Evolving Technology

Multicenter clinical evaluation of the HeartMate vented electric left ventricular assist system in patients awaiting heart transplantation

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Background: Despite advances in heart transplantation and mechanical circulatory support, mortality among transplant candidates remains high. Better ways are needed to ensure the survival of transplant candidates both inside and outside the hospital.

Methods: In a prospective, multicenter clinical trial conducted at 24 centers in the United States, 280 transplant candidates (232 men, 48 women; median age, 55 years; range, 11-72 years) unresponsive to inotropic drugs, intra-aortic balloon counterpulsation, or both, were treated with the HeartMate Vented Electric Left Ventricular Assist System (VE LVAS). A cohort of 48 patients (40 men, 8 women; median age, 50 years; range, 21-67 years) not supported with an LVAS served as a historical control group. Outcomes were measured in terms of laboratory data (hemodynamic, hematologic, and biochemical), adverse events, New York Heart Association functional class, and survival.

Results: The VE LVAS–treated and non–VE LVAS–treated (control) groups were similar in terms of age, sex, and distribution of patients by diagnosis (ischemic cardiomyopathy, idiopathic cardiomyopathy, and subacute myocardial infarction). VE LVAS support lasted an average of 112 days (range, < 1-691 days), with 54 patients supported for > 180 days. Mean VE LVAS flow (expressed as pump index) throughout support was 2.8 L · min^{-1} · m^{-2}. Median total bilirubin values decreased from 1.2 mg/dL at baseline to 0.7 mg/dL (P = .0001); median creatinine values decreased from 1.5 mg/dL at baseline to 1.1 mg/dL (P = .0001). VE LVAS–related adverse events included bleeding in 31 patients (11%), infection in 113 (40%), neurologic dysfunction in 14 (5%), and thromboembolic events in 17 (6%). A total of 160 (58%) patients were enrolled in a hospital release program. Twenty-nine percent of the VE LVAS-treated patients (82/280) died before receiving a transplant, compared with 67% of controls (32/48) (P < .001). Conversely, 71% of the VE LVAS–treated patients (198/280) survived: 67% (188/280) ultimately received a heart transplant, and 4% (10/280) had the device removed electively. One-year post-transplant survival of VE LVAS–treated patients was significantly better than that of controls (84% [158/188] vs 63% [10/16]; log rank analysis P = .0197).

Conclusion: The HeartMate VE LVAS provides adequate hemodynamic support, has an acceptably low incidence of adverse effects, and improves survival in heart transplant candidates both inside and outside the hospital. The studies of the HeartMate LVAS (both pneumatic and electric) for Food and Drug Administration approval are the only studies with a valid control group to show a survival benefit for cardiac transplantation.

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The use of ventricular assist systems has dramatically improved the functional status and quality of life of patients with end-stage heart disease awaiting heart transplantation while at the same time reducing their mortality.[1-6] In fact, many clinical developments in the area of mechanical circulatory support have stemmed from progress in its use in heart transplantation candidates.[7,8] However, because of the constant shortage of donor hearts, heart transplantation has little direct statistical impact on the growing population of patients with end-stage heart disease. Research has continued to support not only the testing of mechanical devices as bridges to transplantation but also the development of long-term devices as alternatives to heart transplantation. One thrust of this research was to develop systems that would permit transplant candidates to be discharged from the hospital, a long-term goal in the development of implantable circulatory assist systems that may ultimately provide "destination therapy" for the many patients for whom heart transplantation is not an option.

Since 1986, more than 2700 patients worldwide have been treated with HeartMate Left Ventricular Assist Systems (LVAS). During this period, two multicenter clinical trials have evaluated the safety and effectiveness of the HeartMate technology as a bridge to transplantation. The first of these trials evaluated the first-generation HeartMate Implantable Pneumatic LVAS (IP LVAS) (Thermo Cardiosystems, Inc, Woburn, Mass), and until now it had been the only trial to compare an LVAS-treated group with a control group.[2,3]

The second of the two multicenter clinical trials evaluated the safety and efficacy of the second-generation HeartMate Vented Electric LVAS (VE LVAS) (Thermo Cardiosystems, Inc) in transplant candidates both inside and outside the hospital. After extensive clinical evaluation, the HeartMate VE LVAS finally received approval from the Food and Drug Administration in September 1998 for use as a mechanical circulatory support bridge to cardiac transplantation, both inside the hospital and at home, in patients at imminent risk of death from heart failure. Here, we report the results of the VE LVAS multicenter trial.

