-transplant and bridge-to-recovery*

Three HTAs (CEDIT[16], AETMIS[13], Oregon[15]) recommended the use of LVAD for bridge-to-transplant for accepted transplant candidates in whom medical treatment has been unsuccessful and who are not expected to otherwise survive to transplantation. These three reviews also supported the use of LVAD for bridge-to-recovery from cardiogenic shock or cardiotomy failure patients who could not be weaned from cardiopulmonary bypass but have potential for recovery of cardiac functions.

Two reviews (ANAES[18] and Wessex Institute[17]) were more cautious. While both reviews indicated that there was a suggestion of potential benefits in using LVAD as bridge-to-transplant and bridge-to-recovery, they expressed concerns that the studies have weak methodology and that the evidence was not of sufficient quality to reach a decision.

The ANAES[18] review emphasized that the LVAD is associated with significant morbidity. ANAES recommended the establishment of a registry for advanced heart failure, a one-stage network responsible for the care of these patients and a Homogenous Disease Group dedicated to the activity and realization of clinical and economic evaluation of LVAD.

*Use of LVAD as an alternative to heart transplant*

HeartMate® and Novacor® are not licensed by Health Canada for use as an alternative to heart transplant.

To date, all systematic reviews have concluded that there is insufficient evidence to support the use of LVAD as an alternative to transplantation and have recommended against this use. It should be noted that all systematic reviews were conducted before the publication of the REMATCH outcomes and the FDA approval of the permanent use of Heartmate LVAS®.

### Change in Regulatory Status by FDA

On November 6, 2002, the FDA announced the conditional approval of the permanent use of HeartMate LVAS® only in "certain very sick patients who have severe end-stage congestive heart failure and are not eligible for heart transplantation". The FDA requires Thoratec (manufacturer of HeartMate®) to conduct a post-approval study to assess the device's long-term safety and effectiveness for permanent use.

As of March 17, 2004, Health Canada has not made any changes to its licensing of ventricular assist devices.

# Economic Analysis

## Summary of Literature

The literature on cost and cost-effectiveness of LVADs are summarized in **Appendix 9.**

### Bank et al, 2000[26]

Based on their cost analysis of 40 HeartMate® implants used for bridge-to-transplantation, Banks et al[26] (US) found that the costs of each LVAD device and implant procedure were $50,000 and $23,000 respectively, with a total cost of $73,000. The average hospital charges from listing as status 1 until after transplant was $343,000 compared to $213,860 for the inotropic group. The average daily hospital charges for the two groups were similar. The LVAD patients had longer hospital stays than inotropic patients before transplant (average of 77 days versus 42 days), because LVAD patients were placed on inactive transplant status until they were recovered and had extensive cardiac rehabilitation. The longer stay is also partly because the pneumatic HeartMate® was only approved for in-hospital use.

The following factors were found to lower the inpatient cost for LVAD patients.

- Shorter ICU stay before heart transplantation (average of 15 days versus 42 days for non-LVAD patients)
- Decreased post-transplant complications
- Potential saving if LVAD patients can be supported as outpatients

Such savings may not be realized by MOHLTC because the funding system in Ontario is different than in the US.

### Arabia et al, 1996

Based on three cases, Arabia et al[32] conducted cost analysis of hospitalization costs for bridging to transplantation using the Novacor® LVAD system. The analysis showed that the average daily hospital admission cost was lower after the implant than pre-implant (US$1,570 versus US$2,240). The average pre-implant hospitalization was 14.6 days and the average post-implant hospitalization was 75 days. The analysis also showed that ICU charges were three times higher in heart failure patients without LVADs than those with LVADs.

### Wessex Institute Systematic Review

In the Wessex Institute HTA, Christopher et al[17] estimated the cost for the LVAD device and implant procedure to be £62,480. Using LVAD supported survival to transplant rate of 71% (Frazier 1995) and transplant survival rates of 75% at one year, 64% at 5 years, 50% at 10 years and 0% at 20 years, the reviewers estimated the cost utility of LVADs for bridging to transplantation to be £39,800 per QALY. Sensitivity analysis over 12 years showed that the cost-utility ranges from £28,500 to £74,000 per QALY (see **Appendix 9** for detailed calculation).

The review concluded that in order to achieve the acceptable cost utility ratio of £20,000 or less, the cost of LVAD device and procedure needs to be reduced to approximately £19,000 per implantation.[17]

**Gelijns et al 1997**

Gelijns et al[33] of the Presbyterian Hospital in New York (US), conducted a retrospective review of all inpatient and outpatient charges related to LVAD implant and maintenance in12 patients with HeartMate® LVAD for an average duration of 177 days. The actual costs were derived using a ratio-of-cost-to-charge. The inpatient costs per patient were $94,542 including regular ward, special care, operating room, laboratory, blood products, drugs, rehabilitation and professional payments. The device cost was $67,085 bringing the total inpatient cost to $161,627 per implantation.

The outpatient cost was $352 per week and included costs for readmission, laboratory tests, drugs and professional payments. Based on this data, the average actual total cost for an LVAD recipient (inpatient and outpatient combined) was $221,313 over an average of 9.5 months. The investigators estimated that the cost will be about $20,000 less if each patient only has a clinically sufficient length of stay in hospital (average17.5 days) instead of the FDA mandated length of stay (average actual of 43.5 days).[33] Detailed calculation is shown in **Appendix 9**.

Moskowitz et al[77] used data from the above study and compared the first year cost of LVADs without professional payments, and first year heart transplant cost without professional payments. The authors concluded that the first year cost of the two procedures is very close ($192,154 and $176,605 respectively). It was noted that the second and subsequent year costs of heart transplant are considerably less, whereas the LVAD costs in later years are not yet known. However, the authors expect the major cost drivers including cost of the device, length of hospital stay and readmission rates to improve over time.[33]

**McGregor et al, 2000 (Canada)**

In 2000, McGregor[38] estimated the cost of LVAD implant in Canada using the following assumptions (all costs in Canadian $):

- Cost of an LVAD implant is comparable to the cost of a heart transplantation ($48,443 each);
- Survival to transplant after LVAD implant =70%
- LVADs improve transplant survival rate from 70% to 90%
- Average of 100 outpatient days with LVAD maintenance cost = 50% of US cost according to Gelijn, 1997 = $38/day
- Re-implant every 4 years

Based on these assumptions, LVAD support would result in an incremental cost of $201,576 per heart transplantation. The cost utility for using LVAD in bridge to transplant under elective circumstances would be $91,000 -$126,000 per life-year ($117,000 -$186,000 per life year discounted at 5%). This does not take into consideration the cost of the transplantation procedure. The cost utility for using LVAD as an alternative to heart transplantation would be $52,000 -$60,000 ($50,000 - $58,000 discounted) per life-year under emergency circumstances and $71,000 ($68,000 discounted) under elective circumstances.

McGregor[38] also projected that performing 50 new LVAD implants in Canada per year as bridge-to-transplant would result in a total of 172 survivors and a total cost of $13 million in the 12$^{th}$ year. The cost of using LVADs as an alternative to heart transplant would mean 7,000 new implants in Canada per year and a total cost (implant, re-implant and maintenance) of $2,661 million in the 12$^{th}$ year.

**Oz et al, 2003**

Oz et al[78] conducted an analysis of the costs of hospital resource use and cost predictors for LVADs used as a destination therapy. The analysis was based on data relating to 52 of the 68 patients in the LVAD arm of the REMATCH randomized control trial. Institution-specific cost reports were used to calculate Ratio-of-Cost-to-Charges for each major resource category. Average annual in-patient costs were calculated by determining the average number of hospitalizations and associated costs per patient-day of LVAD support, and annualized to 1 year. Results of the cost analysis are summarized in Table 11.

Table 11: Cost of Left Ventricular Assist Support As Destination Therapy (Oz, 2003)[79]

| | Costs | Standard Deviation |
|---|---|---|
| **For the entire cohort** | | |
| Mean cost of initial implant-related hospitalization | US$210,187 | US$193,295 |
| Average annual readmission cost per patient | $105,326 | |
| | | |
| **For survivors for more than 1 year** | | |
| Mean cost of initial implant-related hospitalization | $159,271 | |
| Average annual readmission cost per patient | $ 99,118 | |
| Average annual cost per patient | $258,389 | |
| **For patients who did not survive the initial implantation** | | |
| | | |
| LVAD device cost | $62,308 (30%) | |
| ICU & regular floor cost | $69,062 (33%) | |
| Drugs | $15,685 (7.5%) | |

The analysis showed that the mean initial implantation cost was higher for patients who did not survive to discharge than for those who survived ($315,015+/-278,731 vs $159,271+/-106,423), partly because of increased length of stay. Sepsis, pump housing infection and perioperative bleeding were the major drivers of implantation cost. Without these complications, the predicted implantation cost would be $119,874. Sepsis alone would add approximately $140,000 to the implantation hospital cost. If all three of the above adverse events were present, the implantation hospital cost would be expected to reach $869,199.[78;79]

The 52 patients had a total of 18,406 LVAD supported days with 14,510 days being out of the hospital. There was an average of 4.5 readmissions per patient totaling 1,634 hospital days. Sixteen patients required 17 LVAD during the follow-up period. The average annual readmission cost per patient was $105,326 for the entire cohort and $99,118 for the patients who survived more than 1 year. The average implantation and average annual readmission cost together was $196,116 for patients who survived more than 1 year and $309,273 for the entire cohort.[78]

## Synopsis of Findings on Effectiveness and Cost-Effectiveness

There are significant limitations with regards to data from the Canadian setting. The following are based mainly on level 3 and level 4 evidence.

## Safety and Effectiveness

Bridge to Transplant

- Level 3 evidence from prospective comparative studies suggests that LVAD support improved the survival rates of heart transplant candidates waiting for a suitable donor heart when compared to optimal medical therapy (71% for LVAD and 36% for medical therapy). Since there were no randomized controlled trials, no definitive conclusion can be drawn. The survival rates from observational studies were consistent with those of the prospective comparative studies.

