LONG-TERM USE OF A LEFT VENTRICULAR ASSIST DEVICE FOR END-STAGE HEART FAILURE

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ABSTRACT

Background   Implantable left ventricular assist devices have benefited patients with end-stage heart failure as a bridge to cardiac transplantation, but their long-term use for the purpose of enhancing survival and the quality of life has not been evaluated.

Methods   We randomly assigned 129 patients with end-stage heart failure who were ineligible for cardiac transplantation to receive a left ventricular assist device (68 patients) or optimal medical management (61). All patients had symptoms of New York Heart Association class IV heart failure.

Results   Kaplan–Meier survival analysis showed a reduction of 48 percent in the risk of death from any cause in the group that received left ventricular assist devices as compared with the medical-therapy group (relative risk, 0.52; 95 percent confidence interval, 0.34 to 0.78; P=0.001). The rates of survival at one year were 52 percent in the device group and 25 percent in the medical-therapy group (P=0.002), and the rates at two years were 23 percent and 8 percent (P=0.09), respectively. The frequency of serious adverse events in the device group was 2.35 (95 percent confidence interval, 1.86 to 2.95) times that in the medical-therapy group, with a predominance of infection, bleeding, and malfunction of the device. The quality of life was significantly improved at one year in the device group.

Conclusions   The use of a left ventricular assist device in patients with advanced heart failure resulted in a clinically meaningful survival benefit and an improved quality of life. A left ventricular assist device is an acceptable alternative therapy in selected patients who are not candidates for cardiac transplantation. (N Engl J Med 2001;345:1435-43.)

IMPROVING the survival and the quality of life of patients with end-stage heart failure has been the underlying goal of decades of research on mechanical circulatory-support devices. This effort was stimulated by the increasing prevalence of this disorder and its grave prognosis. Heart failure affects an estimated 4.7 million Americans, with 550,000 new cases diagnosed annually and annual cost estimates ranging from $10 billion to $40 billion.[1,2] The aggregate five-year survival rate of patients with heart failure is approximately 50 percent,[1] whereas the one-year mortality rate of those with advanced disease may exceed 50 percent.[3]

Patients with mild-to-moderate heart failure[4] and, recently, some with more severe disease[5] have been shown to benefit from drug therapy. Nevertheless, the survival and the quality of life of patients with severe heart failure remain limited. Cardiac transplantation is the only treatment that provides substantial individual benefit, but with fewer than 3000 donor organs available worldwide per year, its impact is epi-

demiologically trivial.[6] The success and limitations of transplantation have stimulated interest in alternative approaches to myocardial replacement.

Since the inception of the artificial-heart program at the National Institutes of Health (NIH) in 1964, various circulatory-support devices have been developed for short-term use in patients with end-stage heart failure.[7] In 1994, the Food and Drug Administration (FDA) approved pneumatically driven left ventricular assist devices as a bridge to transplantation, and self-contained, vented electric devices were approved for this purpose in 1998.[8] Short-term use of these devices in patients awaiting transplantation normalizes hemodynamics, improves end-organ dysfunction and exercise tolerance, allows patients to be sent home, and provides a reasonable quality of life, with a relatively low incidence of major adverse events.[9-16] One type of left ventricular assist device (HeartMate vented electric device, Thoratec, Pleasanton, Calif.) has textured interior surfaces and is associated with a low incidence of thromboembolic events without systemic anticoagulation.[17,18] We evaluated the suitability of these devices for their ultimate intended use as a long-term myocardial-replacement therapy for patients who are ineligible for cardiac transplantation.

METHODS

Organization of the Trial

The investigator-initiated study was conducted at 20 experienced cardiac transplantation centers under a cooperative agreement among Columbia University, the NIH, and Thoratec. The trial was supervised by a steering committee and executed by an operations committee and an independent coordinating center (the International Center for Health Outcomes and Innovation Research at Columbia University). An independent morbidity and mortality committee reviewed causes of death and adverse events. The NIH appointed a data and safety monitoring board to assess the progress of the trial and review outcomes. The FDA granted an investigational-device exemption to facilitate this pivotal phase 3 trial. Participating institutional review boards approved the protocol, and written informed consent was obtained from all patients.

Patients

Eligible patients were adults with chronic end-stage heart failure and contraindications to transplantation. Initial entry criteria included the presence of symptoms of New York Heart Association (NYHA) class IV heart failure for at least 90 days despite attempted therapy with angiotensin-converting–enzyme inhibitors, diuretics, and digoxin; a left ventricular ejection fraction of 25 percent or less; and a peak oxygen consumption of no more than 12 ml per kilogram of body weight per minute or a continued need for intravenous inotropic therapy owing to symptomatic hypotension, decreasing renal function, or worsening pulmonary congestion.[19] Patients could continue to receive beta-blockers if they had been administered for at least 60 of the 90 days before randomization.

