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Left Ventricular Assist Devices for Destination Therapy

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The production of this *Horizon scanning report* was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

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Introduction

The National Horizon Scanning Unit, Department of Public Health, University of Adelaide, on behalf of the Medical Services Advisory Committee (MSAC), has undertaken an Horizon Scanning Report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the state of play of the introduction and use of left ventricular assist devices (Horizon Scanning Register number: 0000048).

The Thoratec Corporation manufacture left ventricular assist devices (LVAD), which are generally used as a bridge to heart transplantation for patients with chronic cardiac failure. The Thoratec ventricular assist device (Product number 102757) has Australian Therapeutic Goods Administration (TGA) approval (ARTG No 51280) and this technology is available through Australian public and private hospitals for use in patients awaiting heart transplantation. The US Food and Drug Agency recently approved the HeartMate® XVE LVAD for permanent implantation or destination therapy for use in patients deemed unsuitable for heart transplantation. However, the Thoratec HeartMate® XVE currently does not have TGA approval. Several other LVADs are undergoing clinical evaluation for use as destination therapy including VentrAssist™ (Ventracor Ltd Australia), the Jarvik 2000 (Jarvik Heart Incorporated), De-Bakey Micromed (Micromed Technology Incorporated) and the Arrow LionHeart LVD 2000 (Bio-Tek Instruments Incorporated).

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of left ventricular assist devices for destination therapy, their present use, the potential future application of the technology, and the likely impact on the Australian health care system.

This Horizon Scanning Report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with left ventricular assist devices as destination therapy.

Background

Description of the Technology

The procedure

A left ventricular assist device (LVAD) was first used in the clinical setting in 1963 to treat patients with congestive heart failure. These devices did not enter into widespread use until the late 1980s and are now used as circulatory support in patients with chronic heart failure that are awaiting heart transplantation (Nemeh & Smedira 2003).

LVADs receive blood from the left ventricle via an inflow cannula and then pump it into the aorta via an outflow cannula. A LVAD such as the Thoratec is paracorporeal, which means that the pump is external to the body. The inflow

and outflow cannulas traverse the skin, thus increasing the risk of infection. Although the quality of life of patients fitted with this device may be diminished, due to the external mechanism, it has the advantage of being suitable for small patients. To mimic natural blood flow, a LVAD needs to pump blood in pulses. This requires an energy source, pneumatic or electrical, which is supplied via an external drive mechanism connected to a drive line through the skin. This may also be a source of infection. Early devices required the patient to be permanently attached to an external power source. However, newer models now have a controller and power pack that can be placed subcutaneously and charged through the skin via an induction coil. As the pulsatile pump provides a mechanism for air to move in and out as the blood chamber fills and empties, these devices need to be externally vented. Early models used the external drive line to vent the device, however, later models have utilised internal venting systems (Nemeh & Smedira 2003).

The HeartMate® XVE consists of an implanted pump, an external systems controller and external power supply components (see Figure 1). The titanium pump is implanted within the abdomen or the peritoneal cavity. The pump is divided in two by a flexible polyurethane diaphragm, with one half functioning as the blood chamber and the other housing the electric motor chamber. The motor chamber is connected to the external control and power components. The rotation of the motor displaces the polyurethane diaphragm, which results in blood being pumped. The LVAD's inflow cannula is inserted into the apex of the left ventricle and the outflow cannula is grafted to the ascending aorta. Blood returns from the lungs and enters the left ventricle, crosses a unidirectional inflow valve and enters the pumping chamber passively. When pump pressure exceeds the pressure in the patient's ascending aorta, the outflow valve opens and the pump ejects the blood held in the chamber (systole) (Rose et al 2001; Thoratec Corporation 2003a).

The motor may be powered either by a pair of wearable, rechargeable batteries (provides approximately 4-6 hours of power), or by connection to a dedicated power supply (Power Base Unit) when sleeping or anticipating sleep. In addition, a portable, non-rechargeable, back-up power source may be utilised during periods of extended power black out (24 hours). In the event of a critical alarm and no power source, a hand pump may be used to power the LVAD. A flexible drive line is placed percutaneously and contains an electrical lead and an air line for venting the system. The system controller is the primary interface, which initiates motor action and monitors the entire system. The controller provides two modes of operation, fixed (pre-set beat rate per minute) or auto (varying in response to physiological demands) rate mode. The rate range for both modes is 50-120 beats per minute. By initiating audio and visual alarms, the system controller will alert the patient to low flow or low stroke rates and low battery charge levels (Rose et al 2001; Thoratec Corporation 2003a).

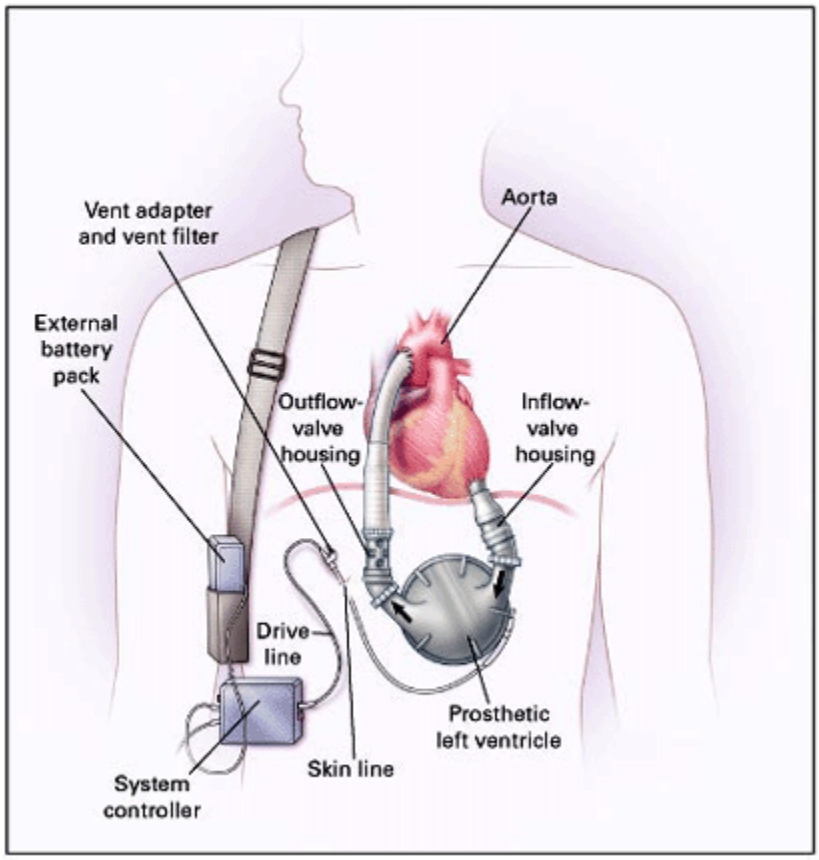

Figure 1 The HeartMate® left ventricular assist device (Rose et al 2001)

The Arrow LionHeart LVD 2000 is the only totally implantable LVAD with an internal venting system and a transcutaneous power pack that can be recharged through the skin (Nemeh & Smedira 2003). The Jarvik 2000, the VentrAssist™ and the MicroMed DeBakey are continuous flow with rotary pumps, which provide non-pulsatile flow and as such are smaller than conventional LVADs and therefore suitable for smaller patients (Frazier et al 2003; Frazier & Delgado 2003; Ventracom 2002). It is anticipated that these smaller pumps will be easier to insert, and will reduce complications associated with the implantation of a LVAD, such as bleeding, infection and thromboembolic events. These devices utilise an external power source and controller unit, which are worn in a belt around the patient (Frazier et al 2003; Frazier & Delgado 2003; Ventracom 2002).

When undergoing implantation of a LVAD, patients receive antibiotic treatment prior to surgery, which is continued for at least 48 hours post-implantation. After the patient is anaesthetised, a cardiopulmonary bypass procedure is initiated to divert blood flow. The pump is then implanted either in the peritoneal cavity or intra-abdominally, and the outflow and inflow cannulas attached. Once implanted the LVAD system is activated and the patient can be weaned from cardiopulmonary support (Thoratec Corporation 2003b). The patient and family members undergo training with the LVAD device immediately, including caring for the driveline exit site, trouble-shooting and managing alarms. Local health care providers also receive device management training (Richenbacher et al 2003; El-Banayosy et al 2001). With the exception of HeartMate®, all pulsatile LVADs require patients to undergo

daily anti-coagulation therapy to prevent thromboembolism (Nemeh & Smedira 2003). The HeartMate®'s blood-contacting surfaces are textured and form a lining similar to that found in arteries and veins, reducing the likelihood of blood clots (Thoratec Corporation 2003a).

Patients considered suitable for out of hospital care and management must be ambulatory, have a New York Heart Association (NYHA) classification of Class III or less, have partial recovery of the left ventricle, have an absence of end-stage organ failure, have met the educational goals of the device management training programme and have adequate family support (Richenbacher et al 2003; El-Banayosy et al 2001).

Patients who have undergone LVAD implantation do not require the administration of immunosuppressive drugs, unlike heart transplant patients. They therefore avoid the development of diseases associated with the use of immunosuppressive drugs, such as certain cancers, as well as the chronic risk of infection. Long-term use of LVADs has, however, been associated with deficiencies in T-lymphocyte function and persistent inflammation (Busund 2002; Hampton & Verrier 2002).

Intended purpose

Transplantation is contraindicated for patients greater than 65 years of age, or with renal failure or with insulin-dependent diabetes mellitus with end-stage organ damage (Rose et al 2001). Patients who are deemed ineligible for transplantation may be suitable for implantation with a LVAD as a destination therapy. Criteria for these patients include class IV heart failure (see Appendix A) for ≥ 90 days despite medical therapy or pharmaceutical therapy, such as β-blockers, digoxin or angiotensin-converting enzyme (ACE) inhibitors, a left ventricular ejection fraction of 25 per cent or less, or peak oxygen consumption of no more than 12 ml/kg body weight/minute (Richenbacher et al 2003; Rose et al 2001). Due to the size of HeartMate® XVE, it is contraindicated for patients whose body surface area is less than 1.5m^2 (Thoratec Corporation 2003b).

Clinical need and burden of disease

Heart failure occurs when the heart is unable to pump blood adequately to the rest of the body. It has been estimated that 300,000 Australians are affected by chronic heart failure with approximately 30,000 new cases diagnosed annually (National Heart Foundation of Australia & Zealand 2002). In Australia, heart failure occurs predominantly amongst those aged 75 years and over and accounted for 40,942 hospitalisations and 2,612 deaths, during the period 2000-01 (AIHW 2003a). The number of public hospital separations for patients with congestive heart disease or left ventricular failure, in 2001-02, was 28,113 and 12,648 respectively (AIHW 2004). Patients with acute heart failure would represent approximately 1.5 per cent of this group. These patients would be candidates for treatment with extracorporeal membrane oxygenation or be implanted with a LVAD (Stevenson & Kormos 2001). The gold standard treatment for patients with irreversible heart failure is heart transplantation however, due to a shortage of donor organs, waiting lists are long and many patients die before receiving a transplant (Rose et al 2001). Patients who undergo successful heart transplantation have a 90 per cent and

85 per cent survival rate at one and five year post-transplantation, respectively (ANZOD 2003). The number of individuals who died from heart failure in Australia during the year 2001 was 2,612, and this figure may represent the upper limit of the number of patients eligible for implantation with a LVAD as destination therapy (AIHW 2003). The number of patients on the heart transplantation waiting list may represent a conservative, lower estimate of the number of patients who may require a LVAD as a permanent implant. The number of heart transplants conducted in Australia for the period January 1-December 31 2002 was 74. In addition, there were 70 patients on the heart transplant waiting list as of January 2003. McGregor (2000) has estimated that the number of patients who may require circulatory assistance in the form of LVADs as destination therapy to be approximately 20 times the number of patients on the cardiac transplantation list (McGregor 2000). In Australia, the average waiting time for heart transplantation is 2.2 years. The number of patients who died while on the heart transplantation list was ten, between July 2002 – June 2003 (ANZOD 2003).

Stage of development

The use of LVADs as a bridge to heart transplantation is an established technology in Australia with programs operating in the Royal Perth Hospital (Perth), the Royal Children's Hospital (Melbourne), The Alfred Hospital (Melbourne), the Prince Charles' Hospital (Brisbane) and St Vincent's Hospital (Sydney) (National Heart Foundation of Australia 2000). It would be expected that these established centres would have the expertise to manage patients undergoing permanent implantation. Although LVADs may be implanted as a bridge-to-transplant for patients awaiting heart transplantation, they usually not implanted as a permanent means of circulatory support (Richenbacher et al 2003). Clinical trials are underway in Australia (VentrAssist), United Kingdom (Jarvik 2000) and the United States (HeartMate®) for the use of LVADs as a destination therapy.

Treatment Alternatives

Existing comparators

Patients eligible to be implanted with a LVAD as destination therapy require heart transplantation but do not satisfy the criteria to be eligible for this procedure. Eligible patients are critically ill, in end-stage left ventricular failure and currently supported by optimal medical therapy. The implantation of LVADs as destination therapy is proposed as an alternative to optimal medical therapy, which currently consists of pharmacological treatment. Patients supported by medical therapy alone may be hospitalised for long periods of time and have shortened life expectancies. Not all patients tolerate medications such as ACE inhibitors and β-blockers, and patient compliance is an issue, with many patients being readmitted to hospital (Boehmer 2003). An alternative to optimal medical treatment is dynamic cardiomyoplasty, which involves bringing the latissimus dorsi muscle into the chest from the lower back and wrapping it around the heart. The muscle is stimulated and is non-

fatiguing, providing systolic support. This procedure is considered to be difficult and is associated with high mortality (Boehmer 2003).

It is expected that the implantation of LVADs as destination therapy will allow patients to return to the home environment, have an increased survival time and an improved quality of life, when compared to medical therapy alone (Blue Cross 2002).

Clinical Outcomes

There are many studies which describe the use of LVADs as a bridge-to-transplantation therapy, however, there is a paucity of literature describing the use of LVADs as destination therapy. From an extensive literature search, only five studies were identified reporting the safety and effectiveness of LVADs for long-term implantation, or destination therapy. The high quality REMATCH study (level II evidence), by Rose et al (2001), was a randomised controlled trial (n=129) and compared the implantation of the HeartMate® LVAD to optimal medical therapy alone (Rose et al 2001). This study was also reported and summarised by the Thoratec Corporation and the Blue Cross, Blue Shield Association (Blue Cross 2002; Thoratec Corporation 2003b). Two studies (level IV evidence) reported on the same small case series patients (n=4) implanted with the Jarvik 2000 LVAD (Frazier et al 2003; Westaby et al 2002). The Jarvik 2000 LVAD was also implanted in a small patient group (n=3) by Siegenthaler et al (2002). One study (level IV evidence) reported on the long-term implantation of patients with a number of different LVADs, including the HeartMate®, Novacor and LionHeart (El-Banayosy et al 2001). This study was included in this report as, although the study implied that patients were implanted as a bridge-to-transplant, these three devices were used as long-term support for greater than six months and patients were not reported as having undergone a heart transplant. Unfortunately, safety and effectiveness data were not reported for the four patients implanted with the LionHeart LVAD, with the exception of the number of patients discharged home. A later study did, however report on a case series of six patients implanted with the LionHeart LVAD as a destination therapy (El-Banayosy et al 2003).

Effectiveness

Survival time and length of time supported by a LVAD

Increased survival time and length of time supported by the LVAD was the main effectiveness outcome reported by all five studies (Table 1). The high quality randomised controlled trial (RCT) (level II evidence) by Rose et al (2001) compared the implantation of the HeartMate® LVAD to optimal medical therapy in 129 patients with end-stage heart failure. The risk of death from all causes at all ages is reduced by almost 50% for patients implanted with a LVAD compared to patients receiving optimal medical therapy (RR =0.52, 95%CI [0.34, 0.78]). One and two year survival rates for the LVAD group were 52 per cent and 23 per cent, respectively, compared to 25 per cent

and 8 per cent in the medical therapy group (Figure 2). Median survival time was 408 days in the LVAD group, with an associated mortality of 60 per cent, compared to survival time of 105 days and an associated mortality of 89 per cent in the medical therapy group.

Table 1 Survival or length of time supported by LVAD

Study	Level of Evidence	Study Design	Population	Outcomes
Rose et al (2001), USA REMATCH study Also summarised by Blue Cross Blue Shield Association, (2002) and Thoratec Corporation (2003b)	II	Randomised controlled trial (RCT) HeartMate® LVAD vs optimal medical therapy	129 patients with end-stage heart failure, ineligible for heart transplantation	LVAD (n=68) Median survival 408 days 1 year survival rate = 52% 2 year survival rate = 23% Number of deaths at end of follow-up = 41/68 (60%) Relative risk of death All cause, all ages RR =0.52 95%CI [0.34, 0.78] 18-59 years RR= 0.47 95%CI [0.17, 1.28] 60-69 years RR=0.49 95%CI [0.25, 0.95] ≥ 70 years RR=0.59 95%CI [0.31, 1.15] 15/68 (22%) of patients or their families chose to have the LVAD switched off or did not agree to surgical replacement[a] Medical therapy (n=61) Median survival 105 days 1 year survival rate = 25% 2 year survival rate = 8% Number of deaths at end of follow-up = 54/61 (89%) 13/61 (21%) of medical therapy patients opted for palliative care only[a]
El-Banayosy et al (2001), Germany	IV	Case series	Patients with end-stage heart failure, implanted with a variety of LVADs for long-term support (> 6 months) Novacor n=85 HeartMate n=54 LionHeart n=4	Length of time supported by LVAD Novacor n=85 6 to 1,090 days, mean 154 ± 15 days HeartMate n=54 1 to 882 days, mean 143 ± 142 days LionHeart n=4 n/a[b]
El-Banayosy et al (2003), Germany	IV	Case series	6 patients with end-stage heart failure, implanted with LionHeart LVAD as destination therapy	Length of time supported on LVAD Range 17 to 670, mean 245 ± 138 days 18 month survival rate = 50% Deaths occurred at 17, 31 and 112 days post-implantation from multiple organ failure

Frazier et al (2003), United Kingdom and Westaby et al (2002), United Kingdom	IV	Case series	4 patients with end-stage heart failure, implanted with Jarvik 2000 LVAD as destination therapy	Length of time supported by LVAD Range 95-889 days, mean 502 ± 341 days Survival rate at end of follow-up = 2/4 50%) Deaths occurred at 95 and 382 days post-implantation Surviving patients supported for 642 and 889 days post-implantation
Siegenthaler et al (2002), Germany	IV	Case series	3 patients with end-stage heart failure, implanted with Jarvik 2000 LVAD as destination therapy	Length of time supported by LVAD Range 91-170 days, mean 118 ± 45 days Number of deaths at end of follow-up = 0

[a] Data from Thoratec Corporation (Thoratec Corporation 2003b), [b] n/a = not available

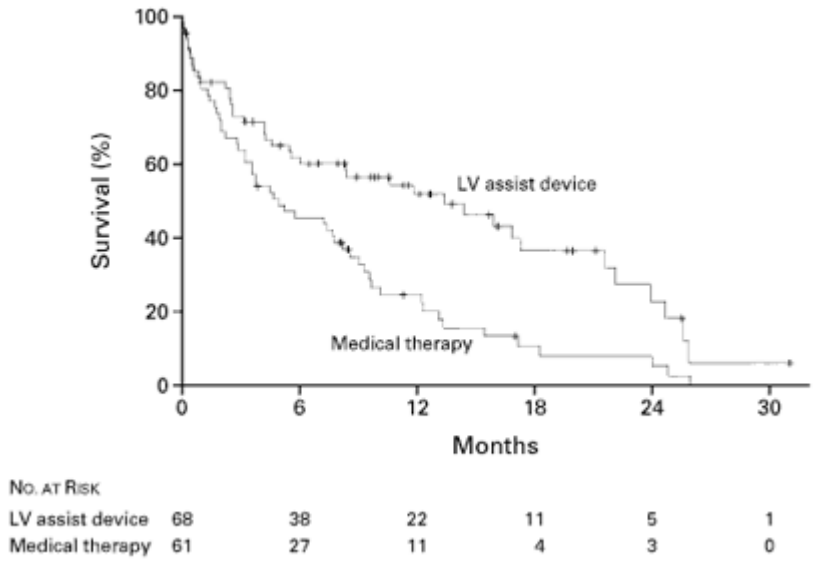

Figure 2 Kaplan-Meier analysis of survival in the optimal medical therapy and LVAD implant groups (Rose et al 2001)

Survival rates in the lower quality studies (level IV evidence) ranged from 50 per cent at 18 months for patients implanted with the LionHeart (El-Banayosy et al 2003), 50 per cent at between 642 and 889 days for the Jarvik 2000 (Frazier et al 2003; Westaby et al 2002) and to 100 per cent at 91 to 170 days for the Jarvik 2000 (Siegenthaler et al 2002). Follow-up was considerably shorter in the study by Siegenthaler et al (2002) compared to all other studies.

Length of time supported by a LVAD ranged from one to 1,090 days in a study of 143 patients by El-Banayosy et al (2001). The mean length of time supported by a LVAD ranged from a mean of 118 ± 45 days in the study of three patients by Siegenthaler et al (2002), to a mean of 502 ± 341 days in the study of four patients described by Frazier et al (2002) and Westaby et al (2002). Both of these patient groups were implanted with the Jarvik 2000. There are currently no trial data available directly comparing different models

of LVAD for destination therapy. However, the American FDA has given conditional approval (February 2004) for the World Heart Corporation to proceed with the RELIANT (Randomised Evaluation of Novacor LVAD in a Non-transplant population) trial (PRNewswire 2004). This multicentre trial in the United States, aims to enrol 225 patients, randomised to either a Novacor LVAD or a HeartMate® XVE LVAD, in a ratio of 2:1. Completion of enrolment is expected to take two years from date of commencement.

Patient heart function

Only two studies reported on heart function pre- and post-implantation with a LVAD (Table 2). The high quality RCT conducted by Rose et al (2001) reported that at baseline, all patients enrolled in both arms of the study were classified as NYHA Class IV (see Appendix A). At one year follow-up, the 24 surviving patients implanted with the HeartMate® were all NYHA Class II, whereas of the eleven surviving patients in the optimal medical therapy group, seven patients were NYHA Class IV and four patients were unable to be assessed. The lower quality study by both Frazier et al (2002) and Westaby et al (2002) also reported an improvement in function from NYHA Class IV to Class I (n=2) and Class II (n=1), after implantation with the Jarvik 2000 in the three surviving patients. These patients also experienced an improvement in their left and right ventricular ejection fractions.

Table 2 Patient heart function

Study	Level of Evidence	Study Design	Population	Outcomes
Rose et al (2001), USA REMATCH study Also summarised by Blue Cross Blue Shield Association, (2002) and Thoratec Corporation (2003b)	II	Randomised controlled trial (RCT) HeartMate® LVAD vs optimal medical therapy	129 patients with end-stage heart failure, ineligible for heart transplantation	LVAD Baseline(65/68) = NYHA[a] Class IV 1 year follow-up (24/24) = NYHA[a] Class II Medical therapy Baseline (60/61) = NYHA[a] Class IV 1 year follow-up (7/11) = NYHA[a] Class IV p<0.001[b]
Frazier et al (2003), United Kingdom and Westaby et al (2002), United Kingdom	IV	Case series	4 patients with end-stage heart failure, implanted with Jarvik 2000 LVAD as destination therapy	Pre (n=4) 4/4 (100%) patients NYHA[a] Class IV LVEF (n=4)[c] 15% ± 5% RVEF (n=4)[d] 38% ± 14% Post (n=3)[e] 2/4 (50%) patients NYHA[a] Class I 1/4 (25%) patients NYHA[a] Class II LVEF (n=4)[c] 38% ± 15% RVEF (n=4)[d] 48% ± 10%

[a] NYHA = New York Heart Association heart failure classification system, [b] Authors statistical analysis, [c] LVEF = left ventricular ejection fraction, [d] RVEF = right ventricular ejection fraction, [e] one patient had died at the end of follow-up for this outcome reported by Westaby et al only

Quality of life

Three of the five studies reported on the quality of life of patients pre- and post-implantation with a LVAD (Table 3). The high quality RCT conducted by Rose et al (2001) reported improvements for all quality of life measures for 23 of the surviving 24 patients, from baseline to one year follow-up, although no statistical analysis was conducted. Of the surviving 11 patients in the optimal medical therapy group, at one year follow-up, only six patients were available or able to have their quality of life assessed.

Quality of life was measured utilising three valid and reliable measurement scales; the SF-36 (ranging from 0 (worst) to 100 (best); the Beck Depression Inventory (BDI) (ranging from 0 (normal) to 64 (severe depression); and the Minnesota Living with Heart Failure (MLHF) ranging from 0 (best quality of life) to 105 (worst quality of life) (Rose et al 2001). There was an improvement in the LVAD patient group from baseline values after one year follow-up in the MLHF score (decreased), the SF-36 (increased) and the BDI (decreased), however a statistical analysis was not presented for these scores. There were significant differences between the LVAD and medical therapy

patients for the SF-36 scores for physical function (p=0.01) and emotional role (p=0.03), in addition to the BDI (p=0.04). However, no significant difference was found in scores on the MLHF scale (p=0.11). The lower quality, case series studies by Siegenthaler et al (2002), and Frazier et al (2002) and Westaby et al (2002) reported improvements, post-implantation, on the MLHF score. A statistical analysis was not conducted due to the small patient group.

Table 3 Quality of life

Study	Level of Evidence	Study Design	Population	Outcomes
Rose et al (2001), USA REMATCH study Also summarised by Blue Cross Blue Shield Association, (2002) and Thoratec Corporation (2003b)	II	Randomised controlled trial (RCT) HeartMate® LVAD vs optimal medical therapy	129 patients with end-stage heart failure, ineligible for heart transplantation	LVAD Baseline (n=68) MLHF score[a] 75±18 SF-36 physical function 19±19 emotional role 33±42 BDI[b] 19±9 LVAD 1 year follow-up (n=23/24) MLHF score[a] 41±22 p=0.11[c] SF-36 physical function 46±19 p=0.01[c] emotional role 64±45 p=0.03[c] BDI[b] 8±7 p=0.04[c] Medical therapy Baseline (n=61) MLHF score[a] 75±17 SF-36 physical function 18±19 emotional role 25±38 BDI[b] 6±8 Medical therapy 1 year follow-up (n=6/11) MLHF score[a] 58±21 SF-36 physical function 21±21 emotional role 17±28 BDI[b] 13±7
Frazier et al (2003), United Kingdom and Westaby et al (2002), United Kingdom	IV	Case series	4 patients with end-stage heart failure implanted, with Jarvik 2000 LVAD as destination therapy	Pre (n=4)[d] MLHF score[a] 84 ± 6 Post (2 months) (n=3)[e] MLHF score[a] 36 ± 11
Siegenthaler et al (2002), Germany	IV	Case series	3 patients with end-stage heart failure, implanted with Jarvik 2000 LVAD as destination therapy	Pre MLHF score[a] 75.2 ± 11.4 Post MLHF score[a] 30.0 ± 18.6

[a] MLHF = Minnesota Living with Heart Failure Scale, [b] BDI = Beck Depression Inventory, [c] Authors own statistical analysis using analysis of covariance, comparing differences between scores for LVAD and medical therapy patient groups after adjustment for baseline values, [d] the method of assessment for quality of life was not stated, [e] one patient had died by time of follow-up for this outcome reported by Westaby et al (2002)

Length of hospital stay or number of patients discharged home

Only the two studies by Rose et al (2001) and Siegenthaler et al (2002) reported on the number of days patients spent in hospital. The remaining three studies reported on the number of patents who were discharged home (Table 4). The high quality study by Rose et al (2001) reported that patients in the HeartMate® LVAD implantation and medical therapy groups spent a median of 88 and 24 days in hospital, respectively. Of the days spent in hospital, 29/88 and 5/24 days were for the implantation of the LVAD or for medical management. In addition, Rose et al reported that patients in the LVAD group spent 340 days at home, compared to 106 days for the medical therapy group. The number of patients discharged home ranged from 43 per cent (23/54) to 100 per cent (3/3).

Table 4 Length of hospital stay or the number of patients discharged home

Study	Level of Evidence	Study Design	Population	Outcomes
Rose et al (2001), USA REMATCH study Also summarised by Blue Cross Blue Shield Association, (2002) and Thoratec Corporation (2003b)	II	Randomised controlled trial (RCT) HeartMate® LVAD vs optimal medical therapy	129 patients with end-stage heart failure, ineligible for heart transplantation	LVAD (median) (n=68) Days spent in hospital = 88 Days spent out of hospital = 340 Days spent in hospital for medical management or implantation of LVAD =29 Medical therapy (median) (n=61) Days spent in hospital = 24 Days spent out of hospital = 106 Days spent in hospital for medical management or implantation of LVAD = 5
El-Banayosy et al (2001), Germany	IV	Case series	Patients with end-stage heart failure, implanted with a variety of LVADs for long-term support (> 6 months) Novacor n=85 HeartMate n=54 LionHeart n=4	Number of patients discharged home Novacor 47/85 (55%) HeartMate 23/54 (43%) LionHeart 2/4 (50%) Duration of home support ranged from 2 to 1,043 days (mean 184 days)
El-Banayosy et al (2003), Germany	IV	Case series	6 patients with end-stage heart failure, implanted with LionHeart LVAD as destination therapy	3/6 (50%) patients discharged home

Frazier et al (2003), United Kingdom and Westaby et al (2002), United Kingdom	IV	Case series	4 patients with end-stage heart failure, implanted with Jarvik 2000 LVAD as destination therapy	3/4 (75%) patients discharged home between 3 and 8 weeks post implantation
Siegenthaler et al (2002), Germany	IV	Case series	3 patients with end-stage heart failure, implanted with Jarvik 2000 LVAD as destination therapy	Length of hospital stay 49 ± 7 days 3/3 (100%) patients discharged home 1/3 patients (33%) resumed work Operative time 285 ± 10 minutes

Safety

Device failure or re-implantation

Device failure or re-implantation was reported in two of the five studies (Table 5). The RCT conducted by Rose et al (2001) reported that 7/68 (10%) of patients died due to a device related failure. In addition, a number of adverse events related to the LVAD were reported including malfunction of the LVAD and infection through the pump interior and drive-line. Rose et al (2001) reported that 24/68 (35%) of patients underwent surgery to replace either components of the HeartMate® LVAD or the complete LVAD device. The case series by El-Banayosy et al (2003) also reported a number of adverse events associated with the implantation of a LionHeart LVAD.

Table 5 Device failure/ reimplantation

Study	Level of Evidence	Study Design	Population	Outcomes
Rose et al (2001), USA REMATCH study Also summarised by Blue Cross Blue Shield Association, (2002) and Thoratec Corporation (2003b)	II	Randomised controlled trial (RCT) HeartMate® LVAD vs optimal medical therapy	129 patients with end-stage heart failure, ineligible for heart transplantation	Number of deaths related to failure of the LVAD = 7/68 (10%) Rates per patient year Adverse events related to the LVAD Suspected malfunction 0.75 Perioperative bleeding 0.46 Infection of drive-line tract 0.41 Infection of pump interior, inflow or outflow tracts 0.23 Right heart failure 0.17 Failure of LVAD system 0.08 Thrombosis in LVAD 0.06 Re-implantation[a] 24/68 (35%) patients underwent surgery to replace the implanted device or components Probability of requiring operation to repair or replace components 7% in first 6 months 30% between 6 and 12 months 78% between 1 and 2 years
El-Banayosy et al (2003), Germany	IV	Case series	6 patients with end-stage heart failure, implanted with LionHeart LVAD as destination therapy	Adverse events related to the LVAD 1/6 (17%) LVAD pump had reduced flow resulted in replacement of controller 1/6 (17%) LVAD battery required replacement 1/6 (17%) LVAD outflow graft kink

[a] Data from Thoratec Corporation (Thoratec Corporation 2003b)

Embolism

With the exception of HeartMate®, all pulsatile LVADs require patients to undergo daily anti-coagulation therapy to prevent thromboembolism. Three of the five studies reported on patients who experienced an embolism after the implantation of a LVAD (Table 6). The high quality study by Rose et al (2001) reported that 2/68 (3%) of patients died from a pulmonary embolism in the LVAD implanted group, compared to no patients in the medical therapy group. The likelihood of patients in the LVAD group experiencing a peripheral embolic event was 2.3 [95%CI 0.048,10.8] times that of patients in the medical therapy group, although the confidence interval was wide and included no difference. The case series (level IV evidence) by El-Banayosy et al (2001) reported 24/85 (28%) of patients implanted with a Novacor LVAD and 4/54 (7%) of patients implanted with the HeartMate® LVAD, experienced an embolism.

Table 6 Embolism

Study	Level of Evidence	Study Design	Population	Outcomes
Rose et al (2001), USA REMATCH study Also summarised by Blue Cross Blue Shield Association, (2002) and Thoratec Corporation (2003b)	II	Randomised controlled trial (RCT) HeartMate® LVAD vs optimal medical therapy	129 patients with end-stage heart failure, ineligible for heart transplantation	Number of deaths from pulmonary embolism LVAD 2/68 (3%) Medical therapy 0/61 (0%) Peripheral embolic event (rate per patient year) LVAD 0.14 Medical therapy 0.06 Rate ratio (95% CI) 2.29 (0.48, 10.8)[a]
El-Banayosy et al (2001), Germany	IV	Case series	Patients with end-stage heart failure implanted with a variety of LVADs for long-term support (> 6 months) Novacor n=85 HeartMate n=54 LionHeart n=4	Novacor 24/85 (28%) HeartMate 4/54 (7%) LionHeart n/a[b]
Siegenthaler et al (2002), Germany	IV	Case series	3 patients with end-stage heart failure implanted with Jarvik 2000 LVAD as destination therapy	1/3 (33%) patient experienced a transient ischemic attack likely due to a small embolus

[a] The study was underpowered for this outcome, which is reflected in the wide confidence limit, [b] n/a = not available

Bleeding

All five studies assessed for this report reported on bleeding post-operatively for patients implanted with a LVAD (Table 7). The one lower quality study by Siegenthaler et al (2002) reported no bleeding complications. The high quality study by Rose et al (2001) reported 1/68 (1.5%) of patients died from peri-operative bleeding after implantation with the HeartMate® LVAD. The same study recorded 9.5 times [95%CI 2.3, 38.9] the risk of non-neurological bleeding in the LVAD group compared to the medical therapy group. The highest rate of post-operative bleeding was reported in the small case series conducted by El-Banayosy et al (2003), where 3/6 (50%) of patients experienced post-operative bleeding and one patient required re-operation, for bleeding after implantation with the LionHeart LVAD. The study by El-Banayosy et al (2001) defined a bleeding complication as $\geq$ 1,500 mL/m^2 in 24 hours.

Table 7 Bleeding

Study	Level of Evidence	Study Design	Population	Outcomes
Rose et al (2001), USA REMATCH study Also summarised by Blue Cross Blue Shield Association, (2002) and Thoratec Corporation (2003b)	II	Randomised controlled trial (RCT) HeartMate® LVAD vs optimal medical therapy	129 patients with end-stage heart failure, ineligible for heart transplantation	Number of deaths from peri-operative bleeding LVAD 1/68 (1.5%) Non-neurological bleeding (rate per patient year) LVAD 0.56 Medical therapy 0.06 Rate ratio (95% CI) 9.47 (2.3, 38.9)
El-Banayosy et al (2001), Germany	IV	Case series	Patients with end-stage heart failure, implanted with a variety of LVADs for long-term support (> 6 months) Novacor n=85 HeartMate n=54 LionHeart n=4	Novacor 19/85 (22%) HeartMate 19/54 (35%) LionHeart n/a[a]
El-Banayosy et al (2003), Germany	IV	Case series	6 patients with end-stage heart failure, implanted with LionHeart LVAD as destination therapy	3/6 (50%) patients 1/6 (17%) patient required re-operation for bleeding
Frazier et al (2003), United Kingdom and Westaby et al (2002), United Kingdom	IV	Case series	4 patients with end-stage heart failure, implanted with Jarvik 2000 LVAD as destination therapy	1/4 (25%) patient died from subdural haematoma
Siegenthaler et al (2002), Germany	IV	Case series	3 patients with end-stage heart failure, implanted with Jarvik 2000 LVAD as destination therapy	No bleeding complications reported

[a] n/a = not available

Infection

Of the five studies assessed in this report, four studies reported on infection as an adverse event in patients implanted with a LVAD (Table 8). The small case series conducted by El-Banayosy et al (2003) and Siegenthaler et al (2002) reported no infection complications in all patients. The high quality RCT conducted by Rose et al (2001) reported that 17/68 (25%) of patients died from sepsis after implantation with the HeartMate® LVAD, compared to 1/61 (1.6%) of patients in the medical therapy group. There was a trend towards twice the risk of sepsis in patients receiving LVAD compared to medical

therapy [RR = 2.0, 95%CI 1.0, 4.1]. There was no difference in local infection between the two groups [RR= 1.6, 95%CI 0.7, 3.7].

Table 8 Infection

Study	Level of Evidence	Study Design	Population	Outcomes
Rose et al (2001), USA REMATCH study Also summarised by Blue Cross Blue Shield Association, (2002) and Thoratec Corporation (2003b)	II	Randomised controlled trial (RCT) HeartMate® LVAD vs optimal medical therapy	129 patients with end-stage heart failure, ineligible for heart transplantation	Number of deaths from sepsis LVAD 17/68 (25%) Medical therapy 1/61 (1.6%) Rates per patient year Sepsis (rate per patient year) LVAD 0.60 Medical therapy 0.30 Rate ratio (95% CI) 2.03 (0.99, 4.13) Local infection LVAD 0.39 Medical therapy 0.24 Rate ratio (95% CI) 1.63 (0.72, 3.7)
El-Banayosy et al (2001), Germany	IV	Case series	Patients with end-stage heart failure implanted with a variety of LVADs for long-term support (> 6 months) Novacor n=85 HeartMate n=54 LionHeart n=4	Driveline infection Novacor 20/85 (24%) HeartMate 16/54 (30%) LionHeart n/a[a] Pocket infection Novacor 6/85 (7%) HeartMate 9/54 (21%) LionHeart n/a[a] Sepsis Novacor 11/85 (13%) HeartMate 6/54 (11%) LionHeart n/a[a]
El-Banayosy et al (2003), Germany	IV	Case series	6 patients with end-stage heart failure implanted with LionHeart LVAD as destination therapy	No infection complications reported in all patients
Siegenthaler et al (2002), Germany	IV	Case series	3 patients with end-stage heart failure implanted with Jarvik 2000 LVAD as destination therapy	No infection complications reported in all patients

[a] n/a = not available

Neurologic dysfunction

Two studies reported on neurological dysfunction post-implantation with a LVAD (Table 9). The high quality RCT conducted by Rose et al (2001) reported the rate per patient year for neurologic dysfunction as 0.39 for patients implanted with the HeartMate® LVAD, compared to 0.09 in the

medical therapy group. The risk of neurologic dysfunction was therefore nearly four and a half times higher for patients implanted with a LVAD [RR= 4.4, 95%CI 1.3, 14.5]. The small case series conducted by El-Banayosy et al (2003) reported 1/6 (17%) of patients suffered from a stroke 35 days post-implantation with a LionHeart LVAD.

Table 9 Neurologic dysfunction

Study	Level of Evidence	Study Design	Population	Outcomes
Rose et al (2001), USA REMATCH study Also summarised by Blue Cross Blue Shield Association, (2002) and Thoratec Corporation (2003b)	II	Randomised controlled trial (RCT) HeartMate® LVAD vs optimal medical therapy	129 patients with end-stage heart failure, ineligible for heart transplantation	Rates per patient year Neurological dysfunction LVAD 0.39 Medical therapy 0.09 Rate ratio (95% CI) 4.35 (1.31, 14.5) Psychiatric disease LVAD 0.04 Medical therapy 0.03 Rate ratio (95% CI) 1.31 (0.12, 14.3)
El-Banayosy et al (2003), Germany	IV	Case series	6 patients with end-stage heart failure, implanted with LionHeart LVAD as destination therapy	1/6 (17%) patient suffered a stroke on post-operative day 35

Re-hospitalisation

Three of the lower quality case series studies reported on rates of re-hospitalisation for patients implanted with a LVAD (Table 10). The highest rate of re-hospitalisation was reported in the study conducted by El-Banayosy et al (2001), which reported that of the 73 patients able to be discharged home after implantation with either the Novacor, HeartMate® or LionHeart LVADs, 41 (56%) of these patients required re-hospitalisation mainly for thromboembolic or infectious complications.

Table 10 Re-hospitalisation

Study	Level of Evidence	Study Design	Population	Outcomes
El-Banayosy et al (2001), Germany	IV	Case series	Patients with end-stage heart failure, implanted with a variety of LVADs for long-term support (> 6 months) Novacor n=85 HeartMate n=54 LionHeart n=4	Of the patients who were discharged for out of hospital care 41/73 (56%) were re-hospitalised Readmission rate was 1.8 patient years

El-Banayosy et al (2003, Germany	IV	Case series	6 patients with end-stage heart failure, implanted with LionHeart LVAD as destination therapy	1/6 (17%) readmitted for urinary tract infection & renal calculi and battery change 1/6 (17%) patients readmitted for controller change 1/6 (17%) readmitted for spontaneous bleeding from femoral haematoma ands late haemolysis
Siegenthaler et al (2002), Germany	IV	Case series	3 patients with end-stage heart failure, implanted with Jarvik 2000 LVAD as destination therapy	1/3 (33%) patients readmitted to hospital for 1 day

Other adverse events

A number of other adverse events were reported by four of the five studies assessed in this report (Table 11). The high quality study by Rose et al (2001) reported a rate per patient year of 1.37 for patients in the LVAD group, compared to 0.98 in the medical therapy group for miscellaneous adverse events. Rates per patient year for ventricular arrhythmia and cardiac arrest were higher in the medical therapy group than the LVAD implanted group. LVAD implantation appeared to protect against ventricular arrhythmia (RR=0.45, 95%CI [0.22, 0.90]. Common adverse events reported by these studies were right heart failure and organ failure, including liver and renal failure.

Table 11 Other adverse events

Study	Level of Evidence	Study Design	Population	Outcomes
Rose et al (2001), USA REMATCH study Also summarised by Blue Cross Blue Shield Association, (2002) and Thoratec Corporation (2003b)	II	Randomised controlled trial (RCT) HeartMate® LVAD vs optimal medical therapy	129 patients with end-stage heart failure, ineligible for heart transplantation	Rates per patient year Supraventricular arrhythmia LVAD 0.12 Medical therapy 0.03 Rate ratio (95% CI) 3.92 (0.47, 32.4) Miscellaneous adverse events LVAD 1.37 Medical therapy 0.98 Rate ratio (95% CI) 1.41 (0.93, 2.12) Cardiac Arrest LVAD 0.12 Medical therapy 0.18 Rate ratio (95% CI) 0.65 (0.21, 2.0) Ventricular arrhythmia LVAD 0.25 Medical therapy 0.56 Rate ratio (95% CI) 0.45 (0.22, 0.90) Right heart failure LVAD 0.17 Renal failure LVAD 0.25 Medical therapy 0.18
El-Banayosy et al (2001), Germany	IV	Case series	Patients with end-stage heart failure, implanted with a variety of LVADs for long-term support (> 6 months) Novacor n=85 HeartMate n=54 LionHeart n=4	Right heart failure Novacor 21/85 (25%) HeartMate 14/54 (26%) LionHeart n/a[a] Liver failure Novacor 10/85 (12%) HeartMate 6/54 (11%) LionHeart n/a[a] Multiple organ failure Novacor n=85 13/85 (15%) HeartMate n=54 4/54 (7%) LionHeart n=4 n/a[a] Acute renal failure Novacor n=85 3/85 (4%) HeartMate n=54 1/54 (2%) LionHeart n=4 n/a[a] Pneumonia Novacor n=85 2/85 (2%) HeartMate n=54 1/54 (2%) LionHeart n=4 n/a[a]

El-Banayosy et al (2003), Germany	IV	Case series	6 patients with end-stage heart failure, implanted with LionHeart LVAD as destination therapy	3/6 (50%) with temporary haemolysis 2/6 (33%) with early arrhythmia
Frazier et al (2003), United Kingdom and Westaby et al (2002), United Kingdom	IV	Case series	4 patients with end-stage heart failure, implanted with Jarvik 2000 LVAD as destination therapy	1/4 (25%) died from right heart failure

[a] n/a = not available

Potential Cost Impact

Cost Analysis

The purpose of this economic analysis is to determine the cost-effectiveness of LVAD as a destination therapy from the perspective of the health care system. An economic evaluation begins with a search of the research literature in order to identify existing economic evaluation studies of LVAD as a destination therapy. Any existing cost-effectiveness information is then expressed as cost per outcome in 2003 Australian dollars. In the absence of, or in addition to published information, a model of the expected cost of using LVAD as a destination therapy may be performed.

Existing cost-effectiveness evidence

At present the majority of clinical studies on Left Ventricular Assist Devices (LVAD) are to determine their effectiveness as a bridging device while patients await heart transplant. However, one study, the REMATCH trial (Randomised Evaluation of Mechanical Assistance for the Treatment of Congestive Heart failure) performed a costing of the utilisation of hospital resources for surgical implantation of LVAD as a permanent heart failure therapy (Oz et al 2003). The resulting mean cost per patient who survived initial hospitalisation was $432,000 ± $376,000 AUD[1], with an annual re-admission cost per patient of $144,300 AUD.

Estimated cost of LVAD in Australia

Only the Thoratec ventricular assist device is currently registered for therapeutic use in Australia on the ARTG (ARTG #51280), and it is not licensed as a destination therapy for heart failure. However, the VentrAssist™ Left Ventricle Assist System (LVAS) developed by Ventracor is currently being trialled by the Alfred Hospital, Melbourne and results are pending. VentrAssist™ is not being marketed currently, although the manufacturer has estimated that one implant unit will cost between $82,000 and $137,000 AUD.

[1] Calculated from 2003 US dollars using the Purchasing Power Parities (PPPs) for OECD Countries 1980-2003 (OECD 2003).

The best approximation of cost for the surgical insertion of a LVAD as a destination therapy is the cost of insertion of LVAD as bridging therapy. This is estimated at $24,700 AUD (Table 12) and includes operating theatre, hotel, nursing and overhead costs for a mean length of stay of 8.54 days in a public hospital. As the average length of stay described by the REMATCH study is 43.5 days (Rose et al 2001), additional hospital costs of approximately $14,000 per patient could be expected (for hotel, nursing and medical care).

Therefore, using the lowest conservative estimate that all patients on the heart transplant list in Australia would be eligible for and receive LVAD as destination therapy (approximately 150 patients per year) (ANZOD 2003), the estimated cost to the health care system would range from at least $16 million per year to more than $24 million per year. Utilising the upper limit of the number of patients who died from heart failure (2,612 patients in the year 2001) (AIHW 2003b), the estimated cost to the health care system would range from at least $282 million per year to more than $425 million per year. Costs of longer length of stay and re-admission to hospital due to complications have not been included.

There are no long term cost-effectiveness data for the implantation of LVADs as destination therapy. Device reliability and longevity will be crucial factors in determining these costs and patients will require ongoing monitoring and follow-up (Moskowitz et al 2001).

Table 12 Cost items for surgical implantation of LVAD

Item description	Fee ($AUD)	Source
VentrAssist™ LVAS	82,000 – 137,000	Ventracor
MBS # 38615 Left or right ventricular assist device, insertion of (Anaes.) (Assist)	1,273.15	MBS
F01Z Implantation/Replacement AICD, Total system	24,700	AR-DRG Version 5.0[a]

[a] DRG assigned by Alfred Hospital, Melbourne (personal communication)

Ethical Considerations

Nonmaleficence (harm to patients)

The availability of the LVAD does not necessarily imply that it ought to be used in all circumstances. The use of the LVAD as destination therapy raises important ethical questions about the circumstances under which we ought to start, stop or refrain from initiating treatment.

Starting or withholding therapy

Patients who undergo implantation of a LVAD are seriously ill, and as such are extremely vulnerable. Patients offered implantation with a permanent LVAD must be fully informed of the potential benefits and harms associated with implantation, especially in view of the experimental nature of the technology, compared to the usual practice of medical therapy alone. Potential harms of implantation with a LVAD include the risk of performing highly

invasive surgery on severely ill patients, death from adverse events such as infection and embolism, device failure, right ventricular failure, T-lymphocyte dysfunction, pro-inflammatory cytokine disturbances, neurological disorders and the risk of re-hospitalisation. Potential benefits include increased survival time and an improved quality of life (Rose et al 2001; Hunt 2002). At this point in time, the balance of benefits over harms is questionable, and the burden of proof should lie with those who propose the therapy for patients.

Therapy withdrawal

Therapy withdrawal is a particular ethical concern with the LVAD. In one trial, 15/68 (22%) of patients, or their families, chose to have the LVAD switched off or did not agree to surgical replacement and 13/61 (21%) of medical therapy patients opted for palliative care only (Thoratec Corporation 2003b).

Patients receiving this therapy are critically ill and the implantation of a LVAD is permanent. Patients who did not receive an LVAD as destination therapy would be expected to have a short life expectancy supported by optimal medical therapy in a hospital environment (Blue Cross 2002). There are no criteria for the withholding or cessation of treatment with an implanted LVAD; however care of unsuccessful implanted patients would follow the National Heart Foundation guidelines with the option of continued medical therapy or palliative care (Krum 2001; National Heart Foundation of Australia & Zealand 2002). The lifetime of the device is difficult to predict, however the probability of device failure at two years is 35 per cent (Blue Cross 2002).

From an ethical perspective, withdrawal of therapy is acceptable when:
1. the aim of treatment withdrawal is not to precipitate death and
2. the withdrawal of treatment does not promote death at a steeper trajectory than the underlying disease, unless another, more important, goal is being achieved (Bramstedt & Wenger 2001).

LVADs present an ethically difficult situation because powering off the device without explantation creates risks that increase the likelihood of death. Leaving the unpowered device in place actually compromises the natural function of the heart. Thus, treatment withdrawal may actively contribute to a patient's death (Bramstedt & Wenger 2001).

At the very least, patients need to be made aware of the mid-term consequences of undergoing implantation with a LVAD. Discussion about the possibility of withdrawal of therapy needs to be included in initial conversations about treatment, and this should include advising patients that powering off the device may contribute in a small way to their death.

Clinical Trials

Patients undergoing this procedure as participants in a clinical trial fall into the category of persons in dependent or unequal relationships. As such, the possibility that their relationship with researchers/clinicians may impair their consent means that Human Research Ethics Committees will need to be satisfied that consent is both informed and voluntary (NHMRC 1999). Allocation to the LVAD or usual care arm of a randomised trial raises the question whether it is ethical to restrict a novel but largely unproven

technology to a certain group of people (Stevenson & Kormos 2001). Researchers must give patients an assurance that their care will not be compromised in any way if they refuse to participate in, or withdraw from, a clinical trial.

Clinical trials for the use of LVADs as a destination therapy are currently underway in Australia, United Kingdom and the United States.

Compromised competence and surrogate decision-making

Patients who undergo implantation of a LVAD are at risk of compromised competence. Both the severity and likely course of their primary illness and the presence of other conditions increase the likelihood that the patient may, at some stage, be unable to make significant decisions for him or herself. Designating a surrogate decision maker while the patient is still competent is crucial (Bramstedt 2001).

Access and equity issues

From a societal perspective the use of the LVAD as destination therapy is of questionable social value. The basic price of a LVAD used in this way is A$82-137,000, with additional associated surgical and ongoing nursing care costs. The high price of this technology, and the small group of individuals who would have access to it for relatively short periods of time, raise concerns about the appropriateness of allocating resources to this therapy that might be better used in other areas.

In addition to concerns about the allocation of resources to the LVAD in preference to other areas of health care, the LVAD is also unlikely to be available equitably to all Australians. The implantation of LVADs for destination therapy should only be performed in centres of excellence in major capital cities, experienced in cardiac transplantation and the implantation of LVADs as a bridge-to-heart transplantation. Rural and regional heart failure patients must travel to these centres and patients from the Northern Territory and South Australia would have to travel interstate, raising issues of geographic inequality. Further, patients undergoing this major surgical procedure require support structures. Family members may have difficulties travelling long distances to accompany the patient or, due to the potential lengthy rehabilitation period, may be unable to spend long periods of time away from their homes, their work and other family members in order to stay with the patient. If the patient is well enough to return home they will require the assistance and support of a trained general practitioner, which may not be possible in rural and remote areas. A guaranteed power source is also essential for the well being of these patients, and again this may not be possible in rural or remote communities. The capacity to benefit from this technology should not be limited by the patient's ability to access support services.

In addition there are issues relating to advance care directives made by interstate patients in their home jurisdiction in respect to palliative care and surrogate decision making options, which may not be legally binding in another state or jurisdiction. However, it is felt that the patient's wishes would

be taken into account in this situation (South Australian Office of the Public Advocate).

Training and Accreditation

Training

It is recommended that the implantation of permanent LVADs be confined to large centres of excellence that have existing surgical and nursing staff with the skills and expertise in the management of chronically ill heart failure patients. The use of LVADs as a bridge-to-heart transplantation is established in Australia with programs operating in the Royal Perth Hospital (Perth), the Royal Children's Hospital (Melbourne), The Alfred Hospital (Melbourne), the Prince Charles' Hospital (Brisbane) and St Vincent's Hospital (Sydney) (National Heart Foundation of Australia 2000). It would be expected that these centres would have the skills to provide pre- and post-operative care and support for patients undergoing implantation of LVADs as destination therapy. There would need to be adequate training (in the use of the LVAD) of the patient and the patient's general practitioner and family once the patient has been allowed to leave hospital and return home. Immediate support personnel must be well versed in recognising the LVAD system alarms, changing the power supply and if necessary maintaining circulation utilising the hand pump until appropriate professional help is available (Kirklin 2003; National Heart Foundation of Australia 2000).

Clinical Guidelines

The current guidelines, written by the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (2002), for the management of patients with chronic heart failure adequately discuss the options available for the management of patients with chronic heart failure. Patients diagnosed with severe symptoms of systolic heart failure (left ventricular ejection fraction <40 per cent and NYHA Class IV) are initially offered the option of non-pharmacological (diet and exercise) or pharmacological treatment (diuretics, angiotensin-converting enzyme inhibitors, digoxin, β-blockers and spironolactone). The guidelines specify that patients who experience no improvement in symptoms or an intolerance to pharmacological agents then have the option of palliative care or surgery. Surgical options include left ventricular free wall excision, cardiomyoplasty, the implantation of left ventricular assist devices or cardiac transplantation. The guidelines state that although LVADs have been used as a long-term alternative to cardiac transplantation, no device is approved for this indication in Australia (Krum 2001; National Heart Foundation of Australia & Zealand 2002). Criteria may need to be developed to clearly identify system standards for devices that may be used in different situations. The clinical circumstances and indications for the use of devices for bridge-to transplantation, bridge-to-recovery and destination therapy may become increasingly similar and less distinct (Stevenson & Kormos 2001).

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon Scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

An Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, an Horizon Scanning Report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

Search Strategy used for the Report

The medical literature was searched (Table 13) utilising the search terms in Table 14 to identify relevant studies and reviews, until February 2004. In addition, major international health technology assessment databases were searched.

Table 13 Literature sources utilised in assessment

Source	Location
Electronic databases	
AustHealth	University library
Australian Medical Index	University library
Australian Public Affairs Information Service (APAIS) - Health	University library
Cinahl	University library
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	University library
Current Contents	University library
Embase	Personal subscription
Pre-Medline and Medline	University library
ProceedingsFirst	University library
PsycInfo	University library
Web of Science – Science Citation Index Expanded	University library

Internet	
Current Controlled Trials metaRegister	http://controlled-trials.com/
Health Technology Assessment international	http://www.htai.org
International Network for Agencies for Health Technology Assessment	http://www.inahta.org/
Medicines and Healthcare products Regulatory Agency (UK). • Medical Device Alert Safety warnings • Device evaluations • Diagnostic imaging review • Disability equipment assessments	http://www.medical-devices.gov.uk/
National Library of Medicine Health Services/Technology Assessment Text	http://text.nlm.nih.gov/
National Library of Medicine Locator Plus database	http://locatorplus.gov
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/greylit/index.shtml
Scirus – for Scientific Information Only	http://www.scirus.com
Trip database	http://www.tripdatabase.com
U.K. National Research Register	http://www.update-software.com/National/
US Food and Drug Administration, Center for Devices and Radiological Health. • Manufacturer and User facility Device Experience (MAUDE). MAUDE data represents reports of adverse events involving medical devices. • PreMarket Approvals database	http://www.fda.gov/cdrh/databases.html
Websites of Specialty Organisations	Dependent on technology topic area

Table 14 Search terms utilised

Search terms
MeSH
Heart diseases, heart failure, heart-assist devices, heart transplantation, cardiac surgical procedures
Text words
destination therapy, bridge to transplant*, left ventricular assist device*, heartmate, LVAD, heart transplant*
Limits
Human, English

Availability and Level of Evidence

Seven papers, which reported on five studies, were included for assessment in this report (see Appendix B). Two papers were assessed which described the REMATCH study, a randomised controlled trial (Level II evidence) (see Table 15), comparing the implantation of HeartMate® LVAD to optimal medical therapy. Two papers described the same case series study (Level IV evidence), which described the implantation of the Jarvik 2000 LVAD. The remaining three studies were case series (Level IV evidence), which described the implantation of the Jarvik 2000, LionHeart, Novacor and HeartMate® LVADs.

Table 15 Designations of levels of evidence*

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

*Modified from (National Health and Medical Research Council 1999)

Sources of Further Information

A clinical trial on the implantation of the VentrAssist™ LVAD is currently being conducted in Australia by Ventracor Limited. The company was approached for initial trial results but these were currently unavailable. In addition, Ventracor Limited are conducting a clinical trial in the United States and are about to begin recruitment for a clinical trial in the United Kingdom (personal communication, Ventracor).

Conclusions

Left ventricular assist devices have been in widespread use as a circulatory support since the late 1980s for use in patients with chronic heart failure that are awaiting heart transplantation. Heart failure, a condition that accounted for over 40,000 hospitalisation episodes in Australia during the period 2000-01, occurs when the heart is no longer capable of pumping blood around the body. The "gold standard" treatment for heart failure is heart transplantation, however with organ donors in short supply, the waiting list for transplant is long and many patients die before receiving a transplant. New types of LVADs have been developed, such as the HeartMate®, LionHeart and the Jarvik 2000 that may be used as a permanent implant or destination therapy, rather than as a bridge-to-transplant.

Patients eligible for implantation with a LVAD as destination therapy require heart transplantation but do not satisfy the criteria to be eligible for this procedure. Criteria for permanent implantation with a LVAD include ≥ 65 years of age, New York Heart Association Class IV heart failure for ≥ 90 days and a left ventricular ejection fraction ≤ 25 per cent. The number of patients waiting on the transplant list may be a reasonable indication of the minimum number of patients who may require permanent implantation with a LVAD. This figure was 70 patients as of January 2003, however, the number of patients who died whilst on the list was ten, between July 2002 and June 2003. However, the maximum number of patients requiring permanent implantation

with a LVAD may be the number of patients who die of heart failure per year, which was 2,612 in the year 2001.

Left ventricular assist devices appear to provide an increased survival time when compared to optimal medical therapy alone. The highest level of available evidence (Level II evidence) indicates that the implantation of an LVAD results in a median survival time of 408 days with an associated mortality rate of 60 per cent, compared to a median survival time of 105 days and an associated mortality rate of 89 per cent in the medical therapy group. The risk of death from all causes at all ages is reduced by almost 50% for patients implanted with a LVAD compared to patients receiving optimal medical therapy (RR =0.52, 95%CI [0.34, 0.78]). One and two year survival rates for the LVAD group were 52 per cent and 23 per cent, respectively, compared to 25 per cent and 8 per cent in the medical therapy group. Level IV evidence also indicates improvements in survival time, quality of life and the number of patients able to return to the home environment for those patients receiving a LVAD.

A number of serious adverse events are associated with the implantation of a LVAD including right heart failure, infection and sepsis, device malfunction, embolism and bleeding.

In addition, a number of serious ethical issues are associated with the implantation of a permanent LVAD, including the process of withdrawing therapy, the balance of benefits and harms of therapy, and access to treatment and ongoing care.

Currently the only device being clinically trialled in Australia is the VentraAssist™ LVAD. The manufacturer has estimated that a single unit would cost between $82,000 and $137,000 AUD. The best approximation of cost for the surgical insertion of a LVAD as destination therapy is the cost of insertion of LVAD as bridging therapy, $24,700 AUD, which includes theatre, hotel, nursing and overhead costs for a mean length of stay of 8.54 days in a public hospital. As the average length of stay for the implantation of a LVAD, as described by the REMATCH study, is 43.5 days, additional hospital costs of approximately $14,000 per patient may be expected.

The Committee formed the view that the use of left ventricular assist devices (LVADs) as destination therapy for patients with cardiac failure is not supported for general use at this time. Trials of LVADs are currently underway and should be confined to centres of excellence that are established cardiac transplantation units, with experience in the implantation of LVADs as a bridge-to-transplantation.

It should be noted that the use of LVADs as destination therapy, in the total context of the management of heart failure, raises significant ethical as well as clinical issues that will need to be addressed in a systematic and considered manner by the Australian community as the evidence becomes available.

Appendix A

New York Heart Association Classification for Congestive Heart Failure

A functional and therapeutic classification for prescription of physical activity for cardiac patients.

Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities.

Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.

Class III: patients with marked limitation of activity; they are comfortable only at rest.

Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

(New York Heart Association)

Appendix B

Profiles of studies included for assessment of the safety and effectiveness of LVADs as destination therapy

Level of Evidence	Study	Location	Study design	Study population	Outcome assessed	Length of follow-up
II	Rose, E.A Gelijns, A.C. Moskowitz, A.J. Heitjan, D.F. Stevenson, L.W. Dembitsky, W. Long, J.W. Ascheim, D.D. Tierney, A.R. Levitan, R.G. Watson, J.T. Meier, P. (2003)	Multi-centre, United States[a]	Randomised controlled trial (RCT)	129 patients with end-stage heart failure, ineligible for heart transplantation LVAD n = 68 Medical therapy n = 61	Survival time Heart function Quality of life Number of days spent in hospital Device failure Embolism Bleeding Infection Neurological dysfunction Cardiac arrest Right heart failure Ventricular arrhythmia Renal failure Supra—ventricular arrhythmia	24 months
IV	El-Banayosy, A. Kőrfer, R, Arusoglu, L. Kizner, L. Morshuis, M. Milting, H. Tenderich, G. Fey, O. Minami, K. (2001)	Bad Oeyn-hausen, Germany	Case series	Patients with end-stage heart failure, implanted with a variety of LVADs for long-term support (> 6 months) Novacor n=85 HeartMate n=54 LionHeart n=4	Length of time supported by LVAD Number of patients discharged home Embolism Bleeding Infection Re-hospitalisation Right heart failure Liver failure Renal failure Multiple organ failure Pneumonia	39 months

IV	El-Banayosy, A. Arusoglu, L. Kizner, L. Morshuis, M. Tenderich, G. Pae, W.E. Kőrfer, R, (2003)	Bad Oeyn-hausen, Germany and Penn-sylvania, United States	Case series	6 patients with end-stage heart failure, implanted with LionHeart LVAD as destination therapy	Length of time supported by LVAD Number of patients discharged home Device failure Bleeding Infection Neurological dysfunction Re-hospitalisation Haemolysis Arrhythmia	24 months
IV	Frazier, O.H. Myers, T.J. Westaby, S. Gregoric, I.D. (2003)[b]	Oxford, United Kingdom	Case series	4 patients with end-stage heart failure, implanted with Jarvik 2000 LVAD as destination therapy	Length of time supported by LVAD Number of patients discharged home Bleeding Right heart failure	32 months
IV	Siegenthaler, M.P. Martin, J. van de Loo, A. Doenst, T. Bothe, W. Beyersdorf, F. (2002)	Freiburg, Germany	Case series	3 patients with end-stage heart failure, implanted with Jarvik 2000 LVAD as destination therapy	Length of time supported by LVAD Quality of life Length of hospital stay Operative time Number of patients discharged home Embolism Bleeding Infection Re-hospitalisation	6 months

IV	Westaby, S. Banning, A.P. Saito, S. Pigott, D.W. Jin, X.Y. Catarino, P.A. Robson, D. Moorjani, N. Kardos, A. Poole-Wilson, P.A. Jarvik, R. Frazier, O.H. (2002)[b]	Oxford, United Kingdom	Case series	4 patients with end-stage heart failure, implanted with Jarvik 2000 LVAD as destination therapy	Patient heart function Quality of life	21 months

[a] REMATCH study also summarised by the Blue Cross, Blue Shield Association TEC bulletin, volume 17, No 19, December 2002 and by the Thoratec Corporation Document #29128, [b] Studies by Frazier et al (2003) and Westaby et al (2003) reported on same patient group

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