- Pre-implant respiratory failure associated with septicemia, pre-implant ventilation, right heart failure, and patient age greater than 60 years were found to be independent risk factors for increased mortality after LVAD implantation.

- LVAD bridging appears to improve the New York Heart Association functional classification and the quality of life of patients. Overall, the quality of life for patients with LVAD implantation was rated superior to QOL of a patient with advanced heart failure without LVAD support, but inferior to the QOL of a heart transplant survivor.

- Three studies reported that 41 - 49% of LVAD patients were able to be discharged from hospital and receive follow-up care as outpatients while waiting for heart transplantation; however, more than 50% required re-admission for adverse events or device malfunction.

- Post-transplant survival rates for LVAD-bridged patients were similar to or better than survival rates of patients who did not receive LVAD bridging prior to heart transplant. Evidence suggests that elective pre-transplant LVAD support improved post-transplant survival from 70% to 90%.

- VAD can be used as a complementary technology to extracorporeal membrane oxygenation to support children waiting for a heart transplant. Outcomes are better for patients with cardiomyopathy and myocarditis than for congenital heart defects and postcardiotomy. Limited evidence suggests that the survival rates on VAD support for pediatric patients with cardiomyopathy and myocarditis were comparable to those reported for adults.

Bridge to Recovery

- The use of LVAD as a bridge-to-recovery has been limited and, particularly in patients with post-cardiotomy shock, has been less successful than bridge-to-transplant. The median survival rate is approximately 26%. The largest series reported that 17% of 95 patients with heart failure from nonischemic idiopathic dilated cardiomyopathy were weaned successfully from LVAD.

- Patients with acute heart failure who received implantable mechanical assist devices for bridge-to-recovery often became candidates for heart transplantation or remained on LVAD for an extended period.

LVAD as Destination Therapy

- Level 2 evidence showed that HeartMate VE LVAS®, when used as an alternative to heart transplantation, significantly increased the one-year median survival time of patients who were not eligible for heart transplantation when compared to inotrope-bridged patients (relative risk reduction in mortality 48%).
- This survival benefit is associated with serious adverse events (2.35 times higher than the controls) and hospitalization throughout the course of the study.
- The two-year survival rate for LVAD patients decreased to 23%; however it was still significantly better than that of the inotrope patients (8%).
- The leading causes of death were sepsis (41% of all deaths) and device failure (occurred in 35% of patients and accounted for 17% of all deaths).
- The long-term effect of using LVADs as an alternative to transplantation is still unknown.

Adverse Events Associated with LVAD Support

- Major adverse events experienced by LVAD patients include:
  - Infection: At a median rate of 53% (range 6-72%), and predominantly involves the drive-line, the pump and other organs. Sepsis has been reported in 3.8–14% of patients and is one of the major causes of death related to the device.
  - Multi-organ failure.
  - Bleeding occurred in 8.6% to 48% of the patients (median 35%), depending on the type of device and anticoagulant regimen.
  - Thromoembolic event (5–37%) is another important cause of mortality on LVAD.
  - Right heart failure in 11% to 20% of LVAD patients, resulted in a 44% reduction in successful bridging rate when compared to that of LVAD patients without right heart failure.
  - Neurologic events occurred at rates ranging from 7% to 28%.
  - Hemolysis 6% to 20%.

- Device failure/malfunction, mainly involving the external components (console or cable), has been identified as a serious adverse event and is often the cause for hospital readmission. A prospective study reported a device malfunction rate of 1.55/patient in the first year with 9% of patients having to use backup components. Fatal mechanical failure has been reported to occur in approximately 1% of patients in short-term LVAD support. However, it became the second leading cause of death in long-term support.

- The use of LVAD support raised ethical issues because of the implications of future explantation, which could be perceived as withdrawal of life support.

**Cost-Effectiveness**

- Reports from the US and Europe showed that the LVAD is a costly procedure, mainly because of the high device cost ($90,000 - $98,000Cdn each), and costs associated with the initial hospitalization and hospital readmission for complications and device malfunction.

- Although LAVD support has been shown to reduce the length of stay in the ICU and the hospital, this technology would not be cost-effective until the cost of the device becomes significantly lower and the rates of adverse events are reduced. The estimated cost-effectiveness ratio of the elective use of LVAD as a bridge-to-transplant in Canada is $91,000 to $117,000Cdn per adjusted quality life year.

# Appendices

### Appendix 1A: New York Heart Association NYHA Functional Classification of Heart Failure

| Class | NYHA functional classification |
|---|---|
| **I** | Patients with cardiac disease but without resulting limitations of physical activity. Ordinary activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain. Symptoms only occur on sever exertion. |
| **II** | Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity (e.g. moderate physical exertion such as carrying shopping up several flights of stairs) results in fatigue, palpitation, dyspnea or anginal pain. |
| **III** | Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity (i.e. mild exertion) causes fatigue, palpitation, dyspnea or anginal pain. |
| **IV** | Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased. |

### Appendix 1B: Ontario Heart Transplant Algorithm

Definition of Medical Urgency (As of May 2001) **[www.OrganDonationOntario.org]**

| | |
|---|---|
| Status 0 | Patient is on hold, accruing waiting time, but not active on the list due to hospitalization or other complication that would interfere with surgery. |
| Status 1 | Patient is waiting at home (out of hospital or residing in a hospice).. |
| Status 2 | Patient is in hospital requiring daily nursing and physician care. |
| Status 3A | Patient has ventricular assist device (VAD) or intravenous inotropes on ward. |
| Status 3B | Patient is on intravenous inotropes and in ICU and invasive cardiac monitoring. |
| Status 4 | Patient is on mechanical ventilatory or circulatory support and in ICU. |

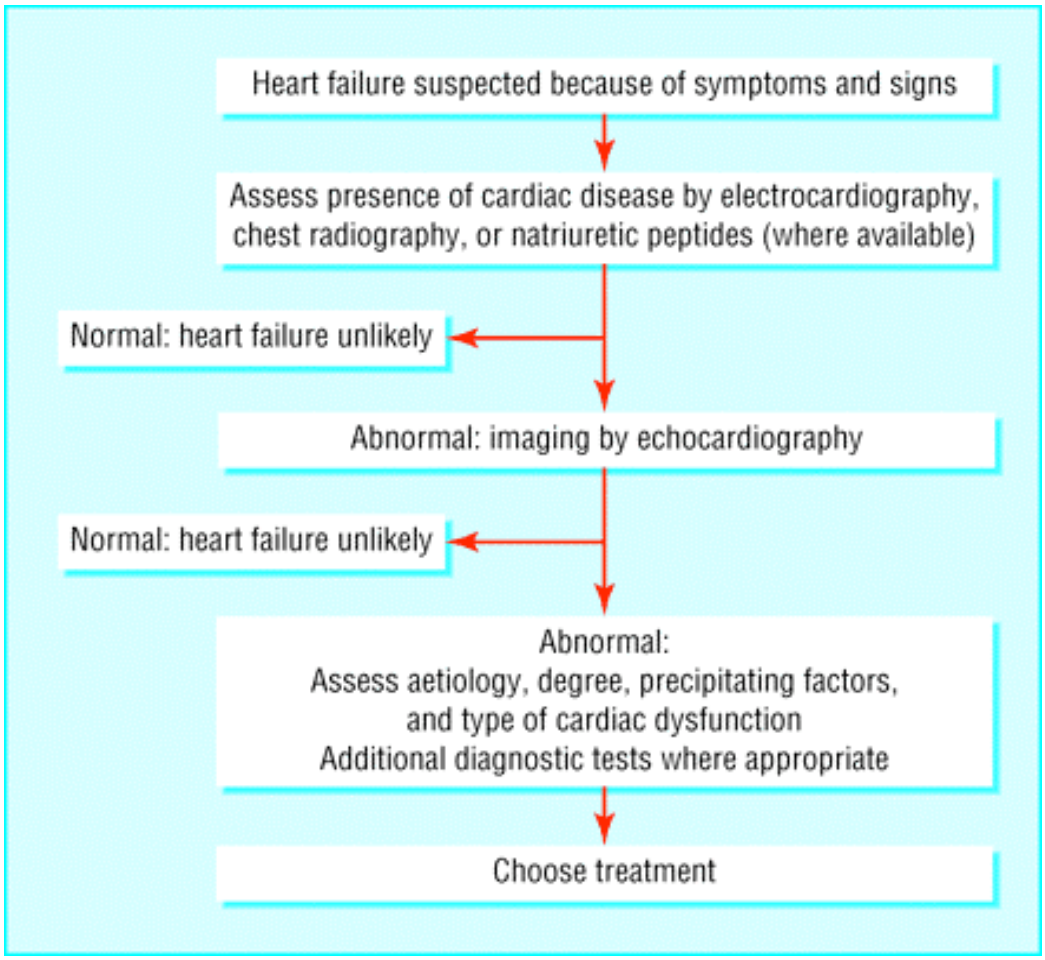
(www.OrganDonationOntario.org)