Eighteen months after enrollment began, the investigators broadened the entry criteria to increase enrollment by including patients who had had symptoms of NYHA class IV heart failure for 60 days and had a peak oxygen consumption of no more than 14 ml per kilogram per minute and patients who had been in NYHA class III or IV for at least 28 days and who had received at least 14 days of support with an intraaortic balloon pump or with a dependence on intravenous inotropic agents, with two failed wean-

ing attempts. Only five patients (three in the group that received left ventricular assist devices and two in the medical-therapy group) were enrolled who met the broadened criteria.

In all patients, transplantation was contraindicated for at least one of the following reasons: an age of more than 65 years, the presence of insulin-dependent diabetes mellitus with end-organ damage, the presence of chronic renal failure with a serum creatinine concentration of more than 2.5 mg per deciliter (221 μmol per liter) for at least 90 days before randomization, or the presence of other clinically significant conditions. Detailed exclusion criteria have been described previously.[19]

Study Design

Patients were randomly assigned in a 1:1 ratio to receive either a vented electric left ventricular assist device or optimal medical therapy. Randomization followed a block design to ensure the continued equivalence of group size and was stratified according to center. The eligibility of patients was determined by investigators at each site and confirmed by a gatekeeper at the coordinating center. The surgical risk associated with the implantation of the left ventricular assist device and the obviousness of the device precluded a double-blind design. However, all investigators except the statisticians were unaware of overall outcome data throughout the enrollment period. In accordance with FDA requirements, Thoratec received ongoing data on patients in the group that received left ventricular assist devices, but was unaware of the data on patients in the medical-therapy group.

All patients who were randomly assigned to receive the assist device received the device (Fig. 1) and associated medical care. The device was implanted into a preperitoneal pocket or the peritoneal cavity, depending on the surgeon's preference. Surgical management followed guidelines developed and updated by a surgical-management committee and included preoperative measures (e.g., prophylaxis with antimicrobial agents), intraoperative measures (e.g., placement of the drive line), and postoperative measures (e.g., changes of exit-site dressing).

Optimal medical management followed guidelines developed by the medical committee, with the goals of optimizing organ perfusion and minimizing symptoms of congestive heart failure. Recognizing the unprecedented severity of illness in this group of patients, the committee provided specific guidance regarding the use of therapy with angiotensin-converting–enzyme inhibitors and encouraged the discontinuation of intravenous inotropic infusions. Patients were followed up monthly when they were out of the hospital.

Statistical Analysis

The primary end point was death from any cause and was compared between groups with the use of the log-rank statistic. We used Cox proportional-hazards regression to estimate relative risks and 95 percent confidence intervals and to adjust for differences in base-line outcome predictors. Analyses were conducted according to the intention-to-treat principle.

The trial was designed to enroll 140 patients and to continue until 92 deaths had occurred. These figures were estimated on the basis of the following assumptions: the two-year mortality rate among the patients in the medical-therapy group would be 75 percent, treatment with a left ventricular assist device would reduce the risk of death by 33 percent, and the study would have 90 percent power (two-sided $\alpha = 0.05$) to detect a significant difference between the treatment groups. We conducted three interim analyses (after 23, 46, and 69 deaths had occurred), using a two-sided significance test with the O'Brien–Fleming spending function and a type I error rate of 5 percent.