Materials and Methods

Device

The HeartMate VE LVAS consists of a pusher-plate blood pump driven by an integral electric motor with a percutaneous power and control circuit. The titanium alloy housing contains a flexible diaphragm that divides the interior into two chambers: one contains a textured blood path; the other houses a motor that is vented to the atmosphere via the percutaneous drive line. All blood-contacting surfaces, except the valves, are textured. The textured polyurethane diaphragm and the sintered titanium surfaces are engineered to trap and firmly anchor blood components, thus creating a stable biologic neointima similar to the lining of natural blood vessels. Once formed, the neointima prevents blood from contacting artificial materials. In addition, the assembled pump contains 25-mm porcine xenograft valves at both the inflow and outflow conduits. The carefully designed blood path and internal flow characteristics of the VE LVAS reduce activation of coagulation and minimize the need for anticoagulants.

Like the HeartMate IP LVAS, the VE LVAS is implanted through a median sternotomy incision extending to just above the umbilicus; this is done with the use of standard cardiopulmonary bypass. An inflow cannula is placed in the left ventricular apex, and an outflow graft is passed over the diaphragm to the ascending aorta, where it is anastomosed end to side at the aortic root. The pump body resides below the diaphragm in either an intraperitoneal position or preperitoneal pocket. A detailed description of the device's orientation and implantation protocol has been published.[1]

The HeartMate VE LVAS operates in one of two modes: (1) an asynchronous, fixed-rate mode programmable to a pump rate of 50 to 120 beats/min or (2) an automatic rate mode with a pump rate responsive to the pump fill rate. Once the patient's recovery from the implantation procedure is complete, wearable external components including batteries and a system controller allow the patient to be fully ambulatory and to participate in an exercise rehabilitation program (Figure 1).

Because the textured blood-contacting surfaces and bioprosthetic valves of the VE LVAS drastically reduce the need for anticoagulation treatment,[9] minimal or no anticoagulant therapy is needed. Most patients (77%) received antiplatelet treatment only in the form of aspirin (80-325 mg once daily) and/or dipyridamole (75 mg 3 times daily). However, 23% of patients received at least 1 dose of warfarin (Coumadin).

Patient Population

Between February 1996 and September 1998, 280 nonrandomized heart transplant candidates were enrolled at 24 medical centers within the United States for treatment with the HeartMate VE LVAS as a bridge to transplantation. The group consisted of 232 men (83%) and 48 women (17%) and had a median age of 55 years (range, 11-72 years).

For comparison, a historical, nonrandomized control group of 48 patients from the IP HeartMate study was used.[2] These 48 patients were enrolled at 14 of the 24 clinical centers mentioned above between April 1988 and April 1994. This group consisted of 40 men (83%) and 8 women (17%) (median age, 50 years; range, 21-67 years) who met all the criteria for device implantation but did not undergo implantation of a left ventricular assist device at the institutions participating in this study because the device was simply unavailable (before Food and Drug Administration approval, the maker's production capabilities were limited) or because the family refused treatment.

All patients in both groups had to meet specific selection criteria (Table 1). Informed consent and data from all patients were obtained in compliance with protocols approved by each institution's institutional review board. In addition, all patients in the treatment group signed an informed consent form that specifically addressed the implantation and hospital discharge (release program) phases of the trial.

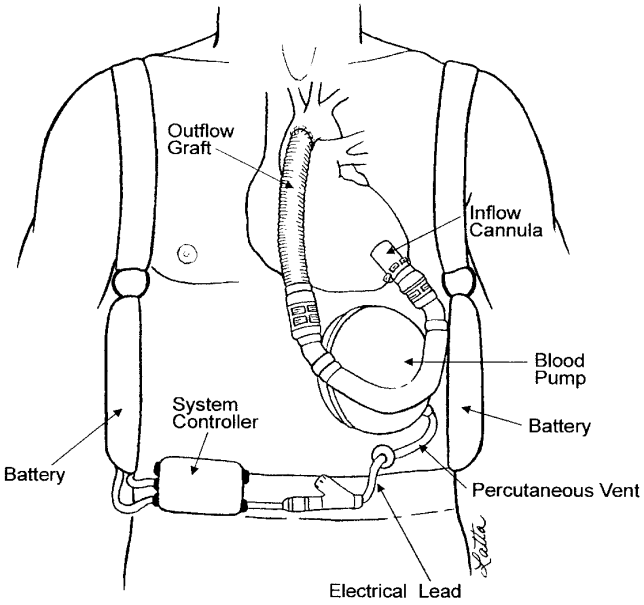

Figure 1. The HeartMate VE LVAS.

Laboratory Data Collection

Laboratory data (hemodynamic, hematologic, and biochemical) were obtained from all treated and control patients for the duration of the study.