## Appendix 2: Current United Network for Organ Sharing [UNOS] Status Codes for Heart Transplant Allocation[3]

| | |
|---|---|
| Status 1A | **Adul**t - Registrant at least 18 years of age, admitted to listing hospital with at least one of the following:<br>(a) mechanical circulatory support for acute hemodynamic decompensation with VAD 30 days or less, TAH, balloon pump or ECMO;<br>(b) mechanical circulatory support with objective medical evidence of significant device-related complications;<br>( c) mechanical ventilation;<br>(d) continuous infusion of a single high-dose intravenous inotrope or multiple intravenous inotropes, in addition to continuous hemodynamic monitoring of left ventricular filling pressures; or<br>(e) meeting none of the criteria specified above but admitted to the listing hospital with a life expectancy without a heart transplant of less than seven days.<br>**Pediatric** - registrant less than 18 years of age and meets at least one of the following criteria:<br>(a) requires assistance with a ventilator<br>(b) requires assistance with a mechanical assist device;<br>(c) requires assistance with a balloon pump;<br>(d) is less than 6 months old with congenital or acquired heart disease exhibiting reactive pulmonary hypertension at greater than 50% of systemic level;<br>(e) requires infusion of high dose or multiple inotropes or<br>(f) meets none of the criteria specified above but has a life expectancy without a heart transplant of less than 14 days. |
| Status 1B | **Adult** - A registrant who<br>(a) has a left and /or right ventricular assist device implanted for more than 30 days ; or (b) receives continuous infusion of intravenous inotropes<br>**Pediatric** - A registrant who<br>(a) requires infusion of low dose single inotropes<br>(b) is less than 6 months old and dose not meet the criteria for status 1A or<br>(c) exhibits growth failure |
| Status 2 | A patient of any age who does not meet the criteria for status 1A or 1B |
| Status 7 | Temporary unsuitable to receive a thoracic organ transplant. |

[3] Policy 3.7 of United Network for Organ Sharing
http://www/transplantliving.org/PoliciesandBylaws/Policies/doc/Policy3.7.doc

**Appendix 3: Algorithm for the diagnosis of heart failure***




**Reprinted from European Heart Journal, Vol. 22(17); Remme WJ, Swedberg K; Guidelines for the diagnosis of Heart Failure; p. 1527-1560, Copyright 2001, with permission from Oxford University Press*

## Appendix 4: Illustration of Novacor® LVAS*

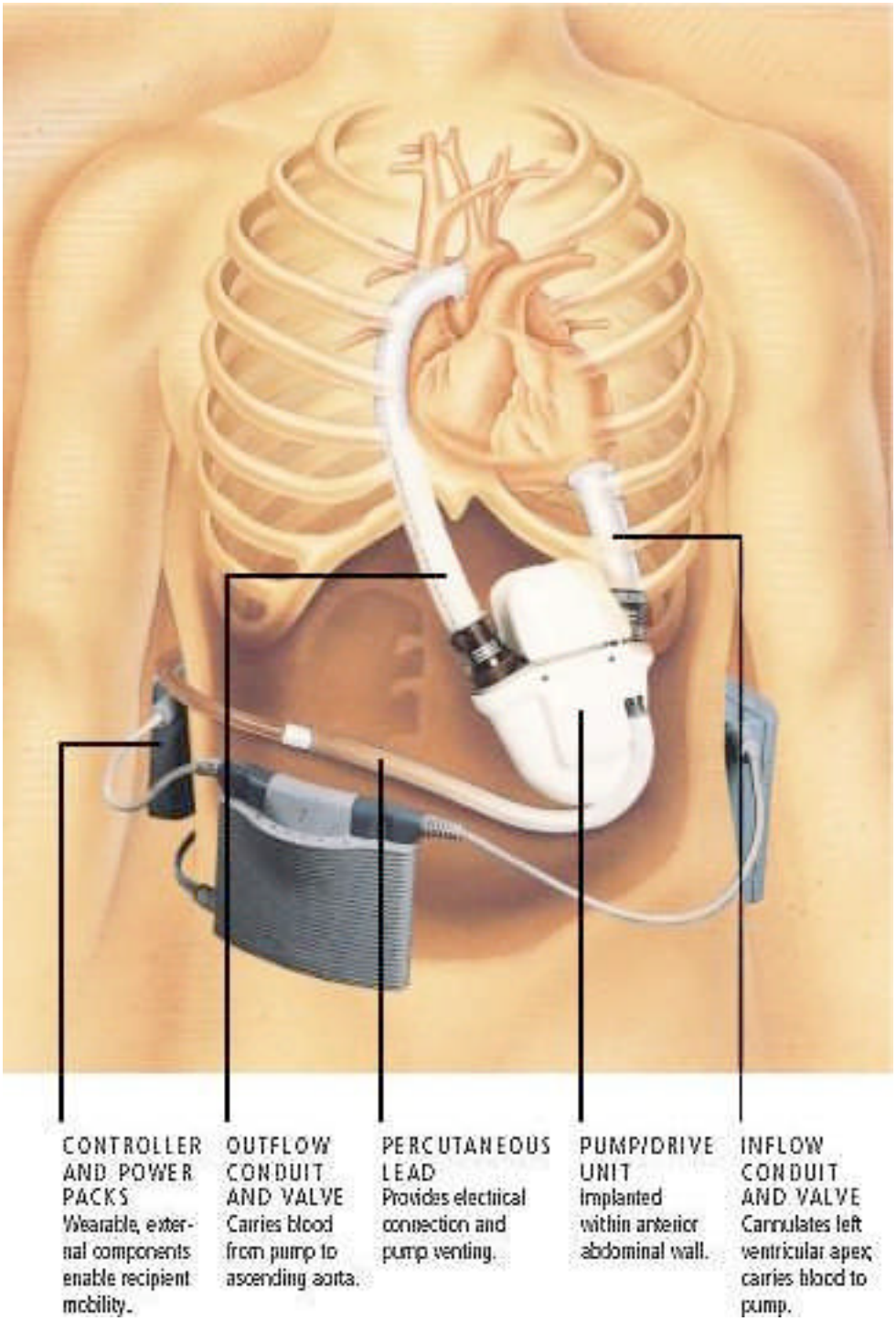



**Image retrieved from http://www.worldheart.com/products/novacor_lvas_works.cfm*

## Appendix 5: Thoratec® Bi-ventricular VAD*

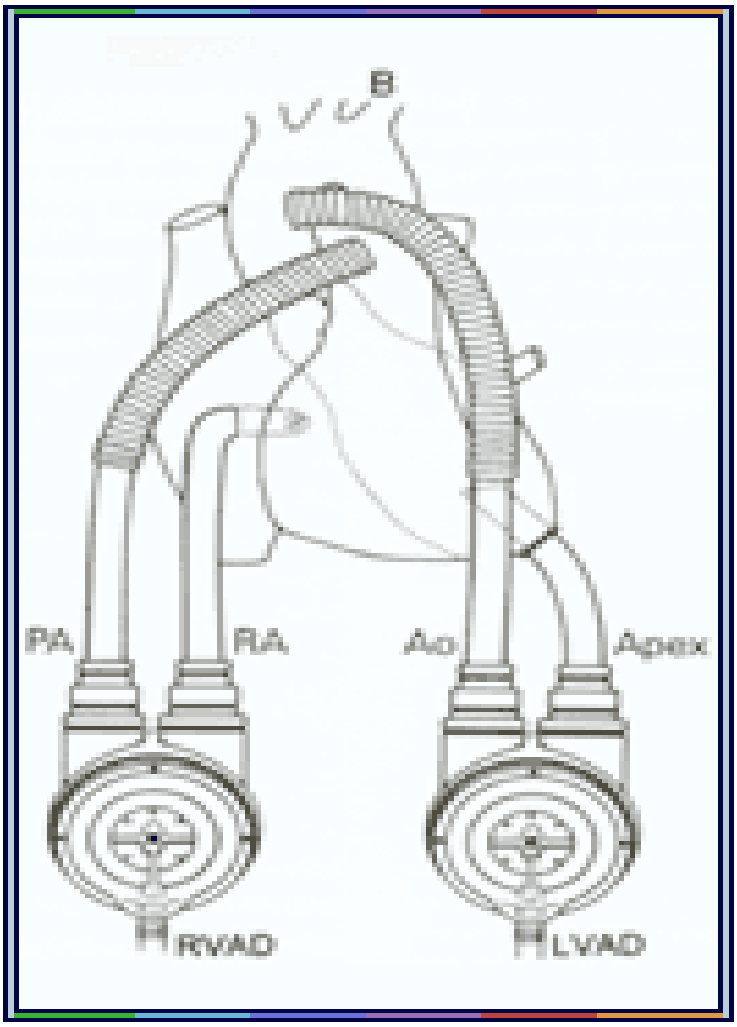



**Image retrieved from http://www.thoratec.com/ventricular-assist-device/thoratec_vad.htm*

## Appendix 6: Inclusion/Exclusion Criteria of Comparative Studies on Bridge-to-Transplant

| Study | Inclusion Criteria & Exclusion Criteria |
|---|---|
| Frazier 1995[19] (Prospective with concurrent controls)<br><br>Aug 1985 - Sept 1993 | **Inclusion Criteria**<br>LVAD group & control met the same criteria:<br>➢ Approved (listed) transplant candidate (required)<br>➢ Current inotropic therapy (required)<br>➢ Intra-aortic balloon pump support (if possible)<br>➢ Left atrial pressure or pulmonary capillary wedge pressure >/=20 mm Hg combined with either:<br>- systolic blood pressure </=80 mm Hg or<br>- Cardiac index</=2.0L/min/$m^2$<br>LVAD & controls were similar in terms of age, sex and distribution by diagnosis.<br><br>**Exclusion Criteria**<br>LVAD & control:<br>➢ Body surface are <1.5 $m^2$<br>Any medical condition that would exclude the patient from transplant |
| Frazier 2001[20]<br>Feb 1996 - Sept 1998 | (Prospective with historic control)<br>Same as above. |
| Novacor study to FDA 1998 [21]<br><br>(Prospective with concurrent control)<br><br>Mar 1996 - June 1998 | Prospective multicenter non-randomized study<br>**Inclusion Criteria**<br><u>LVAS: (156, 104 core)</u><br>➢ NYHA Functional Class IV heart failure<br>➢ United Network Organ Sharing Status I candidates for cardiac transplantation<br>➢ 14-68 years old<br><u>Controls (35)</u><br>➢ Met the above criteria<br>➢ Treated with conventional medical therapy because a device was not available or chose not to accept a device.<br>Trial success = survived to 30 days after transplantation with acceptable neurological function and be NYHA functional class III or better and had an average pump index of 2.0 L/min/m2. |
| Aronson et al, 2002 [22] (retrospective)<br><br>Apr 1996 - May 2001 | **Inclusion Criteria**<br>LVAD group: no information on selection criteria<br>Controls:<br>➢ United Network for Organ Sharing (UNOS) status 1, 1A or 1B waiting list status<br>➢ Bridged exclusively with one or more IV inotropes administered continuously in the hospital or at home. |
| Bank et al 2000 [26] (retrospective, concurrent controls)<br><br>Jan 1995 - Sept 1998 | **Inclusion Criteria**<br><u>LVAD (20)</u><br>➢ On status 1 heart transplantation<br>➢ Initially received same medical therapy as the control in the ICU but developed significant clinical deterioration (worsening & severe low output heart failure, refractory pulmonary edema or oliguric renal failure.<br><u>Inotrope (20)</u><br>➢ On status 1 heart transplantation<br>➢ Managed by IV inotropic agents dobutamine or milrinone in an intensive care unit while standard heart failure therapy of angiotensin converting enzyme inhibitor, diuretics and digoxin was continued.<br>**Exclusion Criteria**<br>➢ Severe right heart failure<br>➢ Histories of several previous sternostomies<br>➢ Presence of prosthetic heart valve<br>Congenital heart disease. |

