ORIGINAL ARTICLE

Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device

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ABSTRACT

BACKGROUND

Patients with advanced heart failure have improved survival rates and quality of life when treated with implanted pulsatile-flow left ventricular assist devices as compared with medical therapy. New continuous-flow devices are smaller and may be more durable than the pulsatile-flow devices.

METHODS

In this randomized trial, we enrolled patients with advanced heart failure who were ineligible for transplantation, in a 2:1 ratio, to undergo implantation of a continuous-flow device (134 patients) or the currently approved pulsatile-flow device (66 patients). The primary composite end point was, at 2 years, survival free from disabling stroke and reoperation to repair or replace the device. Secondary end points included survival, frequency of adverse events, the quality of life, and functional capacity.

RESULTS

Preoperative characteristics were similar in the two treatment groups, with a median age of 64 years (range, 26 to 81), a mean left ventricular ejection fraction of 17%, and nearly 80% of patients receiving intravenous inotropic agents. The primary composite end point was achieved in more patients with continuous-flow devices than with pulsatile-flow devices (62 of 134 [46%] vs. 7 of 66 [11%]; P<0.001; hazard ratio, 0.38; 95% confidence interval, 0.27 to 0.54; P<0.001), and patients with continuous-flow devices had superior actuarial survival rates at 2 years (58% vs. 24%, P=0.008). Adverse events and device replacements were less frequent in patients with the continuous-flow device. The quality of life and functional capacity improved significantly in both groups.

CONCLUSIONS

Treatment with a continuous-flow left ventricular assist device in patients with advanced heart failure significantly improved the probability of survival free from stroke and device failure at 2 years as compared with a pulsatile device. Both devices significantly improved the quality of life and functional capacity. (ClinicalTrials.gov number, NCT00121485.)

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Medical and electrical therapies for systolic heart failure have improved outcomes and altered the natural history of the disease.[1-9] However, heart failure commonly progresses and becomes refractory to current treatments. Continuous intravenous inotropic support may improve clinical status in the short term but results in a survival rate at 1 year of only 10 to 30%.[10,11] Cardiac transplantation is available for only a minority of patients, because of a lack of suitable donor hearts. The paucity of effective therapies for advanced heart failure led to the evaluation of mechanical circulatory-support devices as permanent therapy.

To date, only two completed trials, one randomized[12] and one nonrandomized,[13] have evaluated patients with advanced heart failure who were ineligible for transplantation and compared optimal medical therapy with the use of a pulsatile left ventricular assist device. The survival status, functional capacity, and quality of life were superior in the patients treated with the pulsatile left ventricular assist devices. However, the 2-year survival rate among patients with a left ventricular assist device in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial (ClinicalTrials.gov number, NCT00000607) was only 23%, as compared with 8% among patients receiving medical therapy.[12] Despite these substantial improvements in outcomes, broader application of left ventricular assist devices for advanced heart failure has been limited by the large size of the pump and drive line, clinically significant adverse events, and limited device durability.

Newer designs of left ventricular assist devices, involving rotary-pump technology to provide blood flow with reduced pulsatility, have undergone clinical investigation. These continuous-flow left ventricular assist devices have improved the hemodynamics, end-organ function, quality of life, and functional capacity of patients awaiting transplantation.[14,15] They are also smaller, quieter, and more durable than pulsatile-flow devices, making them potentially better suited for long-term support.

This study reports the results of a randomized trial comparing outcomes in patients with advanced heart failure who were ineligible for transplantation and received either a pulsatile-flow left ventricular assist device or a continuous-flow left ventricular assist device.

METHODS

STUDY ORGANIZATION

The study was conducted at 38 centers in the United States. Data were collected by study coordinators at participating centers, analyzed by the sponsor (Thoratec, Pleasanton, CA), and audited by the sponsor. The authors vouch for the completeness and accuracy of the data and analyses. An independent data and safety monitoring board monitored the study and reviewed the protocol compliance and outcome data. An independent clinical events committee adjudicated the causes of death and adverse events. The protocol was approved by each participating center's institutional review board.