Secondary end points included the incidence of serious adverse events, the number of days of hospitalization, the quality of life, symptoms of depression, and functional status. Adverse events were considered to be serious if they caused death or permanent disability, were life-threatening, or required or prolonged hospitalization. The frequency of adverse events was analyzed by means of
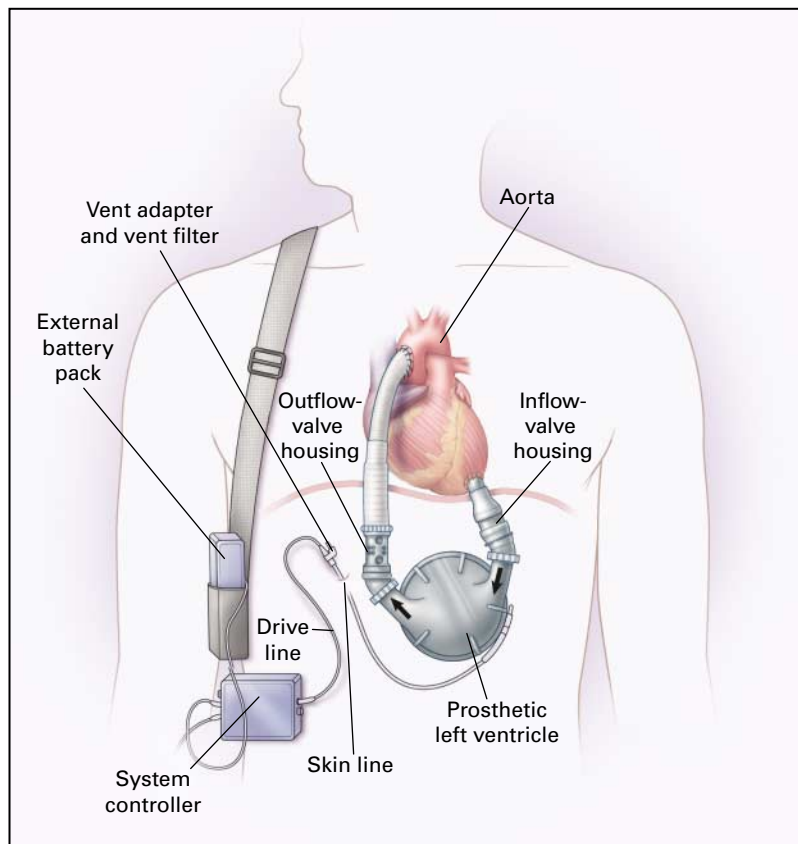
Figure 1. Components of the Left Ventricular Assist Device.

The inflow cannula is inserted into the apex of the left ventricle, and the outflow cannula is anasto-mosed to the ascending aorta. Blood returns from the lungs to the left side of the heart and exits through the left ventricular apex and across an inflow valve into the prosthetic pumping chamber. Blood is then actively pumped through an outflow valve into the ascending aorta. The pumping cham-ber is placed within the abdominal wall or peritoneal cavity. A percutaneous drive line carries the elec-trical cable and air vent to the battery packs (only the pack on the right side is shown) and electronic controls, which are worn on a shoulder holster and belt, respectively.

Poisson regression. The quality of life and functional status were assessed with use of the Minnesota Living with Heart Failure questionnaire, two prespecified subscales — physical function and emotional role — of the 36-item Medical Outcomes Study Short-Form General Health Survey (SF-36), and the NYHA classification.[20-22] Symptoms of depression were assessed with use of the Beck Depression Inventory. We used analysis of covariance to test for significant differences in the mean quality of life among surviving patients, after adjustment for base-line values.

The Minnesota Living with Heart Failure questionnaire contains 21 questions regarding patients' perception of the effects of heart failure on their daily lives. Each question is rated on a scale of 0 to 5, producing a total score between 0 and 105. The higher the score, the worse the quality of life. The SF-36 includes one multi-item scale measuring eight health-related aspects: physical function, social function, physical role, emotional role, mental health, energy, pain, and general health perceptions. The score for each of the eight health concepts ranges from 0 (worst) to 100 (best). The Beck Depression Inventory assesses the severity of depression. Scores of 0 to 9 are considered to be normal, scores of 10 to 18 indicate mild-to-moderate depression, scores of 19 to 29 indicate moderate-to-severe depression, and scores of 30 to 64 indicate severe depression.

RESULTS

Base-Line Characteristics

A total of 129 patients were enrolled from May 15, 1998, to July 27, 2001. Enrollment ended once the predetermined number of 92 deaths had occurred. Sixty-eight patients received left ventricular assist devices, and 61 were assigned to receive optimal medical management. The two groups were similar with regard to base-line characteristics (Table 1). Age was the most common reason for ineligibility for cardiac transplantation. All 129 patients were included in the primary end-point analysis. Two patients in the medical-therapy group withdrew from the trial one and six months after randomization. All patients who

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	MEDICAL-THERAPY GROUP (N=61)	LVAD GROUP (N=68)
Age (yr)	68±8.2	66±9.1
Male sex (%)	82	78
Ischemic cause of heart failure (%)	69	78
Left ventricular ejection fraction (%)	17±4.5	17±5.2
Blood pressure (mm Hg)		
Systolic	103±17	101±15
Diastolic	62±11	61±10
Pulmonary-capillary wedge pressure (mm Hg)	24±7.4	25±9.9
Cardiac index (liters/min/m²)	2±0.61	1.9±0.99
Heart rate (beats/min)	84±15	84±16
Pulmonary vascular resistance (Wood units)	3.2±1.8	3.4±1.8
Serum sodium (mmol/liter)	135±5.8	135±5.4
Serum creatinine (mg/dl)†	1.8±0.66	1.7±0.65
Concomitant medications (%)		
Digoxin	85	87
Loop diuretics	97	96
Spironolactone	39	34
ACE inhibitors	51	62
A-II antagonists	18	10
Amiodarone	46	45
Beta-blockers	20	24
Intravenous inotropic agents	72	65
NYHA class	IV	IV
Quality of life‡		
Minnesota Living with Heart Failure score	75±17	75±18
SF-36		
Physical function	18±19	19±19
Emotional role	25±38	33±42
Beck Depression Inventory	16±8	19±9

*Plus–minus values are means ±SD. There were no significant differences between groups. LVAD denotes left ventricular assist device, ACE angiotensin-converting enzyme, A-II angiotensin II receptor, and NYHA New York Heart Association.