| Study | Inclusion Criteria and Exclusion Criteria |
|---|---|
| Jaski, 2001[25] (Prospective database)<br><br>Jan 1990 - Dec 1997 | Retrospective review of data from the Cardiac Transplant Research Database (prospectively collected data on total heart transplants from multi institutions (1990-1997 followed to 1998).<br>**Inclusion Criteria**<br>LVAD: all patients >/=18 years of age who received LVAD support at the time of transplant (no information on selection criteria for LVAD).<br>Inotrope<br>Patients >/=18 years of age, classified as UNOS status 1 and treated with IV inotropic therapy (dobutamine, dopamine, milrinone, etc) at the time of transplant. These were chosen because their baseline clinical characteristics more closely matched those of the LVAD group. |
| Massad, 1996[27] (Retrospective study with concurrent controls | Retrospective cohort study with concurrent controls<br>Inclusion criteria<br>LVAD<br>➢ Accepted transplant candidates<br>➢ Pulmonary capillary wedge pressure of 20 mm Hg or greater<br>➢ Maximal inotropic and intraaortic balloon pump<br>➢ Despite the above treatment, had either a cardiac index =/< f 2.0 L/min/$m^2$ or a systolic blood pressure =/< 80 mm Hg |

## Appendix 7: Post LVAD Implant Survival Rates and Transplant Rates

### Survival Rates after LVAD Implant

| Study | Survival Rate |
|---|---|
| Holman 1997 | 58% |
| Meyns 2002 | 64% |
| Deng 2000 | 64% |
| McBride | 64% |
| Holman 2002 | 67% |
| Di 2000 | 69% |
| Navia 2002 | 71% |
| Frazier 2001 | 71% |
| DeRose 1997 | 73% |
| Oz, 1997 | 74% |
| Sinha 2000 | 74% |
| Sun, 1999 | 75% |
| Vitali, 2003 | 75% |
| McCarthy 1998 | 76% |
| Loisance 2000 | 81% |
| Baxter 1998 | 81% |
| Granfeldt,2003 | 81% |
| Aaronson, 2002 | 82% |
| Bank 2000 | 90% |

### Heart Transplant Rates on LVAD Support

| Study | Transplant Rate |
|---|---|
| Loisance2000 | 39% |
| Oz 1997 | 52% |
| Deng 2000 | 56% |
| McBride 1999 | 58% |
| Di 2000 | 64% |
| DeRose1997 | 64% |
| Frazier 2001 | 67% |
| Navia 2002 | 68% |
| Sun 1999 | 70% |
| Vitali 2003 | 71% |
| Frazier 1995 | 71% |
| Sinha 2000 | 71% |
| Aaronson 2002 | 73% |
| McCarthy 1998 | 76% |
| Granfeldt 2003 | 76% |
| Griffin 1996 | 77% |
| Baxter 1998 | 78% |
| Massad 1996 | 80% |
| Bank 2000 | 90% |

## Appendix 8: Summary of Observational Studies on LVAD

| Author & year | Period of inclusion | No. of patients | Device/ Mean support in days | Study Design | Death on LVAD | Explanted (%) | Waiting for transplant | Trans-planted | Survival after transplant (%) | Bleeding On LVAD | Infection on LVAD | Thrombo-embolism On LVAD | Right heart failure |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bentz 2004 [43] | 1985 - 2000 | 90 | Novacor® HeartMate® | MonoC Case series | | | | | | HeartMate 14.3% Novacor 9.6% | Heartmate 28.6% Novacor 10% | HeartMate 10.2% Novacor 26.8% | Tamponade HeartMate 6.1% Novacor 4.9% |
| Vitali 2003[44] Italy | 1992-2001 | 53 BTTx | 4 different devices 2.8 months | MonoC case series | 24.5% | 1/53 | 3.7% | 71.1% | 91.9% @ discharge | Major 16.9% Pocket 9.4% | Sepsis 5.6% | Neuro 26.4% Major 11.3% | Severe 1.88% Renal failure 13.2% Liver failure 22.6% |
| Granfeldt 2003[45] Sweden | 1993-2002 | 59 BTTx | Heart mate ® 91.5% 99.5 days | MultiC (5) Retrospectiv e | 18.6% | 6.8% (1.7% had transplant) | 0 | 76% | Not provided | 33.9% reoperated | Overall 44% | 10% transient neurologic | 19% |
| Holman 2002 US[34] | 1997-2001 | 46 (53 devices) | HeartMate Thoratec® 138 days | Retrospectiv e review LVAD patients | 33% | | | | | | | | |
| Meyns, 2002[8] Belgium | 1988 - 2000 | 165 | Novacor® ABIOMED® | MonoC case series | 36% | | | | 5 yr survival 82% | 38% | | 11% | |
| Navia 2002[28] | 1991-2001 | 264 | HeartMate Novacor® | MonoC case series | 29% (1 yr) | 0.7% | 2.5% | 68% | | | 1.88/pt @ 6 mos | 0.3/pt @ 6 mos | |
| Di, 2000[80] Italy | 1992- ? | 36 | Novacor ® 203 days | MonoC case series | 30.5% | 0 | 5.5% | 64% | 69.5% | | 20% device rel | Neurologic 15% | |
| Loisance 2000[50] Europe | ? - 1999 | 36 | Novacor® 1.49 years | MultiC Retrospectiv e registry | 19% | 8% | 34% | 39% | ? | | | | |
| El-Banayosi, 2001[31] | 1987-2000 | 283 26% disch | HeartMate Novacor® Thoratec® | MonoC, Case series 53-154 D | | | | | | 22% - 35% | 7% - 30% | Neurol 7 - 28% | 15% - 26% Liver F 11-20% |
| Deng, 2000[75] | 1993-1996 | 39 bridge-to-transplant | Novacor® HeartMate( 98 days | MonoC case series | 36% (14) | 0 | 7.6% (3) | 56.4% (22) | Actuarial 82% | Intracranial bleed 2, | | Ischemic CV 15% of deaths | Multiorgan failure 6 43% of deaths RHF 6% of deaths |
| Sun, 1999 US [81] | 1990-1997 | 95 | HeartMate® 108 days | MonoC case series | 25% | 4% | 1% | 70% | 100% | 9.5% device rel. | 25 device related | CVA 7.4% - 6/7 died | |
| McBride 1999[59] US | 1982-1998 | 67 | Thoratec® 40.7 days | MonoC case series | 37% | 5% weaned | 0 | 58% | 100% | 31% | 18% dev related | 8% | |
| McCarthy, 1998, US | 1991-1996 | 100 | HeartMate® 70 days | MonoC case series | 24% | | | 76% | | | 59% + blood cult. | 2% | Catastrophic dev failure 12% pts |
| DeRose, 1997[18] US | 1993 - 1997 | 85 | HeartMate® 109 ays | MonoC case series | 27% | 4% | 5% | 64% | 100% | | | | |
| Oz, 1997[18] US | 1990-1995 | 58 | HeartMate® 98 days | P Mono case series | 26% | 3% | 19% | 52% | 100% | 8.6% graft rel. 2 died | 53% clinical | 5% | 33% |
| Holman, 1997[18] US | 1989-1996 | 38 | Thoratec® | MonoC case series | 42% | 8% | | | 100% | | | | |
| Griffith, 1996 | | 162 | HeartMate® Novacor® Thoratec® | MonoC Case series, R | | | | 77% | 93% | | | | |