STUDY PATIENTS

Patients with advanced heart failure who were ineligible for heart transplantation and whose heart failure was refractory to optimal medical management were considered for study enrollment. Detailed inclusion and exclusion criteria are listed in the Supplementary Appendix (available with the full text of this article at NEJM.org). Enrolled patients met the following criteria: a left ventricular ejection fraction of less than 25%; a peak oxygen consumption of less than 14 ml per kilogram of body weight per minute, or less than 50% of the predicted value; and New York Heart Association (NYHA) class IIIB or IV symptoms for at least 45 of the 60 days before enrollment or dependence on an intraaortic balloon pump for a period of 7 days or inotropes for a period of at least 14 days before enrollment. Exclusion criteria included irreversible, severe renal, pulmonary, or hepatic dysfunction or active infection. All patients or an authorized representative provided written informed consent.

STUDY DESIGN

Patients were randomly assigned, in a 2:1 ratio, to receive either a continuous-flow left ventricular assist device or a pulsatile-flow left ventricular assist device. Randomization was stratified according to study center and with the use of permuted blocks to maintain the 2:1 ratio over time. Baseline data — including demographic characteristics, concomitant use of medications, health history, responses on the Minnesota Living with Heart Failure and Kansas City Cardiomyopathy questionnaires, and clinical laboratory values —

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were collected for all patients. After implantation of the left ventricular assist device, device performance, laboratory results, and medication use were initially recorded at daily to weekly intervals and after hospital discharge were recorded monthly. Quality-of-life assessments and the 6-minute walk tests were completed at baseline, 1 month, 3 months, 6 months, and then every 6 months until study completion at 24 months. Adverse events were recorded throughout the study, with the use of standardized definitions (see the Supplementary Appendix). All causes of death were determined by means of autopsy or through examination of medical records, with final adjudication by the clinical events committee.

LEFT VENTRICULAR ASSIST DEVICES

The two left ventricular assist devices used in this study were the pulsatile-flow HeartMate XVE and the continuous-flow HeartMate II (both from Thoratec). These implanted pumps draw blood from the apex of the left ventricle and deliver it to the ascending aorta. Both are electrically driven by means of a percutaneous lead that connects the pump to an external system controller and power source (Fig. 1, and the animation[16] available with the full text of this article at NEJM.org). The continuous-flow left ventricular assist device has a volume of 63 ml and a weight of 390 g, as compared with 450 ml and 1250 g for the pulsatile-flow left ventricular assist device. Both devices are capable of a flow rate up to 10 liters per minute at a mean pressure of 100 mm Hg. Antithrombotic management included aspirin for all patients and warfarin (with a targeted international normalized ratio of 2.0 to 3.0) only for those with the continuous-flow device.

STATISTICAL ANALYSIS

The primary end point was a composite of survival at 2 years, free of disabling stroke (stroke with a Rankin score >3) or reoperation to replace the device. The percentage of patients in whom the primary composite end point was reached was compared between the two treatment groups with the use of Fisher's exact test. Cox proportional-hazards analyses, with the data stratified on the basis of the treatment assignment, were used to calculate hazards ratios and 95% confidence intervals for the primary end point and component events. Analysis of the primary composite end point was conducted on the basis of the intention-to-treat principle. Patients who had undergone randomization but not implantation of a device were considered to have had treatment failure, as were patients who had device failure requiring either device explantation or urgent heart transplantation.

Secondary study end points included actuarial survival, frequency of adverse events, functional status, and the quality of life. The secondary end points were evaluated with the use of an as-treated analysis of all data until use of the treatment device was discontinued. Data on the categorical variables were compared with the use of Fisher's exact test. Longitudinal changes in functional status and quality of life were analyzed by means of linear mixed-effects modeling. Adverse-event rates and relative risks were compared between the two treatment groups with the use of Poisson regression. Actuarial-survival analysis was performed by means of the Kaplan–Meier method and the results were compared between the two groups with the use of log-rank analysis. P values of less than 0.05 were considered to indicate statistical significance. All reported P values are two-sided and were not adjusted for multiple testing.