†To convert the values for creatinine to micromoles per liter, multiply by 88.4.

‡Scores on the Minnesota Living with Heart Failure questionnaire can range from 0 (best quality of life) to 105 (worst quality of life). Scores on each aspect of the 36-item Short Form 36 questionnaire (SF-36) can range from 0 (worst) to 100 (best). Scores on the Beck Depression Inventory can range from 0 (normal) to 64 (severe depression).

were assigned to receive a left ventricular assist device had the device implanted. No patients in either group crossed over, and none underwent cardiac transplantation.
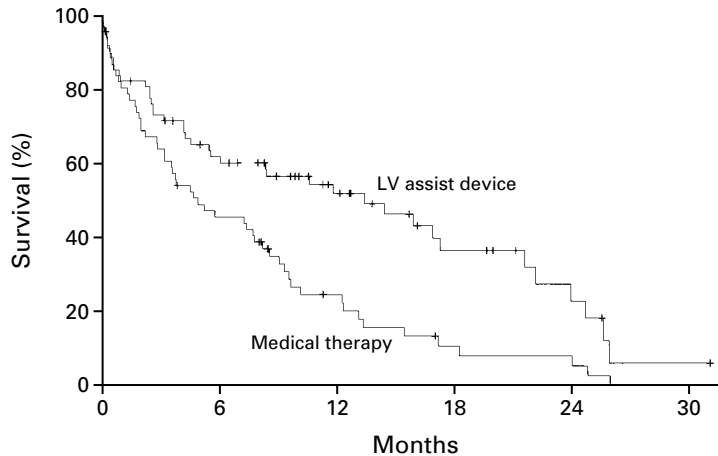
Survival

Figure 2 shows the Kaplan–Meier survival curves. There was a reduction of 48 percent in the risk of death from any cause — the primary end point — in the group that received left ventricular assist devices, as compared with the medical-therapy group (relative risk, 0.52; 95 percent confidence interval, 0.34 to 0.78; P=0.001). The Kaplan–Meier estimates of survival at one year were 52 percent in the device group and 25 percent in the medical-therapy group

(P=0.002) and at two years were 23 percent and 8 percent (P=0.09), respectively. Median survival was 408 days in the device group and 150 days in the medical-therapy group. At the time of the final analysis, 41 deaths had occurred in the device group and 54 in the medical-therapy group. Table 2 lists the causes of death. Terminal heart failure caused the majority of deaths in the medical-therapy group, whereas the most common causes of death in the device group were sepsis (41 percent of deaths) and failure of the device (17 percent).

Although the trial was not designed to have enough statistical power for subgroup analyses, a prespecified analysis with stratification according to age (18 to 59 years, 60 to 69 years, ≥70 years) showed that there was a significant reduction in the risk of death among patients in the device group who were 60 to 69 years old, as compared with patients in the medical-therapy group who were 60 to 69 years old (relative risk, 0.49; 95 percent confidence interval, 0.25 to 0.95), and a trend toward a benefit in the younger age group (relative risk, 0.47; 95 percent confidence interval, 0.17 to 1.28) and the older age group (relative risk, 0.59; 95 percent confidence interval, 0.31 to 1.15). In the overall group of 22 patients who were younger than 60 years, the one-year survival rate was 74 percent in the device group (13 patients) and 33 percent in the medical-therapy group (9 patients) (P=0.05). In the group of 49 patients who were 60 to 69 years old, the one-year survival rate was 47 percent in the device group (29 patients) and 15 percent in the medical-therapy group (20 patients) (P=0.009).

Quality of Life

All patients completed the base-line assessments of the quality of life, and there were no significant differences between groups. Table 3 shows the results one year after enrollment, and Table 4 shows the results of some measures assessed by the physical-function subscale of the SF-36. Five of the 11 patients in the medical-therapy group who were alive at one year did not complete the questionnaires (3 were too ill, 1 could not arrange transportation, and 1 was not tested because of a scheduling error). All but 1 of the 24 patients in the device group completed the questionnaires (1 patient could not arrange transportation). Scores on the physical-function and emotional-role subscales of the SF-36 and the Beck Depression Inventory and the NYHA class were all significantly better in the device group at one year. The Minnesota Living with Heart Failure score was better in the device group than in the medical-therapy group at one year, but the difference was not significant. Videotaped examples of patients who received the device and have good functional outcomes are available as Supplementary Appendix 1 with the full text of this article at http://www.nejm.org.

Figure 2. Kaplan–Meier Analysis of Survival in the Group That Received Left Ventricular (LV) Assist Devices and the Group That Received Optimal Medical Therapy.

Crosses depict censored patients. Enrollment in the trial was terminated after 92 patients had died; 95 deaths had occurred by the time of the final analysis.

TABLE 2. CAUSES OF DEATH.*

CAUSE OF DEATH	MEDICAL-THERAPY GROUP	LVAD GROUP	TOTAL
	no. of patients		
Left ventricular dysfunction	50	1	51
Sepsis	1	17	18
Failure of LVAD	0	7	7
Miscellaneous noncardiovascular causes	0	5	5
Cerebrovascular disease	0	4	4
Miscellaneous cardiovascular causes	1	2	3
Pulmonary embolism	0	2	2
Acute myocardial infarction	1	0	1
Cardiac procedure	1	0	1
Perioperative bleeding	0	1	1
Unknown	0	2	2
Total	54	41	95

*LVAD denotes left ventricular assist device.

TABLE 3. QUALITY OF LIFE AND FUNCTIONAL STATUS OF PATIENTS AT ONE YEAR.*

SCALE†	ONE YEAR		P VALUE
	NO. ASSESSED/ TOTAL NO. (%)	SCORE	
SF-36			
Physical function			0.01
LVAD group	23/24 (96)	46±19	
Medical-therapy group	6/11 (55)	21±21	
Emotional role			0.03
LVAD group	23/24 (96)	64±45	
Medical-therapy group	6/11 (55)	17±28	
Minnesota Living with Heart Failure			0.11
LVAD group	23/24 (96)	41±22	
Medical-therapy group	6/11 (55)	58±21	
Beck Depression Inventory			0.04
LVAD group	22/24 (92)	8±7	
Medical-therapy group	5/11 (45)	13±7	
Median NYHA class			<0.001
LVAD group	24/24 (100)	II	
Medical-therapy group	7/11 (64)	IV	

*Plus–minus values are means ±SD. Only patients who completed testing were included in the analysis. There were too few patients for an analysis of two-year data. LVAD denotes left ventricular assist device.

†Scores on each aspect of the 36-item Short Form 36 questionnaire (SF-36) can range from 0 (worst) to 100 (best). Scores on the Minnesota Living with Heart Failure questionnaire can range from 0 (best quality of life) to 105 (worst quality of life). Scores on the Beck Depression Inventory can range from 0 (normal) to 64 (severe depression).

Adverse Events

Owing to the difference in survival, we reported adverse events as rates per patient-year.[23] One patient in each group died immediately after randomization and was therefore excluded from the analysis. Patients in the device group were more than twice as likely as patients in the medical-therapy group to have a serious adverse event (rate ratio, 2.35; 95 percent confidence interval, 1.86 to 2.95) (Table 5).

TABLE 4. SAMPLE ACTIVITIES ASSESSED BY THE PHYSICAL-FUNCTION SUBSCALE OF THE MEDICAL OUTCOMES STUDY SHORT-FORM GENERAL HEALTH SURVEY QUESTIONNAIRE AT ONE YEAR.*

ACTIVITY	NOT LIMITED AT ALL		LIMITED A LITTLE		LIMITED A LOT		P VALUE†
	LVAD GROUP	MEDICAL-THERAPY GROUP	LVAD GROUP	MEDICAL-THERAPY GROUP	LVAD GROUP	MEDICAL-THERAPY GROUP	
			no. of patients				
Climbing one flight of stairs	15	0	5	3	3	3	0.006
Climbing several flights of stairs	1	0	14	0	8	6	0.008
Walking one block	16	1	6	2	1	3	0.004
Walking several blocks	6	0	10	3	7	3	0.18
Walking more than a mile	2	0	6	2	15	4	0.72
Bathing or dressing	9	2	11	2	3	2	0.43

*In the group that received left ventricular assist devices (LVADs), 23 of 24 eligible patients completed the test (1 patient could not arrange transportation). In the medical-therapy group, 6 of 11 eligible patients completed the test; 3 were too ill, 1 could not arrange transportation, and 1 was not tested because of a scheduling error.

†The Cochran–Mantel–Haenszel test for nonzero correlations was used to compare the LVAD and medical-treatment groups across the range of outcomes.

Events Related to the Device

Within three months after implantation, the probability of infection of the left ventricular assist device was 28 percent (95 percent confidence interval, 15 to 38 percent). Although most of these infections were in the drive-line tract and pocket and were treated with local measures and antibiotics, fatal sepsis was common. Within six months after implantation, the frequency of bleeding was 42 percent. No system had failed by 12 months, but the probability of device failure was 35 percent at 24 months. The device was replaced in 10 patients.

Hospitalization

The protocol required all patients to be hospitalized at the time of randomization. Both the median number of days spent in and the median number spent out of the hospital were greater in the device group than in the medical-therapy group (Table 6).

DISCUSSION

This trial demonstrates that long-term support with a left ventricular assist device resulted in substantial improvement in survival in patients with severe heart failure who were not candidates for cardiac transplantation. The patients in the medical-therapy group received optimal medical care with digoxin, diuretics, angiotensin-converting–enzyme inhibitors, and beta-blockers from heart-failure specialists. The one-year mortality rate of 75 percent in this group exceeded the rates for the acquired immunodeficiency syndrome and breast, lung, and colon cancer[24,25] and was more than four times that in trials of beta-blockers.[5]

The patients we enrolled had more severe disease at base line and a higher mortality rate during subsequent medical therapy than did patients in other randomized trials of treatment for heart failure.[4,5,26] Patients well enough to undergo exercise testing had a peak oxygen consumption of only 9.18 ± 1.98 ml per kilogram per minute, a value that is highly predictive of early mortality.[27] In the 68 percent of patients who could not exercise, an inability to be weaned from intravenous inotropic drugs was documented.

The implantation of a left ventricular assist device was associated with a relative reduction in the risk of death of 48 percent during the entire follow-up period and an absolute reduction in the mortality rate of 27 percent at one year. These findings imply that for every 1000 patients with end-stage heart failure, the implantation of a left ventricular assist device could prevent at least 270 deaths annually. The treatment effect is nearly four times that of beta-blockers or angiotensin-converting–enzyme inhibitors, which have been estimated to prevent 70 deaths for every 1000 patients treated who receive either type of agent.[5,28] Nevertheless, the magnitude of this reduction must be considered in the context of the greater complexity of therapy with a left ventricular assist device than of drug therapy.

Early experience with artificial hearts suggested that any potential survival benefit would be achieved at an unacceptable cost in the quality of life.[29] In our study, measurements of the quality of life at base line and during the study in the medical-therapy group reflected the severe physical, emotional, and functional impairment of these terminally ill patients. Although the scores at one year on the physical-function and emotional-role subscales of the SF-36 were significantly better in the device group than in the medi-

TABLE 5. INCIDENCE OF SERIOUS ADVERSE EVENTS.*

EVENT	MEDICAL-THERAPY GROUP (N=60)	LVAD GROUP (N=67)	RATE RATIO (95% CI)
	rate/patient-yr		
All	2.75	6.45	2.35 (1.86–2.95)
Nonneurologic bleeding	0.06	0.56	9.47 (2.30–38.90)
Neurologic dysfunction†	0.09	0.39	4.35 (1.31–14.50)
Supraventricular arrhythmia	0.03	0.12	3.92 (0.47–32.40)
Peripheral embolic event	0.06	0.14	2.29 (0.48–10.80)
Sepsis	0.30	0.60	2.03 (0.99–4.13)
Local infection	0.24	0.39	1.63 (0.72–3.70)
Renal failure	0.18	0.25	1.42 (0.54–3.71)
Miscellaneous adverse events	0.98	1.37	1.41 (0.93–2.12)
Syncope	0.03	0.04	1.31 (0.12–14.40)
Serious psychiatric disease	0.03	0.04	1.31 (0.12–14.30)
Cardiac arrest	0.18	0.12	0.65 (0.21–2.00)
Nonperioperative myocardial infarction	0.03	0.02	0.65 (0.04–10.30)
Ventricular arrhythmia	0.56	0.25	0.45 (0.22–0.90)
Hepatic failure	0.00	0.02	—
Event related to the LVAD			
Suspected malfunction of LVAD	—	0.75	—
Perioperative bleeding	—	0.46	—
Infection of drive-line tract or pocket	—	0.41	—
Infection of pump interior, inflow tract, or outflow tract	—	0.23	—
Right heart failure	—	0.17	—
Failure of LVAD system	—	0.08	—
Thrombosis in LVAD	—	0.06	—
Perioperative myocardial infarction	—	0.00	—

*One patient in each group died immediately after randomization and thus was not included in the analysis. LVAD denotes left ventricular assist device, and CI confidence interval.

†Neurologic dysfunction included stroke, transient ischemic attacks, and toxic or metabolic encephalopathy.

cal-therapy group, they were not those of healthy people in the general population.[30] However, the physical-function scores were similar to those reported for patients receiving long-term hemodialysis and ambulatory patients with heart failure,[30,31] and the emotional-role scores were better than those reported for patients with clinical depression and similar to those for ambulatory patients with heart failure. Although not statistically significant, the difference of 17 points in the mean scores on the Minnesota Living with Heart Failure questionnaire at one year between patients in the device group and patients in the medical-therapy group greatly exceeded the 5-point threshold for meaningful improvement used in other studies.[32]

Despite the substantial survival benefit, the morbidity and mortality associated with the use of the left ventricular assist device were considerable. In particular, infection and mechanical failure of the device were major factors in the two-year survival rate of only 23 percent. The device employed requires a percutaneous line, which can become a conduit for bacterial and fungal infection. Investigators found that malnutrition was a problem in these patients, which predisposed them to infection and other complications. Factors contributing to postoperative malnutrition include early satiety from the bulk of the intraabdominally implanted device, chronic inflammation associated with heart failure and the device, and severe and often underdiagnosed preoperative debilitation.[33]

Failure of the left ventricular assist device was the second most frequent cause of death in the device group. The findings of inflow-valve failure and late erosions of the outflow graft resulting from kinking have already led to modifications in the device. Malfunction of the mechanical parts, such as rupture of the lining, motor failure, and wear on the bearings, also limits the durability of the device. The rate of neurologic events in the device group was 4.35 times

TABLE 6. HOSPITALIZATION EXPERIENCE.*

VARIABLE	MEDICAL-THERAPY GROUP	LVAD GROUP
	median no.	
Days alive	150	408
Days spent out of the hospital	106	340
Days spent in the hospital	24	88
Days spent in the hospital for medical management or implantation of LVAD	5	29

*LVAD denotes left ventricular assist device.

as high as the rate in the medical-therapy group. However, 76 percent of patients in the device group were free of serious neurologic events without routine anticoagulation. Moreover, 47 percent of the serious neurologic events in this group were transient, with toxic and metabolic causes. The relatively low proportion of patients in the device group who had an ischemic stroke (10 percent) during follow-up is probably related to the unique textured surfaces of the device we used.

We believe that the decreased mortality rates and increased rates of adverse events in the device group represent an acceptable trade-off, given the natural history of end-stage heart failure. The frequency of complications indicates the need for further improvements in patient care and the design of the device. Although this learning-curve phenomenon was not significant, there was a 25 percent decline in the mortality relative risk per year when survival was adjusted for the date of entry in the trial.

Our findings establish the left ventricular assist device as a new long-term myocardial replacement therapy, joining cardiac transplantation in the treatment options for end-stage heart failure. Although transplantation has never been compared with medical therapy in a randomized trial, the 1-year survival rate of more than 80 percent and the 10-year survival rate of nearly 50 percent for transplantation far exceed the survival rate for left ventricular assist devices in our study.[6] However, the outcomes of transplantation do not include the substantial mortality rates among patients who are awaiting transplantation. Currently, fewer than 3000 donor hearts per year are available worldwide.[6] The combination of the availability of left ventricular assist devices and the encouraging one-year survival rate of 74 percent in our patients who were younger than 60 years suggests that a comparison of the long-term use of these devices and transplantation may soon be appropriate.

Many new devices that may be equivalent or superior to the device we used are now in early clinical trials. Such devices include fully implantable pulsatile and smaller, nonpulsatile left ventricular assist devices and a fully implantable artificial heart. We believe that our findings establish new standards for survival, quality of life, and adverse events. The limitations we found clearly justify an intensification of efforts to improve both these devices and patient care, with the goal of improving outcomes in the sickest of patients and paving the way for an assessment of the use of mechanical circulatory assistance in patients with serious, but less severe heart-failure syndromes.

APPENDIX

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REFERENCES

1. 2001 Heart and stroke statistical update. Dallas: American Heart Association, 2000.
2. O'Connell JB, Birstow MR. Economic impact of heart failure in the United States: time for a different approach. J Heart Lung Transplant 1994;13:S107-S112.
3. Califf RM, Adams KF, McKenna WJ, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan International Randomized Survival Trial (FIRST). Am Heart J 1997;134: 44-54.

4. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.

5. Packer M, Coats AJS, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651-8.

6. Hosenpud JD, Bennett LE, Keck BM, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: seventeenth official report — 2000. J Heart Lung Transplant 2000;19: 909-31.