## Appendix 9: Summary of Literature on Economic Analysis

| Review/Study | ANAES HTA<br>April 2001 (France) | AETMIS HTA<br>2000 (Quebec) | Wessex Institute HTA, 1999 (NHS) | CEDIT 1998 (France) |
|---|---|---|---|---|
| **Cost analysis** | No study on cost-effectiveness<br>Initial hosp: device cost, diagnosis, exams, ICU, determine resource consumption; however may reduce certain expenses by reducing ICU stay & post transplant recovery time<br>Ambulating patients on Transplant list make rational use of resources | Elective bridge-to-transplant: CD$91,000-$126,000 ($117,000-$186,000 discounted @ 5%) per life year. $1.4 M if used in 10 pts per year.<br>Alternative to transplantation: emergency $52,000, elective $60,000 per life year ($58,000-$68,000 discounted).<br>$570 M for 1,500 pts/ year after 12 yrs | LVAD device & procedure: US$62,480 (CD$97,470)<br>Cost utility- bridge-to-transplant: $ of LVAD+transplant per QALY discounted at 1.5%: $39,790 (CD$62,070)<br>Sensitivity analysis over 20 years: range: $28,510-$74,000 (CD$44,476-$115,440)<br>Cost of device & procedure need to be approx.$19,300 (CD$30,108) per person for acceptable cost utility ratio. | Equipment costs for 21 VAD systems installed in 1997 was 5 million francs.<br>1 single-use VAD without control consoles :<br>Thoratec - 117,000 FF<br>Novacor II - 346,000 FF<br>The real cost of installing a VAD system is estimated to be similar to that of heart transplantation. |

| Study | Arabia FA et al ASAIO 1996 (US) | Bank AJ et al, 2000 (US) |
|---|---|---|
| **Cost analysis** | Cost analysis of outpatient bridge-to-transplant using Novacor system based on 3 cases:<br>-Average daily hospital admission cost for prior to implant = US$2,240<br>-Average pre-implant hospitalization = 14.6 days (7-21 days)<br>-Average pre-implant hospitalization costs = 14.6 x $2,240 = US$32,704<br>-Average daily hospital cost after implant = US$1,570<br>-Average hospital stay after implant=75 days (58-86 days)<br>-Average post implant hospitalization cost = 75 x $1,570 = US$ 117,750<br>-Pt without LVAD=$4,100 per day in ICU (ICU charges 3x as high as LVAD pts because of inotropic agents, intraaortic balloon pump & intermittent mechanical ventilation), $2,200 per day in intermediate care unit. --Pt without LVAD survived to transplant but required 3 months of physical rehabilitation.<br>-Number of post implant outpatient days = 4, 5 and 78 days representing saving of US$2,632, $5,922 and $132,124 for the three patients??. | Cost analysis of HeartMate LVAD implantation in status 1 (critically ill) patients for bridge-to-transplant (n=40)<br>-Average hospital charges from listing as status 1 until discharge after transplant = US$343,000<br>(2 other sites US302,000 till after transplant, $244,000 for up to time of transplant)<br>-Overall inpatient charges significantly greater in LVAD group (consistent finding).<br>-Factors for higher charges for LVAD pts included:<br>• cost of LVAD approximately US$50,000,<br>• implant procedure cost approx. US$23,000<br>• Longer hospital stay before heart transplant (put on inactive transplant status after LVAD implant until recovered & extensive cardiac rehab) 77+/-42 days vs 42+/-30 days for non-LVAD pts.<br>-Factors that decrease the inpatient cost of the LVAD group:<br>• Shorter ICU stay before heart transplant (15+/-11 days vs 42+/-30 days for non-LVAD pts)<br>• Decreased post-transplant complications<br>• Potential saving as outpatient for $4130/day |

## Appendix 9: Summary of Literature on Cost-Effectiveness of LVAD (continued)

**McGregor 2000 (Review) **Canadian estimates**

Converted costs of LVAD implantation from Gelijns et al to Canadian currency using exchange rate of CDN$1=US$0.65
-Total direct cost of LVAD implantation excluding device (US) =CDN$113,740
-CEDIT reviewers estimated cost of LVAD implantation would be comparable to cost of cardiac transplantation (1998 Canadian study) = CDN$48,443 (43% of US cost) UK study ($50,760) - assumed to be the cost of LVAD implantation in Quebec.
-Cost of HeartMate & Novacor approx. $94,000 & $90,000).
Hospital monitor ($62,000) & personal monitor ($31,000) are reusable. If each hospital monitor was used for 30 pts, it would add $7,000 to each implantation.
-Total estimated cost of each implantation in Canada (Novacor) =$138,443+7,000 =$145,443.
-Cost of maintaining a pt with successful LVAD implantation according Gelinjns equivalent to = CDN$77/day including cost of hospital admissions.
Assuming Canadian cost would be 50% of US cost, Canadian cost of maintaining a patient on LVAD = $38/day or $3,800 for 100 days before transplant.
When used in emergency context, the alternative would be death within days.

100 implant cost =100x $138,443
70% survive implant =70x$3800
Total = $14,110,300 for 70 transplants
Additional cost/transplant for LVAD =$14,110,300/70=$201,576
Cost effectiveness cannot be reliably estimated on the basis of these data.

**Cost-effectiveness scenario**
Bridge-to-transplant (emergency implantation) As long as LVAD is used as a bridge to transplant, save no additional lives, save only different lives, therefore impossible to estimate cost-effectiveness.
Bridge-to-transplant (Elective implantation):
LVAD support of severely compromised patients results in improved transplant survival rates. The extent of improvement varies according to clinical status & is hard to predict.
Study Novacor survival rate 91%, pooled International Society of Heart & Lung Transplantation data 77% with no LVAD support. (Jouveshomme S. et al Dossier CEDIT 1998, Setp:35).
CEDIT reviewers estimated based on the above data that LVAD would raise the five-year post transplant rate from 70% to close to 90%.
However, some studies have shown that survival after LVAD implantation may be less than 70%, and improvement in transplant survival rate due to prior LVAD support may be less than 20% points.
When used electively for patients on transplant list, may save some cost of medical management. Factors: how many patients would live and for how long.
If case selection is such that of 100 patients comparable with those with a device implanted, 75 would have lived on average of one year without LVAD support, then the years of life saved by the procedure would be reduced from 260 to 185.

143 LVAD implant to have 100 survive to transplantation (70% survival), transplant survival improve from 70% to 90%
143 LVAD save an additional 20 lives, each with expected survival of 13 years after 1st year.
Cost of implant [(48,443+90,000) x 143] + cost of transplantation & 13 year maintenance for the additional 20 pts [(48,443x20)+($10,000x20x13)] = $23,746,209
**Total live years saved = 20 x 13 = 260 life-years.**
**Cost effectiveness =$91,332 per year of life or $117,197 discounted at 5%.**

Intensive care cost avoided $50,000 for maintenance of a single patient supported by a centrifugal pump for 11 days. (1998 Canadian study, personal communication by McGregor)

Bridge-to-recovery, cannot be estimate because cannot predict which patient would recover cardiac function as a result of LVAD support.

Permanent alternative to transplant:
*Emergency:* assuming (70% survival for LVAD implant with 3%/yr mortality and re-implant at end of 4th year that has mortality rate of 10%. 40% survival by the end of 12 years, $70,903 per life-year or $67883 discounted pre life-year.

Cost effectiveness of the use of LVAD is highly variable depending on the circumstances of use and assumptions made for each estimate. Without sensitivity analysis of most of the input variables, and only considering direct costs to the health care system:
-Bridge to transplant, emergency- cannot be estimated due to lack of donors, no additional life saved.
-bridge to transplant elective interventions 91,000 (discounted $117,000) per life-year.
As alternative to transplant, emergency: $52,000 discounted $50,000
*Elective*: $71,000 (discounted 68,000)

**Economic impact of bridge-to-transplant:**
Transplant rate in Canada is approx. 150/year. If LVADs are used in 1/3 of transplant patients (50) per year, the cost of LVAD implant and maintenance would be $7 million per year for Canada. Amortized cost of hospital monitors would be $ 62,000 per centre per year and $1,550,000 for 50 personal monitors per year.

**Economic impact of permanent alternative to transplant**: (US estimated 60,000 new LVAD implants per year)
Proportionally, this would be the equivalent of approximately 6,618 new implants per year in Canada.

7,000 new implants per year would involve an annual expenditure of nearly $2,660 million with maintenance of approximately 44,000 patients by the end of 12 years. Until cost falls substantially, the economic impact of unrestricted use of LVADs would be considerable.

**Gelijns AC et al , 1997 US**

Retrospective inpatient & outpatient cost study using actual charges & ratio-of- cost- to- charges (based on 12 patients on HeartMate LVAD, average LVAD days=177).

| **Average Initial Implant -related Hospitalization costs (Actual)** | | **(Clinically sufficient)** |
|---|---|---|
| Inpt cost (regular) | $23,569 +/- 34,047 | $$7,071+/-7,376 |
| Inpt cost (special care) | $15,094 +/- 1762 | $14,765+/-10,874 |
| Operating room | $10,926 +/- 1,762 | $10,818+/-1,725 |
| Diagnostics | $ 4307+/- 3,505 | $3,900+/-3,574 |
| Laboratory | $4,450+/- 1,549 | $3,407+/-1,767 |
| Blood products | $2,955+/- 2,509 | $2,873+/-2,562 |
| Drugs | $3,817 +/- 3,666 | $3,257+/-3,229 |
| Rehabilitation | $1,877+/- 1,619 | $ 670+/-423 |
| Other | $3,345 +/- 1,720 | $3,235+/-1,695 |
| Profess. Payment | $24,203+/- 10,897 | $23,935+/-10,897 |
| LVAD cost (MLP) | $67,085 | $67,085 |

**Total actual cost $161,627 +/- $26,932**
**(Average)**
**Average actual length of stay = 43.5 days**

**Average total cost (with clinically sufficient length of stay of 17.5+/-5.32 days) = $141,287 +/- (including LVAD device)**
Average outpatient days = 211
11 readmission for 5 pts total: 127 hospital days
Total readmission cost = $ 282,178

**Outpatient costs (based on 6 patients)**
Average no. of days using device 288.3days
Clinically sufficient initial hospital days 17.2
Readmission hospital days (5 pts) 127 days
Average readmission hospital days per pt 21.2 days (8.5% of total outpatient period)
Average total hospital days per pt 38.4
Average outpatient days 250
Total readmission cost $282,178
Average weekly professional payment for 4 patients $128
Cost of weekly laboratory tests & drugs $224

Total cost of support per week (lab tests, drugs & professionals fees) $352
Average out patient days 211 (16-328)

**Average actual total cost for an LVAD recipient over a 9.5 month period (inpatient + outpatient) = US$221,313**
If inpatient costs were restricted to the clinically sufficient period, the average cost per patient over 9.5 months =US$201,148 equivalent to $698 per LVD supported day (includes additional outpatient visits that would have been required if there had been an earlier hospital discharge).