A total of two interim analyses were conducted, one each after 27% and 67% of the patients had reached the 2-year time point. The false positive rate was limited to 5% by means of the O'Brien–Fleming spending function.

An animation showing left ventricular assist devices is available at NEJM.org

RESULTS

STUDY PATIENTS

A total of 200 patients were randomly assigned to undergo implantation of a continuous-flow left ventricular assist device (134 patients) or a pulsatile-flow left ventricular assist device (66 patients) between March 2005 and May 2007. The baseline characteristics of each of the two treatment groups were similar, except more women were in the continuous-flow device group (Table 1). Resynchronization therapy had failed in more than 60% of patients, nearly 80% were receiving intravenous inotropic agents, and over 20% had an intraaortic balloon pump at the time of enrollment. There was no significant difference between the two groups in the destination therapy risk score.[17]

CLINICAL COURSE

Five patients randomly assigned to receive a pulsatile-flow left ventricular assist device and three

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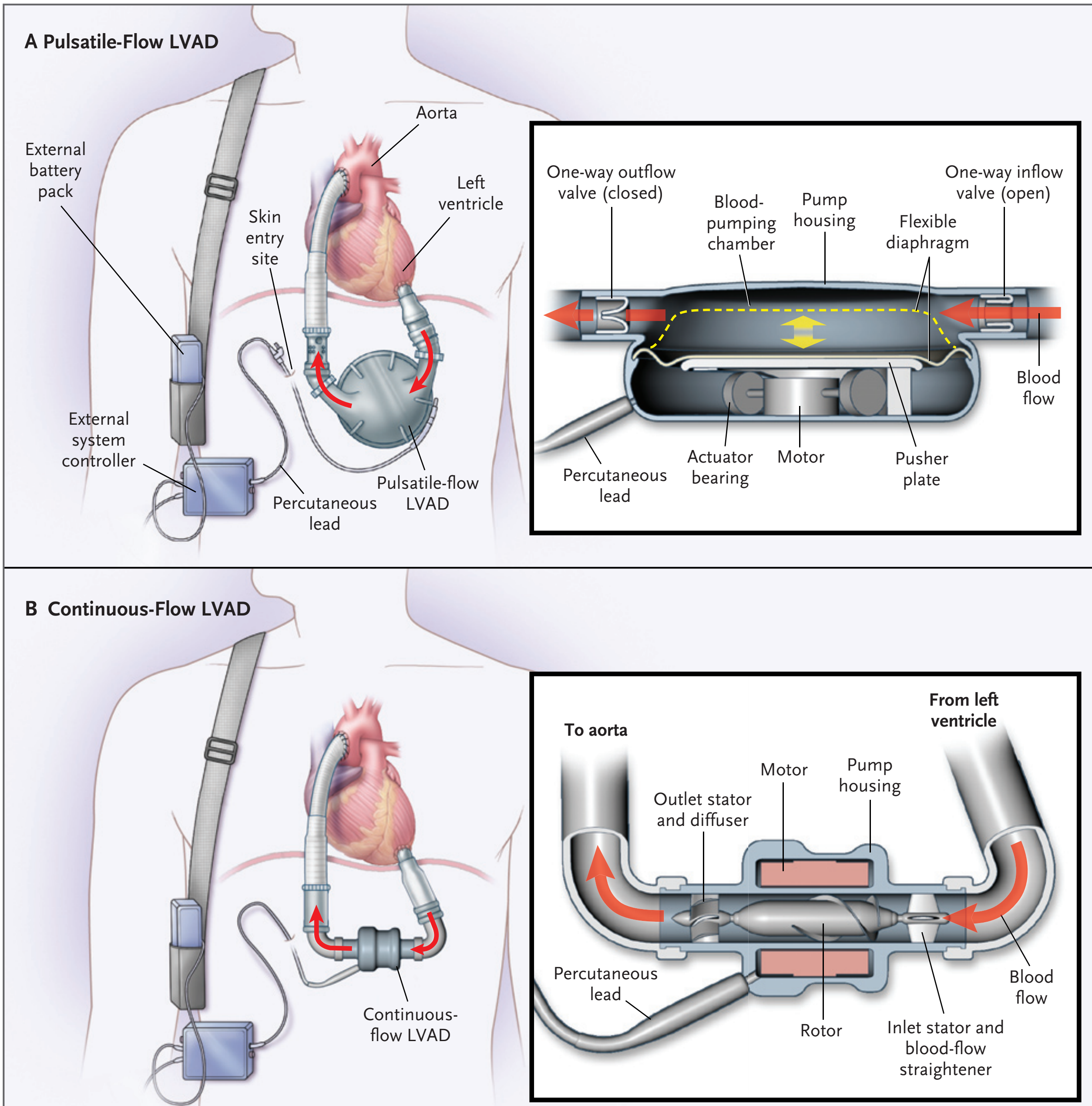