7. The artificial heart program: current status and history. In: Hogness JR, VanAntwerp M, eds. The artificial heart: prototypes, policies, and patients. Washington, D.C.: National Academy Press, 1991:14-25.

8. Goldstein DJ, Oz MC, Rose EA. Implantable left ventricular assist devices. N Engl J Med 1998;339:1522-33.

9. Frazier OH, Rose EA, Macmanus Q, et al. Multicenter clinical evaluation of the HeartMate 1000 IP left ventricular assist device. Ann Thorac Surg 1992;53:1080-90.

10. Pennington DG, McBride LR, Peigh PS, Miller LW, Swartz MT. Eight years' experience with bridging to cardiac transplantation. J Thorac Cardiovasc Surg 1994;107:472-81.

11. Korfer R, El-Banayosy A, Arusoglu L, et al. Single-center experience with the Thoratec ventricular assist device. J Thorac Cardiovasc Surg 2000; 119:596-600.

12. McBride LR, Naunheim KS, Fiore AC, Moroney DA, Swartz MT. Clinical experience with 111 Thoratec ventricular assist devices. Ann Thorac Surg 1999;67:1233-9.

13. Portner PM, Oyer PE, Pennington DG, et al. Implantable electrical left ventricular assist system: bridge to transplantation and the future. Ann Thorac Surg 1989;47:142-50.

14. Moskowitz AJ, Weinberg AD, Oz MC, Williams DL. Quality of life with an implanted left ventricular assist device. Ann Thorac Surg 1997;64: 1764-9.

15. Catanese KA, Goldstein DJ, Williams DL, et al. Outpatient left ventricular assist device support: a destination rather than a bridge. Ann Thorac Surg 1996;62:646-53.

16. Mehta SM, Aufiero TX, Pae WE Jr, Miller CA, Pierce WS. Combined Registry for the Clinical Use of Mechanical Ventricular Assist Pumps and the Total Artificial Heart in conjunction with heart transplantation: sixth official report — 1994. J Heart Lung Transplant 1994;14:585-93.

17. Slater JE, Rose EA, Levin HR, et al. Low thromboembolic risk without anticoagulation using advanced-design left ventricular assist devices. Ann Thorac Surg 1996;62:1321-7.

18. Spanier T, Oz MC, Levin HR, et al. Activation of coagulation and fibrinolytic pathways in patients with left ventricular assist devices. J Thorac Cardiovasc Surg 1996;112:1090-7.

19. Rose EA, Moskowitz AJ, Packer M, et al. The REMATCH trial: rationale, design, and end points: Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure. Ann Thorac Surg 1999;67:723-30.

20. Rector TS, Cohn JN, Pimobendan Multicenter Research Group. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Am Heart J 1992;124:1017-25.

21. Ware JE Jr, Kosinski M, Keller S. SF-36 Physical and Mental Health Summary Scales: a user's manual. Boston: Health Institute, New England Medical Center, 1994.

22. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36). II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31: 247-63.

23. Edmunds LH Jr, Clark RE, Cohn LH, Grunkemeier GL, Miller DC, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. Ann Thorac Surg 1996;62:932-5.

24. Lee LM, Karon JM, Selik R, Neal JJ, Fleming PL. Survival after AIDS diagnosis in adolescents and adults during the treatment era, United States, 1984-1997. JAMA 2001;285:1308-15.

25. Ries L, Eisner M, Kosary C, et al., eds. SEER cancer statistics review, 1973-1998. Bethesda, Md.: National Cancer Institute, 2001.

26. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. N Engl J Med 1991;325:1468-75.

27. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991;83:778-86.

28. Kjekshus J, Swedberg K, Snapinn S. Effects of enalapril on long-term mortality in severe congestive heart failure. Am J Cardiol 1992;69:103-7.

29. The Schroeder Family, Barnette M. The Bill Schroeder story: an artificial heart patient's historic ordeal and the amazing family effort that supported him. New York: William Morrow, 1987:383.

30. Ware JE Jr, Snow KK, Kosinski M, Gandek B. SF-36 Health Survey: manual and interpretation guide. Boston: Health Institute, New England Medical Center, 1993.

31. Singer MA, Hopman WM, MacKenzie TA. Physical functioning and mental health in patients with chronic medical conditions. Qual Life Res 1999;8:687-91.

32. Rector TS, Tschumperlin LK, Kubo SH, et al. Use of the Living With Heart Failure questionnaire to ascertain patients' perspectives on improvement in quality of life versus risk of drug-induced death. J Card Fail 1995; 1:201-6.

33. el-Amir NG, Gardocki M, Levin HR, et al. Gastrointestinal consequences of left ventricular assist device placement. ASAIO J 1996;42:150-3.

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