**Assuming clinically sufficient initial hospital stay and 8.5% of total outpatient days as readmission 7, projected annual costs of LVAD support would be $219,139 (for patients who would not qualify for transplant).**

Comparing 12 HeartMate VE pts with 50 HeartMate IP (older model)
4 right ventricular failure among the first 10 pts vs 10% in among the last 10 patients.

Program experience is correlated inversely with ICU stay. Since ICU stay is among the most costly component of the implantation hospital stay, anticipate a cost reduction related to further growth in institutional skill & experience.

The waiting period for heart transplant in US increased 30% from 1988 to 1994, resulting in longer pre-transplant hospital stay. At some point, the substantial initial cost of implanting an LVAD may be counterbalanced by the additional costs of hospitalizing transplant candidates awaiting donor hearts. When that happens, LVAD bridging will be cost-effective and cost saving.

**Moskowitz AJ, 2001 " Cost of Long-Term LVAD Implantation" (Annals of Thoracic Surgery)**

Same study as Ggelijns
Initial hospital cost of LVAD implant (based on clinically sufficient stay) = $141,287+/-18,513
Outpatient: Average of each weekly visit (lab tests, drugs & professional payment) = $352/week = $18,304/year
Total of 11 admissions among 5 pts totaling 124 hospital days, total cost = $215,093
Readmission average of 2.5 days per month per patients after implantation discharge = $5,550/month =$66,600/year
Total LVAD postimplant hospital care = $81,420
Post cardiac transplant hospital care in year 1 = $63,237
Average total cost for LVAD therapy during year 1 = $222,460

Without professional fees, LVAD therapy cost for year 1 = $ 192,154
Without professional fees, heart transplant cost for year 1 = $176,605

**Considerations**: Heart transplantation is a mature treatment, whereas LVAD implantation is at this time an emerging technology; the length of stay and readmission rate for LVAD & cost of device (major components of overall costs) are expected to decrease over time.

Cost effectiveness Ratios for several medical interventions:

| Treatment | Incremental cost effectiveness ratio |
|---|---|
| Cholesterol testing and diet treatment: | $ 330/QALY |
| Pacemaker implantation | $ 1,650/QALY |
| CABG (Left main disease) | $ 3,135/QALY |
| Home hemodialysis | $ 25,890/QALY |
| Neurosurgery for malignant intracranial tumors | $161,170/QALY |

Cardiac transplant $37,0000 per life-year saved
First year cost of LVAD therapy is close to the first year cost of heart transplant. The second and subsequent year costs of heart transplant are considerably less. Important factors in generating later costs include rejection and coronary artery disease. The LVAD therapy costs for later years are not yet known. Device reliability and longevity will be important factors in determining costs during these years.

## Appendix 10: Assumptions for Ontario-based Cost Analysis

The following assumptions are made with regard to the Ontario-based cost analyses in section VI-4 (Based on information provided by UHN and McGregor, 2002):

- 80 people: Length of waiting list in Ontario for heart transplantation regardless of the adoption of LVAD technology. If the LVAD is adopted, then the length of the list may tend to lengthen; however, the length will be maintained by deciding to change the role of LVADs to a means of permanent coronary support in selected individuals--thereby removing these individuals from the waiting list.
- 20%: The annual rate of mortality of those on the waiting list for heart transplantation without LVAD support (approximately 16 die on waiting lists in Ontario per year).
- 80% of patients on the waiting list receive a transplant within one year = 64 in Ontario (80% x 80).
- 75% of patients surviving LVAD implantation would have died within one year had LVAD been unavailable.
- 33% of waiting list patients would potentially receive LVAD if it were available.
- 70% of LVAD recipients survive the procedure and go on to the wait list for transplantation.
- 90% of those re-implanted with an LVAD (i.e., after four years) survive the procedures.
- 5%: perioperative mortality rate for heart transplant recipients.
- 3% of those on LVAD support die annually after initially surviving LVAD procedure.
- 50% of LVADs are implanted in emergency cases (in which death would occur shortly in its absence) and 50% are used electively for deteriorating patients awaiting transplantation, but who might survive an average of one additional year without LVAD support.
- 4 years: average lifetime of each LVAD device.
- 100 days: average duration of LVAD support.
- 13 years: average expected survival after heart transplant and/or receipt of LVAD support.

Unit Costs:

- The cost of implanting an LVAD is the amount reimbursed by Priority Programs for Cardiac procedures: approximately $12,000 CDN.

- The device cost for the HeartMate LVAD is approximately $94,000 CDN.

- The direct medical maintenance costs for maintaining somebody permanently on LVAD for the average duration of 100 days is approximately $3,800.

- The direct medical maintenance costs for maintaining somebody permanently on LVAD for one year is approximately $14,000.

Average annual medical costs after heart transplantation are approximately $10,000 (includes anti-rejection drugs, etc.).

## Appendix 11: Summary of HTAs on LVAD

| Review/Study | ANAES HTA April 2001 (France) | AETMIS HTA 2000 (Formely CETs, Quebec) | Wessex Institute HTA, 1999 (NHS) Christopher F, Clegg A | CEDIT HTA 1998 (France) Jouveshomme S et al | Oregon Commission HTA, 1997 (US) |
|---|---|---|---|---|---|
| **Objective** | Assess LVAD as bridge or alternative to transplantation. | Assess efficacy & cost-effectiveness of LVAD | Assess effectiveness, cost & utility of LVADs for ESHF | Evaluate mechanical ventricular support systems (VADs) and to estimate the needs of the AP-HP. | Assess all VADs except intra-aortic balloon pumps & artificial heart. |
| **Methodology** | Syst. review: 18 efficacy studies (6 multicenter, 5 non-random compared with hx control, 13 case series), search 01/95-02/01 | Did not state the number and type of studies included | Systematic review based on 10 cohort studies & 619 pts (bridge to tx), 1 cohort study of 17 pts on bridge-to-recovery | | Systematic review included RCTs, non-random. CT & well-designed cohort/case controlled analytical studies 1993-1997, expert opinion |
| **Survival to transplantation** | 52 - 89%<br>Explanted: 0 - 8% | Approximately 70% of implanted pts | 3 of 4 studies suggested increased survival | | Level II evidence: effectiveness of VAD as: bridge-to-transplant |
| **Impact on NYHA functional class** | 3 series reported improvement after implantation | | 4 of 6 studies showed improvement, ? stat. significance | | |
| **Liver/renal function** | improved | | | | |
| **Hospital Discharge/release** | | | In 1 observ. Study, 5 of 17 patients had significant recovery of heart functions after 160-794 days | All 4 VAD systems have demonstrated efficacy - providing support for more than 100days pending transplant. | Level II evidence that VADs improved survival potential when used as bridge-to-recovery |
| **Device related adverse events** | Bleeding 3 - 31%<br>Infection 15-68%<br>Thromboembolism 5-25% | Bleeding requiring re-op 20-44%<br>Systemic or local infection 50% of pts<br>Thromboembolism | | Iatrogenic risk of VAD poorly evaluated because it is difficult to distinguish device related complications from those related to the severity of pt's clinical condition. | Bleeding 25%-50%, Infection 15% -50%, thromboembolism 10-25%, death 2-7%, neurologic: 10-20%, hemolysis 6-20%, organic dysfunction 5-50% |
| **Quality of life** | Improved; intermediate between patients not implanted & transplanted patients. | Many can return home, resume work & recreational activity<br>Overall QOL >pt in advanced heart failure, <transplant survivor. | 1 study suggested submaximal exercise capacity significantly better than that of dobutramine dependent patients | | |
| **Impact on transplant survival rates** | Implanted pts return to work more frequently & early after tx | May improve 5 yr rates from 70% to approx. 90% in elective cases | | Transplantation rate > 60%<br>Global 1-year survival > 50% | Level II evid: not significantly different in VAD bridge to tx patients. |
| **Issues identified** | May appear expensive from point of view of hospital. Need to consider opportunity cost. | Ethical, research, centralization in single heart transplantation centre, access (network), budget & evaluation | Need good quality research particularly from a UK perspective. | | Need better quality research on long-term effectiveness, appropriate protocol, clinical & cost-effectiveness. |
| **Conclusion/ Recommendation** | Weak study methodology<br>LAVD implant associated with survivals of 52-89%; improved functioning capacity, functions of other organs & quality of life.<br>LVAD assoc. with significant morbidity from complications<br>Few data available re LVAD as alternative to transplant<br>Recommended registry for advanced heart failure, for 1 stage network responsible for patients & a Homogenous Disease Group for clinical & economic evaluation. | Demonstrated effectiveness<br>Not ethically acceptable to refuse all access on grounds of cost alone.<br>Reasonable to initially limit LVAD for use as a bridge-to-transplantation or to rescue cases in cardiogenic shock who would otherwise be fatal (est. 10/yr for Quebec)<br>At present, use of LVAD as a permanent substitute for transplantation would lead to inappropriate use of resources.<br>Will be difficult to limit the use of LVADs because of social, political & medical pressure to expand its use. | For bridge-to-transplantation, although there was suggestion of potential benefits, particularly from hemodynamic studies, the evidence was not of sufficient quality to reach a decision;<br>In the case of LVAD as a long-term alternative to transplantation, there is as yet no good evidence of effectiveness in this setting. | VAD systems have been sufficiently well evaluated in their indication as a bridge pending transplantation in patients in a state of cardiogenic shock in which medical treatment has been unsuccessful.<br>The Extension of their use to other indications cannot yet be recommended without prior evaluation.<br>CEDIT recommended an increase in VAD provision in the two public hospital departments that already have some experience of this technology, to meet needs within the AP-HP; additionally, a register must be kept listing the indications for VAD use in these two departments. | Recommended use of VAD for bridge-to-transplant for accepted transplant candidates who are not expected to otherwise survive to transplantation.<br>Recommended use of VAD for bridge-to-recovery with cardiotomy failure patients who meet appropriate selection criteria.<br>Recommend NOT using VAD as long-term bridge-to-recovery in non-acute & non-life threatening cases.<br>Recommend NOT using VAD in long-term destination therapy. |