Figure 1. **Pulsatile-Flow (Panel A) and Continuous-Flow (Panel B) Left Ventricular Assist Devices (LVADs).**

patients randomly assigned to receive a continuous-flow device did not undergo implantation with a device; however, these patients were counted as having treatment failure (see the flow chart in the Supplementary Appendix). Three patients who had a small body size and who had been randomly assigned to the pulsatile-flow device group received the smaller continuous-flow device instead, because of difficulty with anatomical fitting. One patient randomly assigned to the continuous-flow device group received a pulsatile-flow left ventricular assist device instead, because the patient's health insurance would only cover the pulsatile-flow device.

The remaining patients, whose data were included in the as-treated analyses, consisted of 133 who underwent implantation of a continuous-flow left ventricular assist device and 59 who underwent implantation of a pulsatile-flow left ventricular assist device. The median duration of support

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Table 1. Baseline Characteristics of the Study Patients, According to Treatment Group.*

Characteristic	Continuous-Flow LVAD (N=134)	Pulsatile-Flow LVAD (N=66)	P Value
Age — yr			0.81
Mean	62±12	63±12	
Median (range)	64 (26–79)	65 (29–81)	
Male sex — no. (%)	108 (81)	61 (92)	0.04
Body-surface area — m^2	2.0±0.3	2.1±0.3	0.54
Ischemic cause of heart failure — no. (%)	88 (66)	45 (68)	0.75
Left ventricular ejection fraction — %	17.0±5.5	16.8±5.4	0.81
Arterial blood pressure — mm Hg			
Systolic	104±14	104±18	0.93
Diastolic	61±13	61±12	0.94
Pulmonary-capillary wedge pressure — mm Hg	24±8	24±9	0.82
Cardiac index — liters/min/m^2 of body-surface area	2.0±0.6	2.1±0.6	0.36
Pulmonary vascular resistance — dyn•sec•cm^{-5}	264±128	264±152	0.98
Central venous pressure — mm Hg	13±6	13±8	0.67
Serum sodium — mmol/liter	134.7±4.3	133.9±6.0	0.31
Serum creatinine — mg/dl	1.6±0.6	1.8±0.7	0.08
History of stroke — no. (%)	21 (16)	11 (17)	0.84
Concomitant medication or intervention — no. (%)			
Intravenous inotropic agent	103 (77)	55 (83)	0.36
Diuretic	123 (92)	57 (86)	0.32
ACE inhibitor	43 (32)	22 (33)	0.87
Angiotensin II–receptor antagonist	12 (9)	3 (5)	0.39
Beta-blocker	71 (53)	38 (58)	0.55
Biventricular pacemaker	85 (63)	39 (59)	0.64
ICD	111 (83)	52 (79)	0.56
IABP	30 (22)	15 (23)	1.00
Mechanical ventilation	9 (7)	6 (9)	0.57
Destination therapy risk score†			
Mean	10.4±5.4	9.9±4.7	0.78
Score denoting high or very high risk — no. (%)	24 (18)	5 (8)	0.06

* