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Multicenter Evaluation of an Intrapericardial Left Ventricular Assist System

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Objectives The aim of this study was to conduct an initial clinical evaluation of the new HeartWare Ventricular Assist System (HeartWare, Inc., Framingham, Massachusetts) in a multicenter, prospective, nonrandomized single-arm clinical trial.

Background Heart failure is a worldwide epidemic. The effectiveness of heart transplantation and medical therapy is limited, resulting in the emergence of mechanical circulatory support as a primary treatment for end-stage heart disease. Left ventricular assist devices that use rotary pumps are small and durable, which might reduce morbidity and mortality during support.

Methods Fifty heart transplant candidates with New York Heart Association functional class IV symptoms were supported at 5 international centers by the HeartWare System for 180 days, until heart transplant, myocardial recovery and device explant, or death. Patients who continue to be supported have been followed for a minimum of 2 years.

Results Of the 50 patients, 20 (40%) received transplants, 4 (8%) had the pump explanted after myocardial recovery, and 17 (34%) continue support at 2 years. Nine (18%) patients died during support from sepsis (n = 3), multiple organ failure (n = 3), or hemorrhagic stroke (n = 3). The actual survival at 6, 12, and 24 months was 90%, 84%, and 79%, respectively. In the survivors, measures of quality of life showed a significant improvement over baseline values. Significant improvements were found for recognition memory at 3 months after implant ($p = 0.006$). The most frequent adverse events were infection and bleeding.

Conclusions Patients with end-stage heart failure can be safely and effectively supported by the HeartWare Ventricular Assist System with improved quality of life and neurocognitive function. (J Am Coll Cardiol 2011;57:1375–82)

Heart failure is a worldwide epidemic that contributes considerably to the overall cost of health care in developed nations. The number of people afflicted with this complex disease is increasing at an alarming pace—a trend that is likely to continue for many years. Medical therapy has limited effectiveness, with expected 1- and 5-year mortality rates nearing 30% and 60%, respectively (1). Heart transplantation is an effective treatment, but it is restricted by the number of available donor organs. Mechanical circulatory support with a left ventricular assist device (LVAD) is emerging as a primary treatment for patients with advanced-stage heart failure. When compared with medical therapy, support with an LVAD as a bridge to heart transplant or for destination therapy provides a better chance for survival with an enhanced quality of life (2,3).

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The first generation of pulsatile LVADs has been effective in supporting patients for bridge to transplant (BTT) and destination therapy, but persistent complications related to the size and durability of the devices have limited acceptance

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Abbreviations and Acronyms

BTT = bridge to transplant
HVAD = HeartWare Ventricular Assist Device
INR = international normalized ratio
KCCQ = Kansas City Cardiomyopathy Questionnaire
LV = left ventricle/ventricular
LVAD = left ventricular assist device
RVAD = right ventricular assist device
SHFM = Seattle Heart Failure Model

of this therapy (4). Bleeding, infection, and device failure have been leading causes of morbidity and mortality during support with these devices. Smaller and more durable rotary blood pumps have been developed in an effort to minimize LVAD-related complications and to broaden the population of patients who might benefit from heart assist device therapy (5). The HeartWare Ventricular Assist System (HeartWare, Inc., Framingham, Massachusetts) is a new mechanical circulatory support system that is smaller and more durable than previous LVAD systems (6). The small HeartWare Ventricular Assist Device (HVAD) pump can be placed within the pericardial space, which avoids the need for abdominal surgery and the creation of a pump pocket. Durability is enhanced by the wearless and friction-free movement of the device's single, moving internal component: the impeller. The peripheral components have been designed for ease of use by the patient in outpatient settings. The HVAD system is intended to provide long-term left ventricular (LV) support in patients with advanced heart failure.

In this report, we present the results of a multicenter clinical trial designed to evaluate the safety and efficacy of the HVAD system to support patients with end-stage heart failure.

Methods

Study design. This multicenter, prospective, nonrandomized, single-arm trial was designed to evaluate the safety and efficacy of the HVAD system when used as a bridge to heart transplant. Patients with end-stage heart failure who were eligible for cardiac transplantation were candidates for the study. The study inclusion and exclusion criteria are listed in the Online Appendix. Fifty patients were enrolled between March 2006 and December 2008 at 5 medical centers in Europe (3) and Australia (2). The dates of follow-up for adverse events were from March 22, 2006, through June 3, 2009. Adverse events were collected until all 50 patients reached end point. Patients who remain on support have been followed for status only up to a minimum of 24 months. The study was in compliance with U.S. Food and Drug Administration guidelines and was approved by the ethics committee (institutional review board) at each of the participating centers. All patients gave informed consent.

End points. The primary study end point was survival to transplant, cardiac recovery with device explant, or continuing device support at 180 days. Secondary end points included a comparison of baseline cardiac index to the mean pump flow index (pump flow/body surface area) and the incidence of all adverse events and device failures as defined by the INTERMACS registry (Inter-Agency Registry for Mechanically Assisted Circulatory Support) (7). Measures for quality of life (Kansas City Cardiomyopathy Questionnaire [KCCQ]) and neurocognitive function (neurocognitive evaluations included 4 standard neurocognitive measures with 8 procedures and surveyed cognitive domains such as verbal learning, memory, knowledge of visually presented drawings, cognitive speed, and visual spatial abilities) were obtained at baseline and at 1, 3, and 6 months of support. Under the direction of the site investigators, data were collected and then submitted to a contracted clinical research organization for analysis. All data were analyzed and adjudicated by a Clinical Events Committee and Data Safety and Monitoring Board. The Seattle Heart Failure Model (SHFM) was used to generate a virtual control arm with the baseline clinical parameter obtained within 1 week before implantation.

HVAD system. The implanted components of the HVAD system comprise the HVAD blood pump with integrated inflow cannula, an outflow graft, and a percutaneous driveline. The HVAD pump weighs 140 g, has a displacement volume of 50 ml, and has an external diameter of 53 mm. The pump operates within the range of 1,800 to 4,000 rpm and can pump up to 10 l/min of blood. Within the titanium pump housing is a single moving component, the impeller, which is suspended by magnetic and hydrodynamic forces for frictionless rotation. Communication from the pump to the external power and control components is provided by a flexible, polyurethane-covered driveline that is externalized through the abdominal wall. A microprocessor-based controller monitors pump function and regulates power to dual motors within the pump. The controller displays pump speed, blood flow rate, power, alarm conditions, and instructions for resolving alarm conditions. A continuous power supply is provided by either AC or DC sources, including lithium-ion batteries for portable operation. A system monitor provides a means for adjusting pump operating parameters, monitoring pump function and storing data.

During the study period, the HVAD pump was implanted through a median sternotomy and with normothermic cardiopulmonary bypass. A sewing-ring made of Dacron and titanium was sewn onto the epicardial surface of the heart at the apex of the LV. An opening into the LV was made through the center of the sewing-ring by using a circular coring knife, after a cruciate incision. The 21-mm integrated inflow cannula of the pump was then inserted into the LV through the opening in the sewing ring and secured in place by tightening the C-ring portion of the sewing cuff. The 10-mm outflow graft was trimmed to the proper length and anastomosed to the ascending aorta. The pump was positioned within the pericardial space at the apex of the heart, and the driveline was externalized through the right upper quadrant of the abdomen (Fig. 1). After air was removed from the

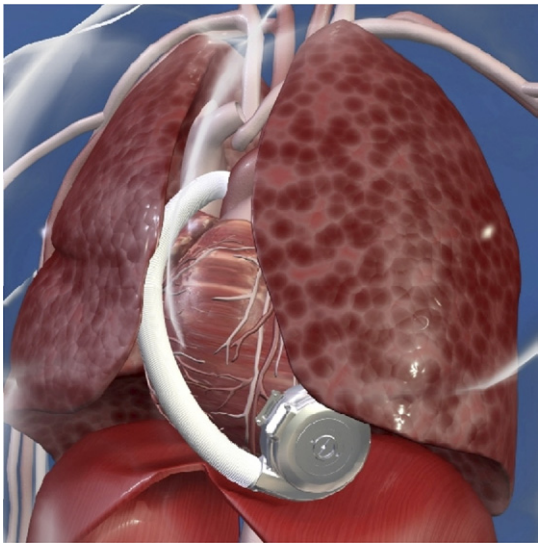

Figure 1 HVAD Pump Positioned in Pericardial Space

Position of the HeartWare Ventricular Assist Device (HVAD) pump (HeartWare, Inc., Framingham, Massachusetts) after implantation.

pump and graft, the patient was weaned from cardiopulmonary bypass, and HVAD pump support was initiated. Pump speed was adjusted to achieve the desired level of cardiac output.

Continuous anticoagulation therapy is recommended for patients with HVAD pumps, but therapy is individualized for each patient. In this study, patients were given an intravenous heparin infusion after risk of surgical bleeding had passed to increase activated partial thromboplastin time to a target range of 50 to 60 s or an activated clotting time of 140 to 160 s. Once patients were able to take oral medications, warfarin and aspirin or clopidogrel were given and continued throughout support. Warfarin of each patient was adjusted toward a targeted international normalized ratio (INR) value between 2.0 and 3.0. Cardiac function was supported with inotropic medications, by managing fluid volume, and adjusting the speed of the HVAD pump between 2,400 and 3,200 rpm to achieve a cardiac index >2.0 l/min/m^2. After they recovered from the implant surgery, patients received rehabilitative care and education about the HVAD system. Once the patients were clinically stable, had demonstrated their ability to provide self-care, and were able to maintain the HVAD system properly, they were discharged from the hospital.

Statistical analyses. Statistical differences of continuous variables between baseline and post-implant data were determined by a paired *t* test with a significance level of 0.05. Hemodynamic and biochemical data are presented as the mean ± SD. Measures of quality of life and neurocognitive function are reported for patients who received evaluations before implantation and at 1 month and 3 and 6 months after implant. The testing was not completed for all patients at all time intervals, therefore repeated measures analysis of variance was used to evaluate change across testing sessions for group data. Patients were included in the repeated measures analyses of variance if they had complete data for the specific time points being reported. Quality of life and neurocognitive function data are given as the mean and SEM. Competing outcomes data were calculated with actual percentages for each outcome, because all ongoing patients were followed for a minimum of 24 months.

Table 1 Baseline Characteristics

Age (yrs)	48.5 (20–75)
Sex, male	43 (86%)
BSA (m^2)	1.9 (1.4–2.6)
BMI (kg/m^2)	25.6 (16.5–40.8)
Heart failure etiology	
Idiopathic CMP	22 (44%)
Ischemic CMP	20 (40%)
Familial or congenital CMP	5 (10%)
Myocarditis	3 (6%)
INTERMACS profile	
Profile 2	11 (22%)
Profile 3	35 (70%)
Profile 4	4 (8%)
Inotropic support	50 (100%)
Intra-aortic balloon pump	4 (8%)
LVEF (%)	18.7 ± 5.9
LVEDD (mm)	68.6 ± 8.0
Cardiac index (l/min/m^2)	1.94 ± 0.54
PCWP (mm Hg)	23.7 ± 6.5
CVP (mm Hg)	12.3 ± 5.9
Heart rate (beats/min)	89.1 ± 20.2
Arterial blood pressure (mm Hg)	
Systolic	101.5 ± 13.9
Diastolic	64.2 ± 10.9
Mean	76.7 ± 10.6
Pulmonary artery pressure (mm Hg)	
Systolic	47.6 ± 15.7
Diastolic	27.7 ± 9.3
Laboratory values	
BUN (mg/dl)	28.9 ± 15.6
Creatinine (mg/dl)	1.3 ± 0.5
ALT (IU/l)	63.5 ± 127
AST (IU/l)	75.8 ± 132
LDH (IU/l)	316 ± 159
Total bilirubin (mg/dl)	1.5 ± 1.0
Hgb (g/dl)	12.5 ± 2.0
HCT (%)	36.8 ± 6.0
PFH (mg/dl)	10.1 ± 13.8
Platelets (×10^9/l)	243 ± 101
INR	1.6 ± 0.6
APTT (s)	39.7 ± 10.6

Values are median (range), n (%), or mean ± SD.

ALT = alanine aminotransaminase; APTT = activated partial thromboplastin time; AST = aspartate aminotransaminase; BMI = body mass index; BSA = body surface area; BUN = blood urea nitrogen; CMP = cardiomyopathy; CVP = central venous pressure; HCT = hematocrit; Hgb = hemoglobin; INR = international normalized ratio; INTERMACS = Inter-Agency Registry for Mechanically Assisted Circulatory Support; LDH = lactic dehydrogenase; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; PCWP = pulmonary capillary wedge pressure; PFH = plasma-free hemoglobin.

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Survival data comparing actuarial survival of the 50 HeartWare patients with the SHFM estimated survival with medical therapy were analyzed with the Kaplan-Meier actuarial survival method and the SHFM (8). An estimated LVAD hazard ratio for benefit was calculated with the SHFM estimated survival and the Kaplan Meier observed survival. The p value was derived with a Z test. Multiple comparisons were made without correction for multiplicity.

Results

Baseline characteristics. Summarized in Table 1, the baseline characteristics of the group were similar to those of other BTT studies and reflect the composition of the heart transplant waiting lists at the participating institutions. Most patients were men (86%), and the mean age was 48.5 years (range 20 to 75 years). The cause of heart failure was idiopathic in 22 patients (44%), ischemic in 20 patients (40%), familial in 5 patients (10%), and myocarditis in 3 patients (6%). All patients had New York Heart Association functional class IV symptoms. Baseline clinical conditions were used to categorize patients according to INTERMACS profiles, which classify the severity of heart failure of patients (9). Of the patients, 11 (22%) were in profile 2 (progressive decline), 35 (70%) were in profile 3 (stable but inotrope dependent), and 4 (8%) were in profile 4 (recurrent advanced heart failure). All were receiving inotropes. So why were these not profile 3? Were they not deemed inotrope dependent? All patients were receiving intravenous inotropic medications, and 4 (8%) of the patients were also being supported by an intra-aortic balloon pump. Cardiac function was considerably impaired in the group, on the basis of analysis of hemodynamic parameters. Pre-operative risk factors are summarized in Table 2.

Outcomes. The survival to heart transplantation; myocardial recovery and HVAD pump explant; or ongoing support at 6, 12, and 24 months after implant was 90%, 84%, and 79%, respectively (Figs. 2 and 3). The SHFM estimated survival (mean ± SEM) of this cohort if medical therapy was continued was 73 ± 3% at 180 days, 58 ± 4% at 1 year, and 40 ± 4% at 2 years (Fig. 3). Twenty of the 50 patients had a >50% estimated mortality at 1 year. The estimated hazard ratio for LVAD therapy, with the SHFM as a virtual control arm, was 0.33 at 180 days, 0.29 at 1 year, and 0.26 at 2 years (all p values ≤0.001) (Fig. 3).

The median duration on HVAD pump support during the trial interval was 322 days (range 12 to 847 days), mean duration of HVAD pump support was 348 days, and the cumulative support time was 47.8 years. There were no mechanical failures of the HVAD system. As of May 1, 2010, 20 (40%) patients had undergone heart transplant, 4 (8%) recovered myocardial function and had the device explanted, and support was ongoing in 16 (32%). The median time to heart transplant was 267 days (range 45 to 769 days). Nine patients (18%) died during support at a median duration of 94 days (range 13 to 515 days). The

Table 2 Pre-Operative Risk Factors

Parameter	Patients (n)
Inotropic support	50
Previous myocardial infarction	10
Coronary angioplasty	13
Previous sternotomy	6
Arrhythmias	25
Implantable cardioverter-defibrillator	32
Pacemaker	9
Moderate-severe right ventricular dysfunction	19
Hypertension	15
Diabetes	7

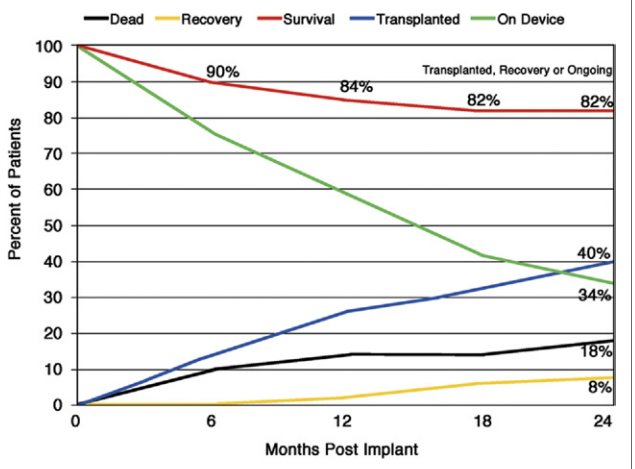

Figure 2 Competing Outcomes

Competing outcomes from the time of implant to 24 months.

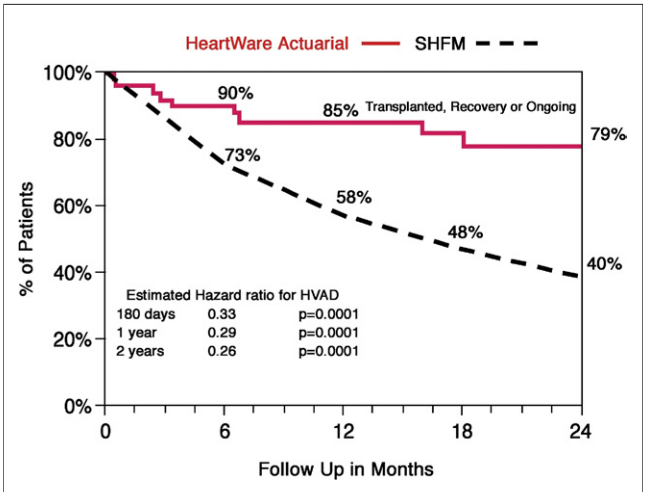

Figure 3 Actuarial Success Rates With HVAD and Predicted Survival Rates Based on the SHFM

Actuarial success rates with HeartWare Ventricular Assist Device (HVAD) and prediction of survival with continued medical therapy (on the basis of the Seattle Heart Failure Model [SHFM]).

Table 3 Hemodynamic Changes From Baseline to 24 and 48 h of HVAD Support

	Baseline	24 h	p Value (Baseline vs. 24 h)	48 h	p Value (Baseline vs. 48 h)
CI (l/min/m^2)	1.94 ± 0.54	2.9 ± 0.76	0.0001	2.83 ± 0.63	0.0001
MAP (mm Hg)	76.7 ± 10.6	79.8 ± 11.6	NS	82.4 ± 10.5	0.01
PCWP (mm Hg)	23.7 ± 6.5	15 ± 3.6	0.001	15.5 ± 3.4	0.0001
HVAD flow index (l/min/m^2)	N/A	3.32 ± 0.6	0.0001	3.14 ± 0.54	0.0001

Values are mean ± SD.
CI = cardiac index; HVAD = HeartWare Ventricular Assist Device; MAP = mean arterial pressure, PCWP = pulmonary capillary wedge pressure.

causes of death were sepsis (n = 3), multiple organ failure (n = 3), and hemorrhagic stroke (n = 3). Hemodynamic variables improved significantly after the HVAD was implanted (Table 3). At baseline, the mean cardiac index was 1.94 ± 0.54 l/min/m^2; it increased to 2.9 ± 0.76 l/min/m^2 ($p < 0.001$) at 24 h and 2.83 ± 0.63 l/min/m^2 at 48 h ($p < 0.0001$) after the implant. The mean pulmonary capillary wedge pressure decreased from 23.7 ± 6.5 mm Hg at baseline to 15.0 ± 3.6 mm Hg ($p < 0.001$) at 24 h and 15.5 ± 3.4 mm Hg ($p < 0.0001$) at 48 h. The HVAD pump flow index at 24 and 48 h after implant was 3.32 ± 0.6 l/min/m^2 and 3.14 ± 0.54 l/min/m^2, respectively; both values were significantly greater ($p < 0.0001$) than the baseline cardiac index (1.94 ± 0.54 l/min/m^2). There were no significant changes in the central venous pressure or mean arterial blood pressure.

Serial laboratory analyses for the entire cohort from baseline to 6 months are listed in Table 4. Measures of renal and hepatic function were abnormal after the implant surgery but returned to normal ranges by 2 weeks. A post-implant decrease in hemoglobin and hematocrit levels, secondary to operative bleeding, returned to normal ranges by 3 months. Anticoagulation therapy was the cause for elevated activated partial thromboplastin times. The mean INR reached therapeutic range by 14 days and remained within that range at 180 days.

The mean hospital stay was 45 days; of this time, 13.1 ± 9.3 days were in the intensive care unit, 16.4 ± 12.6 days in a step-down unit, and 15.4 ± 10.2 days in a regular floor unit. Of the 50 patients, 47 (94%) were discharged from the hospital; the cumulative outpatient support time was 42.6 years. There were 53 readmissions to the hospital for various medical reasons. The readmission rate for medical complications was 1.24 admissions/patient-year, which is a 74% reduction when compared with the average admission rate of this group for the year before their HVAD implants. Patients discharged from the hospital recorded pump performance parameters, which showed that the mean pump speed was 2,709 ± 164 rpm and the mean flow was 6.4 ± 0.8 l/min at 4.6 ± 0.7 W.

Adverse events. There were 92 adverse events reported for 39 patients during a cumulative support time of 47.8 years (1.92 events/patient-year) (Table 5). Eleven of the 50 patients (22%) did not experience any adverse event during the follow-up period. The most common adverse events were infection-related. Infection of the driveline exit site (0.20 events/patient-year) did not cause any deaths and occurred mainly after 30 days of support. Five patients (10%) developed sepsis, and sepsis was the cause of death in 3 patients. The causes of sepsis were varied (pneumonia: 2, fungal sepsis: 1, bacteremia: 1, and driveline exit site: 1) and occurred between 48 h and 970 days after implant. Bleeding

Table 4 Laboratory Values From Baseline to 6 Months After HVAD Implant

	Baseline	1 Week	2 Weeks	3 Months	6 Months
Sodium (mEq/l)	136.1 ± 4.7	137.6 ± 8.5	136.8 ± 6.4	138.6 ± 3.3	139.4 ± 2.5
Creatinine (mg/dl)	1.3 ± 0.5	1.1 ± 0.6	1.1 ± 0.7	1.0 ± 0.3	1.2 ± 0.3
BUN (mg/dl)	28.9 ± 15.6	24.4 ± 19.5	21.9 ± 21.0	19.7 ± 9.9	25.5 ± 15.8
LDH (IU/l)	325 ± 176	802 ± 756	628 ± 675	467 ± 520	338.6 ± 157.7
ALT (IU/l)	63.6 ± 127.0	89.1 ± 191.0	73.5 ± 104	30 ± 10	34.6 ± 14.0
AST (IU/l)	75.8 ± 132.0	73.6 ± 91.0	57.3 ± 63.4	23.1± 13.7	29.5 ± 17.3
Bilirubin (mg/dl)	1.5 ± 1.0	2.6 ± 3.8	1.4 ± 1.2	0.8 ± 0.5	0.8 ± 0.4
Hgb (mg/dl)	12.4 ± 2.0	10.4 ± 1.2	10.9 ± 4.4	12.5 ± 1.8	12.9 ± 2.6
HCT (%)	36.8 ± 6.0	31.5 ± 3.9	31.0 ± 3.2	37.6 ± 4.5	37.6 ± 6.0
PFH (mg/dl)	10.1 ± 13.8	13.7 ± 45.2	7.8 ± 15.7	7.1 ± 7.1	7.0 ± 8.5
APTT (s)	39.7 ± 10.6	54.8 ± 20.0	50.2 ± 17.3	46.6 ± 19.5	49.1 ± 13.4
INR	1.6 ± 0.6	2.3 ± 1.4	2.0 ± 0.9	2.7 ± 0.7	2.8 ± 0.7
Platelets (× 10^9/l)	243 ± 102	201 ± 106	374 ± 169	269 ± 66	223 ± 54
WBC (×10^9/l)	8.6 ± 2.9	11.4 ± 4.9	12.4 ± 4.5	7.8 ± 1.9	7.0 ± 1.3

Values are mean ± SD.
WBC = white blood cells; other abbreviations as in Tables 1 and 3.

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Table 5 Adverse Events

Adverse Event	Overall (Support Duration 47.8 Patient-Yrs)			0–30 Days (Support Duration 4.0 Patient-Yrs)			>30 Days (Support Duration 43.8 Patient-Yrs)		
	Patients With Event, n (%)	Number of Events	Event Rate	Patients With Event	Number of Events	Event Rate	Patients With Event	Number of Events	Event Rate
Infection									
Localized nondevice related	7 (14%)	7	0.15	2	2	0.50	5	5	0.11
Sepsis	5 (10%)	5	0.10	1	1	0.25	4	4	0.09
Driveline exit site	9 (18%)	10	0.20	0	0	0.00	9	10	0.21
Bleeding									
Surgery	10 (20%)	11	0.23	8	8	2.00	3	3	0.07
Transfusion ≥2 U	2 (4%)	2	0.04	1	1	0.25	1	1	0.02
Hospital stay	3 (6%)	3	0.06	1	1	0.25	2	2	0.05
Ventricular arrhythmias	2 (4%)	2	0.04	1	1	0.25	1	1	0.02
Neurological dysfunction									
Ischemic stroke	2 (4%)	2	0.04	2	2	0.50	0	0	0.00
Hemorrhagic stroke	4 (8%)	4	0.08	0	0	0.00	4	4	0.09
TIA	2 (4%)	3	0.06	0	0	0.00	2	3	0.07
Pulmonary dysfunction	8 (16%)	9	0.19	7	8	2.00	1	1	0.02
Device replacement	7 (14%)	7	0.15	4	4	1.00	3	3	0.07
Manufacturing defect	2 (4%)	2	0.04	2	2	0.50	0	0	0.00
Left heart embolus	4 (8%)	4	0.08	1	1	0.25	3	3	0.07
Inflow occlusion	1 (2%)	1	0.02	1	1	0.25	0	0	0.00
Pleural effusion	6 (12%)	7	0.15	5	5	1.25	1	2	0.05
Right heart failure									
RVAD	3 (6%)	3	0.06	2	2	0.50	1	1	0.02
IV inotropes	3 (6%)	3	0.06	1	1	0.25	2	2	0.05
Renal dysfunction	5 (10%)	5	0.10	5	5	1.25	0	0	0.00
Hepatic dysfunction	3 (6%)	3	0.06	1	1	0.25	2	2	0.05
Hemolysis	1 (2%)	1	0.02	1	1	0.25	0	0	0.00
Heart failure	3 (6%)	3	0.06	1	1	0.25	2	2	0.05
Chest pain	1 (2%)	1	0.02	0	0	0.00	1	1	0.02
Femoral embolism	2 (4%)	2	0.04	1	1	0.25	1	1	0.02

On the basis of Inter-Agency Registry for Mechanically Assisted Circulatory Support definitions. Event rate is number of events/patient-year.
IV = intravenous; RVAD = right ventricular assist device; TIA = transient ischemic attack.

events that required surgery, blood transfusion, or repeat hospital stay occurred primarily within the first 30 days after implant (0.33 events/patient-year) and were observed less frequently after 30 days (0.11 events/patient-year). Ventricular arrhythmias were uncommon (0.04 events/patient-year). Ischemic stroke occurred in only 2 patients within the first 30 days. Hemorrhagic stroke occurred in 4 patients—all after 30 days, and 3 of these patients died. The INRs at the time of the hemorrhagic stroke were 3.1, 2.9, 2.2, and 3.5. Other neurologic events included 3 transient ischemic attacks. Devices were exchanged in 7 patients. In 2 patients (4%), the device was exchanged due to manufacturing variability of the thrust bearings. Four devices (8%) were exchanged because thrombus, suspected to be from the LV, entered the pump. The 4 exchanges due to thrombus occurred at 3, 71, 97, and 560 days. No clot was identified by pre-operative echocardiography in these cases. At the time of implant after LV apex coring, the LV was visually examined for thrombus—which, if found, was removed. However, for the early exchange, a remaining thrombus in the left heart is likely; this patient was receiving IV heparin with a partial thromboplastin time of 54 s. The other 3 patients were taking warfarin, with INRs of 2.6, 2.7, and 3.2. In 2 of them, platelet inhibitors were withdrawn for minor (nose) bleeding. In 1 patient (2%), the device was exchanged due to complications of surgical implantation. Renal, hepatic, or pulmonary dysfunction was uncommon, and end-organ function improved in most patients (Table 5). However, severe end-organ dysfunction did occur in the 3 patients who died of multiple-organ failure. Right heart failure occurred in 6 patients (12%); 3 of these patients required right ventricular assist device (RVAD) support, and 3 received intravenous inotropic support for >14 days. A Levitronix CentriMag pump (Levitronix, Waltham, Massachusetts) was used as an RVAD on all 3 patients. One patient died during RVAD (RVAD support 4 days) support, 2 RVADs were electively removed after 7 and 25 days of support, and 1 of these patients expired on post-operative day 84.

Quality of life and neurocognitive function. The results of complete paired data from the KCCQ at baseline and at intervals of 1 month (n = 28), 3 months (n = 27), and 6 months (n = 15) are shown in Figure 4. For this group, health-related quality of life improved for every subscale of

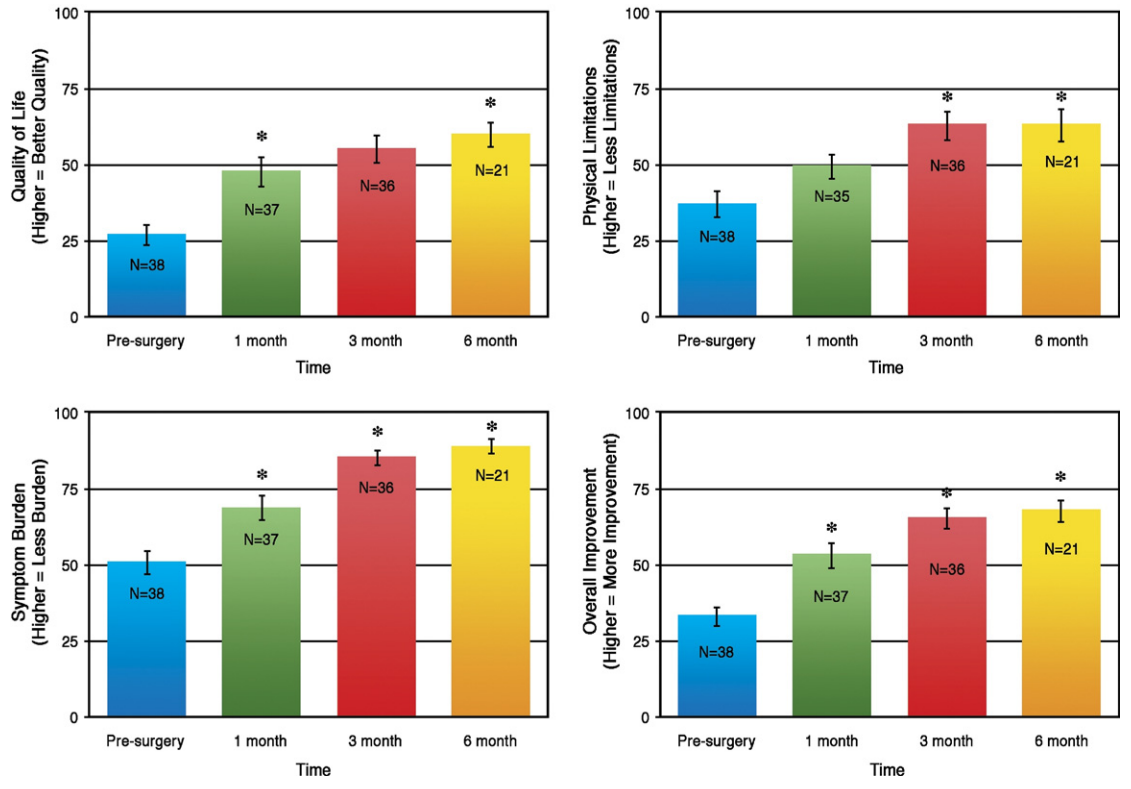

Figure 4 **Quality of Life Measures**

Results of the Kansas City Cardiomyopathy Questionnaire (KCCQ) subscales before implant surgery and at 1 month and 3 and 6 months of HeartWare Ventricular Assist Device support. A higher score represents improved self-report for a domain. *Statistically significant improvement in KCCQ score at $p < 0.05$.

the KCCQ. The improvement in symptom burden, quality of life, physical limitations, and overall functional status across all testing periods for all patients was statistically significant ($p < 0.05$). The largest improvements were observed in the first 30 days after the HVAD implant. There were no statistically significant declines in neurocognition for any of the cognitive domains from baseline to 1, 3, and 6 months after the implant. Significant improvements were found for recognition memory at 3 months after surgery ($p = 0.006$), Trail Making Test Part A at 3 months after surgery ($p = 0.039$) and at 6 months after surgery ($p < 0.001$), and Trail Making Test Part B at 6 months after surgery ($p = 0.002$) as compared with values before the implant.

Discussion

Over the past decade, survival rates in the BTT population have steadily increased because of improvements in patient selection and management and the introduction of rotary blood pump technology (10,11). The results of this study indicate that patients with severe heart failure can be bridged to heart transplant with a small, levitated continuous-flow LVAD that is implanted within the pericardial space and that provides full circulatory support. Most patients recovered from the negative effects of chronic heart failure during HVAD pump support, as evidenced by improvements in measures of end-organ function, quality of life, and neurocognitive function. All patients who have continued with HVAD pump support are outpatients, and they have had few medical problems requiring hospital readmission. Patients who were bridged to a heart transplant had a 6-month survival of 95% after transplant. The positive results achieved in this trial resulted from the ability of the device to restore normal circulation and the low incidence of life-threatening adverse events. This is demonstrated again in the 93% 6-month survival in patients 60 years of age and older ($n = 14$).

The small size of the HVAD pump and its integrated inflow cannula allow for its placement within the pericardial space, thus eliminating the need to create an abdominal pocket as is required for most other LVAD systems. Avoiding entry into the abdomen for LVAD implantation might reduce the potential for surgical bleeding and device-related infection. The abdominal surgery has been a source of serious device-related infections in some LVAD technologies, and it is associated with significant morbidity and mortality (12). In this study, there were no cases of device-related abdominal complications. Device-related infections have been reduced with the pericardial placement of the HVAD, although the need for

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skin penetration of the driveline continues to be a source of infectious complications.

Post-operative bleeding complications have been a leading cause of morbidity, when LVADs were first implanted 30 years ago. The principal factors contributing to bleeding are pre-existing coagulation disorders of patients caused by renal and hepatic dysfunction, the extensive surgery required for device placement, and clotting factor depletion that results from the use of cardiopulmonary bypass. Experienced clinicians have made progress in optimizing the pre-operative coagulation status, but the extent of improvement is limited by the underlying low cardiac output of patients. Implantation of the HVAD pump minimizes the amount of tissue damage and cardiopulmonary bypass time. These factors might contribute to the low incidence of postoperative bleeding observed in this study.

Early in the trial, a series of HVAD pumps developed unexplained thrombi. After a review of the clinical and technical data, it was determined that manufacturing variability of the thrust bearings resulted in an area of reduced flow that could have been more prone to thrombus formation. In these 2 cases, a thrombus formed within the HVAD that was resistant to anticoagulation and thrombolytic therapy, necessitating device replacement. This problem was resolved by optimizing the manufacturing process and no further events have occurred in over 450 additional implants. The wide-blade impeller design of the HVAD pump seems to be durable and hemocompatible, demonstrating effective support in patients for over 1,000 days without failure of any internal components of the device.

Study limitations. This study is limited mainly by its noncontrolled and nonblinded methods. In this severely ill patient population, randomization to no therapy or continued medical therapy is not appropriate, considering the established superiority of LVAD therapy. In addition, some bias might occur in patient selection, even though study inclusion and exclusion criteria define the population. Although the participating centers are all experienced with LVAD therapy, center variability in the supportive care of patients also cannot be completely standardized. Although the study was designed as a BTT trial, the low incidence of heart transplant within the first 180 days is in contrast other BTT trials. The prolonged waiting times to locate a donor heart in Australia and Europe reflect the reality of donor shortage in these countries. That most patients had ongoing support for more than 1 year allowed for analysis of median term use of this novel device. However, the follow-up of continuous variables is affected by the attrition of patients who receive heart transplants or undergo device explant.

The use of a virtual control arm by predicting survival on medical management with the SHFM does not reach the statistical impact of a 2-armed randomized trial. However, given the large differences in predicted and observed survival, it is evident that there is a survival benefit with the use of LVADs. These data strongly suggest that patients in end-stage heart failure should be evaluated for the implantation of a continuous flow blood pump.

Conclusions

The HVAD system provided safe and effective circulatory support in a population of end-stage heart failure patients. During HVAD system support, hemodynamic status, quality of life, and neurocognitive function improved for the majority of patients. In this first clinical study with a miniaturized LVAD placed in the pericardial space, the 2-year survival rate was similar to that of heart transplant, which suggests that this long-term therapy is promising for the heart failure population.

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Key Words: circulatory support ■ heart transplantation ■ HeartWare ■ left ventricular assist device (LVAD).

APPENDIX

For study inclusion and exclusion criteria, please see the online version of this article.