## Appendix 12: Summary of Major Clinical Studies on LVAD

| Review/Study | Frazier O et al, non-random trial, Dec 2001 | Frazier O et al, non-random trial 1995 | Novacor 1998 (Submitted to FDA) | Aaronson K 2002 (Michigan US) | Bank 2000 | Jaski BE et al, 2001, (Alabama, US) |
|---|---|---|---|---|---|---|
| **Device** | HeartMate VE | HeartMate IP | Novacor | HeartMate | HeartMate IP | Mixed |
| **Methodology** | Prospective, multicenter (24 US) non-randomized clinical trial | Prospective, multicenter (17 US) non-random clinical trial, concurrent control | Prospective, multicenter (22) non-random trial, concurrent control | Non-randomized comparative | Retrospective non-randomized controlled Single center<br>(40 consecutive pts listed as status 1 HF) | Research data base (surveillance) |
| **Sample Size** | LVAD 280<br>Inotrope 48 (historical, matched ) | LVAD 75<br>Intraaortic balloon pump or Inotrope 33 | LVAD (156 implanted, 129 met selection criteria - core)<br>Inotrope 35 (concurrent) | LVAD 66<br>IV Inotrope 104 | LVAD 20 Status 1<br>Inotrope 20 Status 1 | 5,880 pts with heart transplant<br>IV inotropic support: 2,514<br>LVAD support = 502 |
| **Mean Age** | | LVAD 45 +/- 13 years<br>Control 48+/-12 years | | | LVAD 49+/-9 years<br>Inotrope 48+/-11 years | Kaplan-Meier analysis, regression |
| **VAD support duration (mean)** | | Average time to Tx LVAD = 76 days<br>Control = 12 days. | For Core LVAD pts = 80+/-83 days<br>104 pts reached trial end-pt at end of study (30 days post transplant) | | | |
| **Survival to transplantation** | LVAD 71% (67% bridged toTx )<br>Inotrope 67% | LVAD 71%<br>Inotrope 36% | No information | Survival to transplantation at 3 months: LVAD =81+/-5%<br>Inotropes = 64+/-11% not significant. | LVAD 90%<br>Inotrope 95% | |
| **Impact on NYHA functional class** | Significantly better than controls | | | | | |
| **Hospital Discharge/release** | 58% of patients enrolled in stepwise hospital release program | | 35% LVAD patients discharged from hospital or took excursions | | | |
| **Device related adverse events** | Total adverse events<br>Bleeding 48%, Infection 45%<br>Thromboembolic events 12%<br>Neurologic dysfunction 5%<br>Right heart failure 11%, 2/3 fatal<br>Device related adverse events<br>Bleeding 11%, infection 40%, thromboembolic events 6%, neurologic dysfunction 5%<br>mortality 1% | LVAD Control<br>Bleeding 41% (31) 0%<br>Infection 41% (31) 15% (5)<br>Thromboembolism 4% (3) 0%<br>RV failure 15% (11) 3% (1)<br>Hemolysis 8% (6) 3% (1)<br>Septic embolism 3% 0%<br>Renal dysfunction 53% (40) 61% (20) NS | LVAD Control<br>Bleeding 39.7% 0%<br>Infection 66% 45.7%<br>Embolism CNS 28.9% 0%<br>Embolism non-CNS 14.7% 22.9%<br>Hemolysis 0.6% 0%<br>Renal dysf. 26.9% 42.9%<br>RV dysf. 10.3% 14.3% | | Most frequent complication in LVAD: major infection (1 died of sepsis, 1 LVAD explanted)<br>Infection rate: LVAD 45% Inotrope 40% similar<br>LVAD: signifcantly higher BP, significantly lower BUN & Creatinine.<br>Post Tx renal failure: LVAD 16.7%, Inotrope 52.6%<br>RHF: LVAD 5.6%, Inotrope 31.6% (P<0.05) | Risk factors for post transplant mortality in LVAD group were:<br>-extracorporeal LVAD use (p=0.0004)<br>-elevated serum creatinine (p=0.05)<br>-older donor age (p=0.03)<br>-increased donor ischemic time (p=0.0001)<br>-earlier year of transplant (p=0.03) |
| **Impact on transplant survival rates** | 2-yr post- transplant survival rate: LVAD pts 84%, control 63%, significant | Survival Rates 60 days 1 year<br>LVAD 92% 91%<br>Inotrope 83% 67%<br>(p=0.0001) | Tranplanted: LVAD 78%, Control 37%<br>Actuarial Post transplant Survival<br>1 yr LVAD 78%, control 85% | @ 3 yrs: LVAD = 95+/-4%<br>Inotropes =65+/-10%<br>(p=0.007) | Survival Rates 6 months<br>LVAD 88.9%, Inotrope 73.7% NS 6 month event free: LVAD 55.6%<br>Inotrope 15.8% (p<0.05) | No significant difference in post-transplant survival (p=0.09) |
| **Conclusion/ Recommendation** | -The HeartMate vented electrical LVAD provides adequate hemodynamic support, has an acceptably low incidence of adverse effects and improves survival in heart transplant candidates both inside and outside the hospital. | -56% LVAD with renal dysfunction survived versus 16% in the controls.<br>-LVAD group had a 55% decrease in pre-transplant mortality and probability of surviving 1 year was significantly higher.<br>-HeartMate proved safe and effective as a bridge-to-transplant and decreased the risk of death for pts waiting for transplantation. | Data showed that treatment with circulatory support improved hemodynamics and increased survival in cardiac transplant candidates when compared to those patients who are maintained with conventional medical therapy. | Overall survival @ 3 yrs<br>LVAD = 77+/-6%<br>Inotropes =44+/-9% (p=0.01)<br>Overall survival for pts bridged to heart transplant with implantable LVAD was superior to that of patients who were bridged with inotropes. | Status 1 HF pts treated with LVAD had improved clinical & metabolic function at the time of transplant and improved survival without major complications at 6 months after transplant. Total costs are higher in LVAD pts but average daily costs are similar. | Use of LVAD 2%(1990)- 6%(1997) of transplants, increased # of intracorporeal LVADs<br>** intracorporeal LVAD helps the sickest pts survive to transplant & provides post Tx outcome similar to that of patients supported on inotropic med. Therapy. |

## Appendix 12: Summary of Major Clinical Studies on LVAD (continued)

| Review/Study | Massad, 1996 (US) | El-Banayosy A, 2001 (Germany) | Navia JL, 2002 (Cleveland, US) | Gordon SM et al, 2001 (Ohio US) | Malani PN 2002 | Holman 2002 |
|---|---|---|---|---|---|---|
| **Device** | HeartMate IP or HeartMate VE | Thoratec, Novacor, HeartMate | Novacor, HeartMate IP or HeartMate VE | Nosocomial & bloodstream infection (BSI)of LVAD patients | | Thoratec para-corporal VAD, HeartMate VE or pneumatic VAD |
| **Methodology** | Retrosp, non-random controlled | Case series | Case series | Retrospective review med records | Prospective cohort study | Retrospective review med records |
| **Sample Size** | Transplanted LVAD 53<br>Transplanted Inotrope 203<br>(Single Center) | Thoratec 144 (bi-ventricular or short-term, < 6 months), Novacor 85, HeartMate 54 (total=283pts) | Total pts = 264, total device =277<br>Novacor 57, HeartMate IP 81<br>HeartMate VE 137 | 214 patients (total 17,831 LVAD days) | 35 patients | 46 pts (53 devices) |
| **VAD support duration (mean)** | | Thoratec 53 days, Novacor 154 days, HeartMate143 days | | | 73+/-60 days | 138+/-195 days<br>(2-948 days) |
| **Survival to transplantation** | No information | | 83% at 30 days, 73% at 3 months, 60% at 6 months, 41% at 12 months and 19% at 24 months.<br>Pre-transplant risk of death 29% within 1 year. | | | 11/20 (55%) outpatient received transplant, 5 died, 4 ongoing on VAD. |
| **Hospital Discharge/release** | | A total of 73 (26%) pts discharged from hospital with mean period of 184 days | Chance of transplant within 1 year 29%. | | | 20 patients (43%) disch with VAD outpatient days median = 83 days. |
| **Device related adverse events** | | Despite careful post-op management, LVAD pts prone to:<br>Bleeding: 22-35% (HM) of pts<br>Right heart failure 15-26%<br>Neurologic disorders 7-28%<br>Infection 7-30%<br>Liver failure 11-20%<br>Complications varied with device & pre-op condition | Infection most common especially in HeartMate device & in IP models<br>(pocket infection)<br>Device failure 17% risk in HeartMate.<br>Cerebral embolic events, particularly in Novacor despite anticoagulation | 140 BSI in 104 patients (Attack rate of 49% & incidence of 7.9 BSI/1,000 LVAD days)<br>38% BSI was LVAD associated.<br>Most common pathogens: coagulase -ve staphylococci (33), staphlococcus Aureaus (19), Candida (19), pseudomonas aeruginosa (16).<br>Cox proportional hazard model found BSI inpatients with LVAD to be significantly associated with death.<br>Fungemia had the highest hazard ratio followed by gram -ve bacteremia and gram +ve bacteremia. | 16 pts (46%) developed surgical site infection SSI (6.2 infections/1,000 LVAD days)<br>9/16 deep tissue infections<br>7 cases of pneumonia<br>6 cases venous infections<br>2 cases blood stream infections<br>3 urinary tract infections<br>2 skin & soft tissue infections.<br>Deep SSI associated with need for postop hemodialysis<br>Extensive overuse of antibiotics<br>Trend towards antibiotic resistant organisms noted | Major output complications:<br>5 deaths from sepsis (25%)<br>1 conduit tear (5%)<br>3 neurologic events (15%)<br>4 device infections (3 sepsis) 20%<br>3 device malfunctions - surgical replacement (15%) |
| **Impact on transplant survival rates** | Transplanted LVAD 80%<br>Transplanted Inotrope 84%<br>Survival Rates<br>30 Day One-year<br>LVAD 96.2% 94%<br>Inotrope 95.6% 88%<br>Not significant | | | Patients with implantable LVAD have a high incidence of BSI associated with significantly increased mortality.<br>Strategies for prevention of infection in LVAD recipients should focus on the drive-line exit site until technical advances can achieve a totally implantable device. | Infections were a frequent complication of LVAD implantation. Further studies of interventions for preventing infection in LVAD recipients are warranted. | |
| **Conclusion/ Recommendation** | | Novacor or HeartMate systems offer the additional possibility of discharging patients during support if they fulfill certain criteria.<br>Main reasons for rehospitalization were thromboembolism and infectious complications | | | | VAD effectively support outpatients for months to years.<br>The anticipated time for postoperative recovery and VAD training before discharge is approx. 14-21 days. |

| Review/Study | Meyns B et al. 2002 (Belgium) | Rogdrigus IE et al, 2001, Antwerp | Samuels LE et al, 2001, US | Loisance DY et al, 2000 France | Morales DL et al, 2000 , US | Di, B et al, 2000 , Italy |
|---|---|---|---|---|---|---|
| **Device** | Centrifugal, axial flow, Abiomed, Medos & Novacor | Abiomed BVS® 500, VAD | ABIOMED BVS® 500 | Novacor | HeartMate vented electric LVAD | Novacor |
| **Methodology** | Cohort. All pts implanted 1988-2000. LVAD: stopped inotropic transplant, heparin, anti-aggregant. Prophylactic dose of 2nd generation antibiotic cephalosporin. | Retrospective review of patients bridged to Tx (5) or recovery (15)in emergency situation using Abiomed device. | Single center case series of all cardiogenic shock patients implanted 1994-2000 Hahnemann U Hospital | Retrospective review of patients (> 1yr LVAD support) from Novacor European Registry | Single center case series | Single center case series<br>Postoperative anticoagulant- heparin after bleeding is controlled followed by Warfarin. Aspirin triclopidin or dipyridanol also used |
| **Sample Size** | 47 bridged to tx (9.6% total Tx)<br>118 bridged to recovery | Post CABG cardiotomy card. Shock =15 (BVAD)<br>Other acute HF (myocarditis, cardiomyopathy, graft failure) = 5 (VAD, LVAD) | Total = 45<br>Postcardiotomy shock = 80%<br>Precardiotomy shock = 20% | 36 | 90 consecutive recipients of LVAD<br>44 as outpatients | 36 patients - all pts implanted |
| **Mean Age** | BTX=45 yrs, BTR >65 yrs | Post cardiotomy (mean 58yrs)<br>Others (35 yrs) | 57.9 years (33 - 80 years) | Median age 55 (18-67 years) | | 50.4 years (29 - 68 years)<br>32 males |
| **VAD support duration (mean)** | | | Average = 8.3 days (1 - 31 days) | Median 1.49 years (1.03 - 4.1 years) | Outpatient support of 44 pts average of 103 days (9 - 436 days) | 203.1 days (12-1297 days) |
| **Survival to transplantation** | Significant mortality in early days. Overall survival 64%.<br>Cause of death: death due to shock state, CVA, mortality 36% | Post Cardiotomy gp = 60% mortality on device, 40% weaned from VAD, 27% death after weaning.<br>Overall survival = (2/15) **13%,** 0 TX<br>Non-post cardiotomy gp = 20% mortality on device, 40% weaned from device, 40% tx, overall survived = **80%**<br>**Cause of death:** respiratory failure, multiple organ failure, hypoxia, R HF 60% & 40% | Overall<br>?% mortality<br>22 (49%) weaned from support<br>14 (31%) discharged from hospital<br>Subgroup implanted according with established protocol:<br>60% weaned from support<br>43% discharged from hospital | 81% survived (19% died on LVAD after a median of 1.24 years)<br>39% transplanted<br>8% weaned<br>33% still on LVAD<br>Information on organisms found in blood cultures and device pocket and drive line infection. | Of the 44 outpatients:<br>42 successfully bridged to transplant<br>2 planned explantation<br>None of the outpatient died. | 69.5% survived (30.5% died on the device)<br>64% (23) transplanted, 5.5% waiting for transplant<br><br>31 pts needed inotrope support to improve R ventricular performance |
| **Impact on NYHA functional class** | | All surviving pts in good physical condition with follow up 49-89 months | | | 30% OP returned to work or school<br>33% returned to sexual activity<br>44% returned to driving | Statistical significant improvement in cardiac output |
| **Hospital Discharge/release** | | | | | 49% discharge with LVAD | 19.4% disch. to rehab centre on LVAD<br>25% disch to home on LVAD |
| **Device related adverse events** | Excessive bleeding 38%<br>Thromboembolic events 13%<br>Hemolysis 8%, infection 6%<br>Severe renal failure 17% but not contraindication to transplant. | Sever complication in 80% in post cardiotomy, 40% in others.<br>Bleeding 80% in post cardiotomy, 40% in others needed surgical exploration.<br>hypoxia, Renal failure, neurologic complications 25% in cardiotomy pts- brain death in 2 pts<br>20% infection in Cardiotomy resulted in septic shock & death. 20% of all pts had hemolysis. | Most common morbidity included bleeding and adverse neurologic events | No mechanical failure observed -1 pump replaced electively after 3.67 years due to pump drive wear out. | Cummulative event per outpatient months:<br>Bleeding 0.02<br>Device infection 0.053<br>Thromboembolus 0.0068<br>Major malfunction 0.02 | Most occurred in first 3 months: 33pts<br>Neurologic events: 58.9%<br>Bleeding 30.5%<br>Pocket/cable infection 24.9%<br>Peripheral embolism 8.3%<br>Sepsis 5%; Lung infection 5.5%<br>Right ventricular failure 2.7%<br>Multiorgan failure 8.3% |
| **Impact on transplant survival rates** | 5 yr survival for bridged pts was 82% vs 84% for non-bridged pts. 10 yr survival for bridge >70% | | | | | 69% of transplanted patients survived (7 died after procedure) |
| **Conclusion/ Recommendation** | | Better survival rates with emergency Abiomed. L atrial cannulation a risk factor for neurologic complications.<br>For postcardiotomy group, outcome of bridging is negatively influenced by cardiac arrest & resuscitation before CABG. | ABIOMED® BVAS 5000 VAD a valuable form of short-term mechanical assist for acute cardiogenic shock. A uniform VAD insertion algorithm has helped to standardize protocols | LVAS therapy may offer a safe and realistic option for patients no other effective therapy is available. The patient sub-population that would benefit most remains to be defined. | Cost of bridging to TX after discharge = $13,200<br>Cost of bridging as inpatient over the same length of time (room and board) = $165,200 | Mortality rate severely influenced by cerebrovascular events 45.5%<br>Most complications occur in the first 90 days. A reduction of high rate of thromboembolic events mandatory in order to improve the clinical results. |

## Appendix 13: Summary of Pediatric Studies on LVAD Implantation

| Review/Study | Reinhartz O, 2001 (California, US) | Helman DN, 2000 New York, US | Hendry PJ, 2003 Ottawa, Canada |
|---|---|---|---|
| **Device** | Thoratec in children & adolescents | Heart Mate LVAD in adolescents | Thoratec, 1 CardioWest |
| **Methodology** | Multicenter retrospective case series (27 centers) | Single center series | Single center series<br>Retrospective review |
| **Sample Size** | 58 children & adolescent <18 years of age (Mean body wt 51.6Kg, mean body surface area 1.5 sq. m | 12 patients under 21 years of age<br>Mean body surface area 1.8 sq. m (1.4 - 2.2 sq. m), 13 devices | 7 patients age 18 years or younger<br>Mean body surface area 1.7+/-0.1 sq.m. |
| **Mean Age** | 13.8 years (7-17 years) | 16 years (11 - 20 years) | 14.9+/-0.9 years |
| **VAD support duration (mean)** | | 123 days (0-397 days) | 59.3+/-17.2 days |
| **Survival to transplantation** | 60% (survived to transplantation<br>10% survived to recovery of native heart. 29% (17) died. | 62% (8 cases) successful transplant<br>15% (2) explanted<br>23% (3) died | 100% successful transplant |
| **Impact on NYHA functional class** | | | |
| **Hospital Discharge/release** | 66% survived through discharge. | 28% | |
| **Device related adverse events** | Complications with largest incidence:<br>-infection: 52%<br>-prolonged-ventilation 37%<br>-bleeding requiring take back 33%<br>-neurologic complications 27%:<br>18 Neurologic events in 15 (27%) patients, 6 events (33 %) were fatal.<br>-Significant hypertension during support in 18%<br>-technical malfunction 13%<br>Patient age and size were not associated with significantly increased risk for death or adverse events. | Complications:<br>-Systemic infection (4)<br>-re-operation for hemorrhage (3)<br>-embolic event (1)<br>-intraoperative air embolus (1) | |
| **Quality of life** | | | |
| **Transplant survival rates** | 34/35 (97%) survived through hospital discharge after transplant. | 6/8(75%) survived transplant with follow-up period of 8 - 43 months | 6/7 (86%) are alive 1 month - 3 years after transplant. |
| **Conclusion/ Recommendation** | Thoratec VAD has successfully been used in a large number of children and adolescents with similar morbidity and mortality results as with adults. The risk of neurologic complications may be increased in patients cannulated in the left atria. | Adolescent patients with heart failure can be successfully supported on a long-term basis to heart transplantation with HeartMate LVAD. The techniques of prosthetic graft closure of the abdominal wall facilitate the use of this device in smaller patients. | Pediatric patients with fulminant heart failure may be bridged to cardiac transplant successfully with mechanical circulatory support devices. |

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