Hemodynamic data. Hemodynamic data included mean pulmonary capillary wedge pressure (mm Hg), mean systolic blood pressure (mm Hg), and cardiac index ($L \cdot min^{-1} \cdot m^{-2}$). These data were collected from patients at baseline (study entry), when all were already receiving maximal medical and more than half (166/328) were receiving intra-aortic balloon pump support therapy. After that, systolic blood pressure was recorded weekly throughout the study. Device performance data (ie, pump rate, pump stroke volume, pump flow, and operating mode) were recorded daily for 14 days after VE LVAS implantation and then weekly thereafter.

Hematologic data. Hematocrit, hemoglobin, platelet count, leukocyte count, plasma free hemoglobin, prothrombin time, and activated partial thromboplastin time were measured at baseline and weekly thereafter.

Biochemical data. Blood urea nitrogen, serum creatinine, total bilirubin, aspartate aminotransferase, and alanine aminotransferase were measured at baseline and weekly thereafter.

Adverse Events

Adverse events (as defined below) were monitored throughout the study and were recorded as they occurred. Adverse events included bleeding, hemolysis, infection, right heart failure, renal dysfunction, hepatic dysfunction, neurologic dysfunction, pulmonary dysfunction, thromboembolic events, device malfunction, mechanical failure, and death. According to our definitions of adverse events, each adverse event was judged by the principal investigator to be either device- or patient-related. An adverse event was considered device-related if it was related or attributable to the malfunction or failure of the device or if its new onset could not be attributed to another source.

TABLE 1. Study inclusion and exclusion criteria

Inclusion criteria
Approved (listed) transplant candidate (required)
Current inotropic therapy (required)
Intra-aortic balloon pump support (if possible)
Left atrial pressure or pulmonary capillary wedge pressure ≥ 20 mm Hg combined with either:
Systolic blood pressure ≤ 80 mm Hg or
Cardiac index ≤ 2.0 $L \cdot min^{-1} \cdot m^{-2}$
Exclusion criteria
Body surface area < 1.5 m^2
Any medical condition that would exclude the patient from transplantation

Bleeding. Bleeding was defined as blood loss serious enough to necessitate returning the patients to the operating room or to cause death (eg, cardiac tamponade).

Hemolysis. Hemolysis was defined as 2 consecutive measurements of hemoglobin values greater than 40 mg/dL.

Infection. Systemic infection was defined as infection detected by positive blood, urine, sputum, or tissue cultures in association with an elevated white blood cell count (≥12,500/mL), fever (≥38.1°C), and treatment with antimicrobial agents. Additionally, data were collected on drive-line infection, which was defined as any infection that (1) was detected by the positive cultures obtained from the drive-line exit site and (2) required treatment with antimicrobial agents.

Right heart failure. Right heart failure was defined as the inability of the heart to provide sufficient flow from the right ventricle to the left ventricle, thus necessitating the use of a right ventricular assist device.

Renal dysfunction. Renal dysfunction was defined as a serum creatinine value of 2.2 mg/dL or more or a blood urea nitrogen value of 50 mg/dL or more.

Hepatic dysfunction. Hepatic dysfunction was defined as a total bilirubin value of 1.4 mg/dL or more or as either an aspartate aminotransferase or alanine aminotransferase value of 50 U/L or more in cases in which the elevation in bilirubin level was not due to hemolysis.

Neurologic dysfunction. Neurologic dysfunction was defined as any central nervous system or gross neuromuscular disorder identified by standard neurologic examination of reflexes, speech, vision, and so on.

Pulmonary dysfunction. Pulmonary dysfunction was defined as a forced expiratory volume in 1 second of less than 45%. It was measured after VE LVAS implantation only if the patient had symptoms.

Thromboembolic event. A thromboembolic event was defined by clinical symptoms of stroke or by sudden neurologic, pulmonary, renal, hepatic, or peripheral vascular changes.

Device malfunction. A device malfunction was defined as any instance in which any component of the system failed to perform in the intended manner.

Mechanical failure. Mechanical failure was defined as the inability of the VE LVAS, including its backup components, to provide circulatory support.

TABLE 2. Inclusion and exclusion criteria for participation of VE LVAS–treated patients in the release program

Inclusion criteria
LVAS implanted for ≥ 14 days
NYHA class I or II
Left ventricular contractility sufficient to open the aortic valve while LVAS operating at 50 beats/min
Exclusion criteria
Residence > 2 hours from hospital
Companion not available
No desire by patient or companion to participate in release program
Uncertainty regarding patient's or companion's ability to manage equipment
LVAS malfunction that affects patient's safety or device effectiveness
Patient's need for medications that require hospitalization
Inadequate backup equipment
Potential availability of a donor heart
Unresolved adverse event that may threaten patient's safety (eg, active systemic infection)
Known medical condition that might jeopardize patient's safety (eg, severe arrhythmia)

Functional Status

New York Heart Association (NYHA) functional status was evaluated in all patients at baseline, on enrollment in the release program, weekly during release, and after transplantation.

Evaluation of Patients Outside the Hospital (Release Program)

The performance of the VE LVAS outside the hospital was also evaluated. Release from the hospital (the "release program") was limited to those patients who qualified to await transplantation outside of the hospital (see Table 2 for inclusion criteria).

All patients in the release program received backup and emergency equipment and training in its use. Before release, each patient also had to identify a companion who could assist the patient in an emergency. Both patient and companion were then trained in the proper setup and operation of the VE LVAS and in emergency response procedures, and both were required to demonstrate competency in the use of the supplied equipment before release.

Under the release program, patients were released from the hospital in a controlled, stepwise fashion. In general, they were initially allowed to leave the hospital for short day trips; they could then progress over time to full outpatient status (ie, they were allowed to live at home or outside the hospital while awaiting a transplant). All patients were required to return to the hospital weekly for evaluation (ie, NYHA functional status and hemodynamic, hematologic, and biochemical tests) and to report on their activities while away from the hospital. All adverse events (anticipated and unanticipated) that occurred away from the hospital were recorded.

TABLE 3. Patient demographics at baseline

Variable	VE LVAS–treated patients (n = 280)	Historical controls (n = 48)	*P* value
Median age, y (range)	55 (11-72)	50 (21-67)	.379
Sex			
Male (%)	232 (83%)	40 (83%)	
Female (%)	48 (17%)	8 (17%)	1.000
Diagnosis			
Ischemic cardiomyopathy (%)	129 (46%)	28 (58%)	
Idiopathic cardiomyopathy (%)	131 (47%)	17 (35%)	.285
Myocardial infarction (%)	20 (7%)	3 (6%)	
Mean body surface area, m^2 (range)	1.97 (1.45-2.75)	1.92 (1.55-2.30)	.128

Survival Outcomes

Survival to transplantation and survival after transplantation of treated and control patients were recorded.

Statistical Methods

Comparisons between VE LVAS–treated patients and controls were performed by the Fisher exact test or the Student unpaired *t* tests as appropriate. Changes in hemodynamic and biochemical data from baseline to final measurement before transplantation or death were analyzed by the Student paired *t* test. (Baseline and final values were expressed as either mean ± SD or median and range.) Probability was 2-tailed. Survival to transplantation and survival after transplantation were analyzed by the Kaplan-Meier product limit method. Differences in survival distributions between VE LVAS–treated and control groups were analyzed by means of a log-rank test. Variables for predicting survival to transplantation were identified by the Cox proportional hazards model and entered stepwise into the model. All variables selected for the hazards model were visually assessed by log-log curves to ensure compliance with the proportional hazards assumption.

Results

Patient Demographics

The VE LVAS–treated and control groups were similar in terms of age, sex, and distribution of patients by diagnosis (ischemic cardiomyopathy, idiopathic cardiomyopathy, and subacute myocardial infarction) (Table 3).

Median Waiting Time to Transplantation

In the control group, the median waiting time from study entry to transplantation was 4 days and in the VE LVAS–treated group, 105.5 days ($P < .0001$).

Average Length of VE LVAS Support

VE LVAS support lasted an average of 112 days (range, <1-691 days), with 54 patients supported for more than 180 days.

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TABLE 4. Baseline hemodynamic data*

Variable	VE LVAS-treated patients (n = 280)	Historical controls (n = 48)	*P* value
IABP support (%)	137 (49%)	29 (60%)	.160
PCWP (mm Hg)	27.4 ± 6.6	27.8 ± 7.6	.737
Systolic blood pressure (mm Hg)	75.5 ± 9.7	86.1 ± 15.4	<.0001
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	1.67 ± 0.41	2.03 ± 0.72	<.0001

IABP, Intra-aortic balloon pump; *PCWP,* pulmonary capillary wedge pressure.
*Variables expressed as mean ± standard deviation.

TABLE 5. Hematologic data

Variable	Baseline (mean ± SD)	During VE LVAS use (mean ± SD)
Hemoglobin (g/dL)	11.1 ± 2.3	10.0 ± 3.8
Hematocrit (%)	32.4 ± 6.0	32.2 ± 5.5
WBC ($\times 10^3$)	11.2 ± 4.9	9.2 ± 5.0
Platelet count ($\times 10^3$)	198.1 ± 94.3	259.3 ± 107.0
Prothrombin time (s)	15.4 ± 6.3	14.5 ± 4.4
Partial thromboplastin time (s)	51.2 ± 29.6	32.8 ± 15.5
Plasma free hemoglobin (mg/dL)	8.5 ± 12.8	7.4 ± 16.0

SD, Standard deviation; *WBC,* white blood cell count.

TABLE 6. Baseline renal and hepatic function*

Variable	VE LVAS-treated patients (n = 280)	Historical controls (n = 48)	*P* value
Blood urea nitrogen (mg/dL)	38.9 ± 23.2	37.5 ± 20.1	.697
Creatinine (mg/dL)	1.72 ± 1.02	1.58 ± 0.54	.325
Total bilirubin (mg/dL)	2.08 ± 2.91	1.69 ± 1.29	.373

*Variables expressed as mean ± SD.

TABLE 7. Improvement in renal and hepatic function from baseline to final measurement*

Variable	No.	Baseline	Final value before transplant or death	*P* value
BUN (mg/dL)	271	32 (7-135)	20 (6-174)	.0001
Creatinine (mg/dL)	271	1.5 (0.4-8.9)	1.1 (0.1-6.2)	.0001
Total bilirubin (mg/dL)	240	1.2 (0.2-23.3)	0.7 (0.2-59.8)	.0001
ALA (IU)	219	47 (4-3612)	26 (2-1910)	.0001
AST (IU)	237	42 (9-5146)	32 (6-1008)	.0001

BUN, Blood urea nitrogen; *ALA,* alanine aminotransferase; *AST,* aspartate aminotransferase.
*Variables expressed as median (range). Data were analyzed by the Student paired *t* test.

Baseline Hemodynamic Data

The hemodynamic indices of treated and control patients at baseline and after pharmacologic and intra-aortic balloon pump therapy were evaluated and compared (Table 4). Whereas no difference was found in the pulmonary capillary wedge pressure, the mean systolic blood pressure and mean cardiac index were significantly lower in the VE LVAS–treated group than in the control group ($P < .0001$).

Hemodynamic Performance of the VE LVAS

Mean VE LVAS flow (expressed as pump index) was 2.8 ± 0.5 $L \cdot min^{-1} \cdot m^{-2}$. The average pump index 1 month after implant (2.85 ± 0.52 $L \cdot min^{-1} \cdot m^{-2}$) was significantly greater than the average cardiac index recorded at baseline (1.68 ± 0.43 $L \cdot min^{-1} \cdot m^{-2}$) ($P = .0001$).

Hematologic Data

No significant changes were found in levels of plasma free hemoglobin before (8.5 ± 12.8 mg/dL) or during LVAS support (7.4 ± 16.0 mg/dL) or in other hematologic variables (Table 5).

Hepatic and Renal Function Data

No significant differences in renal and hepatic function at baseline were observed between the treated and control groups (Table 6). However, renal and hepatic function in VE LVAS–treated patients significantly improved between baseline and final measurement before LVAS removal ($P = .0001$) (Table 7). Blood urea nitrogen levels fell from 32 to 20 mg/dL ($P = .0001$). Creatinine values fell from 1.5 to 1.1 mg/dL ($P = .0001$). Total bilirubin values fell from 1.2 to 0.7 mg/dL ($P = .0001$). Alanine aminotransferase values fell from 47 to 26 IU ($P = .0001$). Aspartate aminotransferase values fell from 42 to 32 IU ($P = .0001$).

Adverse Events

Adverse events in VE LVAS–treated patients throughout the study were recorded (Table 8).

Bleeding of any kind was noted in a total of 133 treated patients (48%). Bleeding arising directly from the device itself (including its connectors or grafts) or from the abdominal implant site was identified in 31 patients (11%). Eighty-three percent of the treated patients (111/133) who had bleeding events bled perioperatively (within 5 days of implant, reimplant, or explant).

Infections occurred in 125 (45%) patients, most frequently at the drive-line exit site (90/125; 72%).

After device implantation, renal and hepatic dysfunction (detected by at least 1 abnormal laboratory test) was present

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TABLE 8. Summary of adverse events in all patients treated with VE LVAS

	Cause			
	Independent of cause		Device related	
Adverse event	No. of patients	%	No. of patients	%
Bleeding	133	48	31	11
Infection	125	45	113	40
Right heart failure	31	11	0	0
Renal dysfunction	158	56	0	0
Hepatic dysfunction	263	94	0	0
Neurologic dysfunction	75	27	14	5
Pulmonary dysfunction	5	2	0	0
Thromboembolic events	34	12	17	6
Mechanical failure	3	1	3	1
Death	82	29	3	1

in 158 (56%) patients and 263 (94%) patients, respectively. Of these patients, 94 (59%) had entered the trial with renal dysfunction and 174 (66%) had entered with hepatic dysfunction.

Right heart failure occurred in 31 (11%) patients, 10 of whom subsequently underwent transplantation and 21 of whom died before transplantation.

Neurologic complications occurred in 75 (27%) patients but were deemed device-related in only 14 (5%). Other neurologic complications included metabolic encephalopathy, seizures, confusion, and syncope that were attributed to a cause other than the device. Thromboembolic events occurred in 34 (12%) patients. In 17 (6%) of these, the event could not be attributed to another cause and was deemed device-related.

Mechanical failure occurred in 3 (1%) patients and in all 3 instances resulted in death. The mechanical failures were due to 2 disconnections of the outflow assembly from the pump body and 1 pump diaphragm failure. Both of the failure modes have been analyzed and pump improvements implemented. In addition, 435 confirmed device malfunctions occurred during the study period. Most of these (375/435; 86%) were malfunctions of external accessories, including the controller, batteries, battery clips, power base unit cable, and display module (external component malfunction rate = 1.192 per 100 patient-days). The controller accounted for more than half (195/375; 52%) of the external component malfunctions.

During the present study, 25 (9%) of the 280 treated patients needed to use the backup components (hand pump or IP console) because of controller or cable malfunction (11/25 patients) or pump stoppage (14/25 patients). The pump stoppages were largely due to either electrostatic discharge or component malfunctions within the pump commutator. Fixes to both of these malfunctions have been implemented. Of the 25 patients who used the backup components, 18 (72%) survived to transplantation.

TABLE 9. Improvement in NYHA functional status of patients in release program (n = 160)*

NYHA functional class	At VE LVAS implantation	At entry into release program
Class I	0	69
Class II	1	91
Class III	6	0
Class IV	153	0

*Median time from implantation to entry into release program = 35 days.

TABLE 10. Number of patients surviving to transplantation

	Weeks					
	0–1	1–2	2–5	5–10	10–25	25–50
VE LVAS–treated patients (n = 280)	280	247	233	207	166	55
Historical controls (n = 48)	48	17	13	6	0	0

Experience Outside the Hospital (Release Program)

Patient outcomes. Of 228 VE LVAS–treated patients eligible to participate in the release program phase of this study, 160 (70%) actually did participate. Ultimately, only 115 of the 160 released patients achieved full outpatient status. The remaining 45 patients only left the hospital for day trips, overnight trips, and 3-day releases from the hospital and did not reach full outpatient status for a variety of reasons (eg, they were receiving transplants, the study investigators were cautious about allowing them outside the hospital, or the patients chose not to leave). The 160 patients in the release program accumulated 33.9 patient-years away from the hospital. The median length of outpatient stay was 82 days (range, 3–660 days). Of the 160 patients, 138 (86%) ultimately received a transplant, 10 (6%) elected to have the device removed without a subsequent transplant, and 12 (8%) died while awaiting a transplant.

Improvement in NYHA functional class. Of the 160 VE LVAS–treated patients enrolled in the release program, 153 (96%) had NYHA class IV function at baseline and 7 (4%) belonged to classes I-III. By the time these patients qualified for outpatient treatment, 91 (57%) belonged to NYHA class II and 69 (43%) belonged to NYHA class I. This change in NYHA functional class was significant ($P < .001$) and indicated that the improvement in functional class was due to mechanical circulatory support (Table 9).

Survival Outcomes

Pretransplantation survival. The VE LVAS underwent 86 patient-years of use during the present clinical trial. A total of 188 (67%) patients were successfully bridged to transplantation, 10 (4%) patients elected to have the device removed, and 82 (29%) patients died before transplantation.

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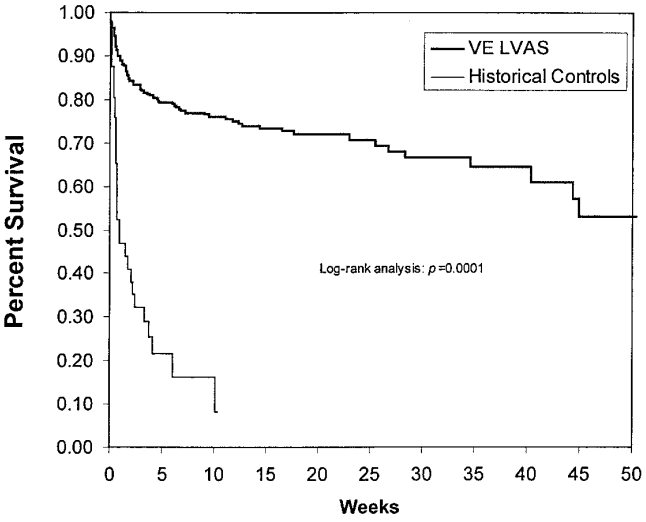

Figure 2. Probability of survival to transplantation for VE LVAS–treated versus control patients.

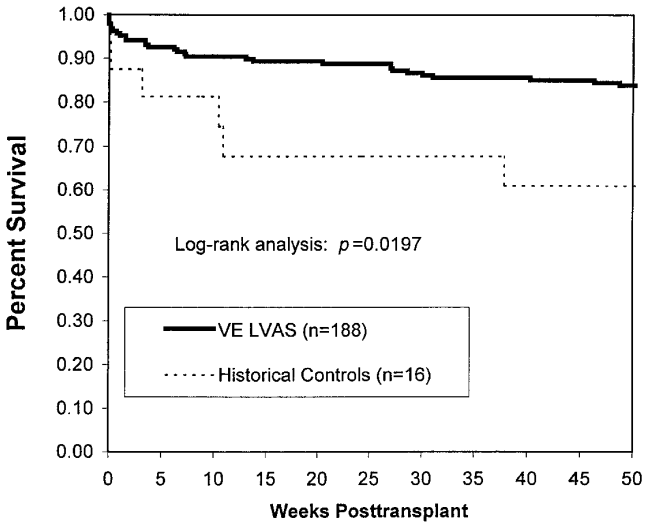

Figure 3. Probability of 1-year post-transplantation survival for VE LVAS–treated versus control patients.

TABLE 11. Experience of 10 patients undergoing explantation

Patient	Reason for explantation	Outcome	Postexplantation survival (d)	Cause of death
1	Myocardial recovery	Died	209	Heart failure
2	Myocardial recovery	Died	1358	Heart failure
3	Infection	Reimplantation, transplantation, alive	175	
4	Myocardial recovery	Alive	1207	
5	Myocardial recovery	Died	160	Pancreatic cancer
6	Infection	Alive	367	
7	Infection	Died	32	MSOF
8	Myocardial recovery	Died	1021	Unknown
9	Pump malfunction	Died	8	MSOF
10	Infection	Died	0	Sepsis

MSOF, Multiple system organ failure.

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Thirty-two (67%) of 48 control patients died. Overall, as shown by log-rank analysis, the probability of survival to transplantation was significantly greater for the VE LVAS–treated patients than for the controls (P = .0001) (Figure 2 and Table 10). In the first 7 days of the trial, 22 (46%) control patients died compared with 30 (11%) VE LVAS–treated patients.

Of the 10 treated patients who elected to have the device removed, 5 had experienced myocardial recovery. Another 4 had the pump explanted because of infection and 1 because of a pump malfunction. The survival duration for the 10 patients who underwent explantation ranged from 0 to 1358 days (Table 11), and the 1-year survival was 43%.

Post-transplantation survival. Post-transplantation survival significantly improved in VE LVAS–treated patients compared with that in control patients (P = .0197) (Figure 3 and Table 12). The 1-year post-transplantation survival was 84% (158/188) for VE LVAS–treated patients versus 63% (10/16) for controls.

Predictors of poor survival. Four factors were associated with significantly poorer survival of VE LVAS–treated patients: age, prior cardiac surgery, elevated baseline creatinine level, and elevated baseline total bilirubin level (Table 13).

Discussion

Despite improvements in medical therapy for heart failure, such therapy is still of limited efficacy in patients with advanced disease.[10] This assessment is corroborated by the dismal survival (33%) in our group of control patients with end-stage disease who were not supported with an LVAS. The only survivors in the control group were those who

TABLE 12. Number of patients surviving after transplantation

	Weeks after transplant					
	5	10	15	20	25	50
VE LVAS–treated patients (n = 188)	173	169	167	166	165	134
Historical controls (n = 16)	13	12	10	10	10	7

TABLE 13. Risk factors for poor survival to transplantation*

Variable	Hazard ratio	*P* value	95% CI
Age (range, 11-72 y)	1.03	.0163	1.01-1.05
Prior heart surgery	1.69	.0366	1.03-2.76
Baseline creatinine (range, 0.4-8.9 mg/dL)	1.38	.0005	1.15-1.65
Baseline total bilirubin (range, 0.1-23.0 mg/dL)	1.08	.0043	1.03-1.14

CI, Confidence interval.
*Data were analyzed by using the Cox proportional hazards model. Predictor variables were selected for the model by means of a stepwise technique. Variables evaluated for addition to the model included patient age, prior heart surgery (either coronary artery bypass grafting or valve surgery), sex, ischemic heart disease, baseline white blood cell count, baseline infection, baseline blood urea nitrogen, baseline aspartate aminotransferase, baseline alanine aminotransferase, baseline total bilirubin, baseline creatinine, prior myocardial infarction, and prior coronary artery disease.

received a heart transplant. The median waiting time for the patients who received a transplant was only 4 days. This short waiting time would be impossible today, even after aggressive medical therapy. Mechanical circulatory support with subsequent transplantation thus appears to be the only alternative for many patients with end-stage heart disease. When the long-term limitations of heart transplantation (eg, 50% mortality at 10 years), limited donor availability (2000 donors yearly), and drug-related morbidity (eg, hypertension, renal dysfunction) are considered, the role of long-term assist devices appears even more important.[11-13]

In the present study, the HeartMate VE LVAS provided adequate hemodynamic support, had an acceptably low incidence of adverse effects, and improved NYHA functional class and survival in heart transplant candidates both inside and outside the hospital. The best indicator of its safety and efficacy in transplant candidates was the survival benefit it conferred—both before and after transplantation. (A similar post-transplantation survival benefit was also shown for the HeartMate IP LVAS in its earlier clinical trial.) This benefit can be attributed to the normalization of end-organ function and return to NYHA class I function in the majority of cases.[14] Consequently, concerns over the negative immunologic impact of using the VE LVAS as a bridge to transplantation (eg, an increase in reactive antibodies) are not warranted, because the survival in this patient group was excellent with no evidence of increased infection or rejection episodes.[15]

Another indicator of the VE LVAS device's safety and efficacy was the rate of adverse events in this study, which mirrored the rate established in the earlier IP LVAS trial.[2] Although to a certain extent our assignment of adverse events to the device or to the patient in this study was subjective, it represented an effort to distinguish between the 2 types of causes and to assess the relative contribution of the device to adverse events while still reporting their total incidence.

In the present study, organ dysfunction, seen in most patients before implantation or immediately after implantation, was substantially corrected during LVAS support. Although in most cases aspirin and dipyridamole were the only antiplatelet agents used, the incidence of thromboembolic events in the present trial was low and constituted one of the major advantages of using the VE LVAS. On the other hand, the incidence of bleeding was relatively high but not surprisingly so in light of the severity of the disease and expected development of coagulopathies.[16,17] In present clinical practice, this problem is apparently being reduced by the more routine use of antifibrinolytic agents.[17,18] Similarly, the incidence of infections, and especially driveline infections, was high; however, design modifications in the VE LVAS, along with better timing of device placement, might decrease infection rates in the future.[19,20] Our pulmonary dysfunction data were of limited value because forced expiratory volume in 1 second was not measured in all patients. The incidence of right heart failure and subsequent high mortality justifies the more routine use of nitric oxide, prostaglandins, and phosphodiesterase inhibitors to prevent this complication.[21] Unfortunately, no data have been collected on the incidence of right-sided dysfunction and the subsequent need for prolonged use of intravenous inotropic agents.

Another interesting finding of the present multicenter trial, which followed the experiences of several single centers in the use of LVAS as a bridge to recovery,[4,22] was the outcome of patients who underwent elective device explantation. Most previous findings have been limited to that subset of patients being bridged to transplantation and therefore not selected as candidates for recovery. Thus, as our understanding of end-stage myocardial disease and the processes involved in recovery improves, so might the outcomes of patients treated with the VE LVAS. In fact, experience gained from the use of left ventricular assist devices as a bridge to transplantation could be useful in selecting patients with end-stage cardiac disease who would be good candidates for implantation (ie, those at low risk for perioperative complications and thus having a better chance of recovery).

The ultimate goal in developing ventricular assist systems is to create technology that will allow the transplant candidate to lead a normal, active life while receiving

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mechanical circulatory support. The present multicenter trial suggests that the VE LVAS improves the outcome of patients with end-stage heart disease who are awaiting a transplant, and it has defined a subset of patients who cannot be supported by medical therapy. It also provides important insights into any future application of this technology for permanent use as heart replacement therapy (eg, the REMATCH trial).[23] Moreover, in the field of heart transplantation, it is the only study with a control cohort (ie, patients who did not have an LVAS implanted but otherwise met all inclusion criteria) to show a survival benefit for transplantation. This observation is especially important since data on comparable groups of patients (eg, patients with end-stage heart disease who fulfill criteria for left ventricular assist device implantation) are hard to obtain now owing to the ethical issues involved. We believe that the control group we used is the best comparison group for patients with terminal disease that we are likely to develop.

With better medical therapy, it is more difficult to determine the survival benefit of heart transplantation. In a recent study of German heart transplant programs, Deng and colleagues[24] showed that a survival benefit was achieved only in the sickest patients. However, that study lacked a control cohort. In the present study, the patients who were on the waiting list for a transplant and reached the level of cardiac deterioration that would qualify them for insertion of a HeartMate LVAS (either pneumatic or electric) achieved a survival benefit only after LVAS implantation and subsequent cardiac transplantation. Furthermore, the survival benefit was much greater for those patients who received the pump than for those who did not.

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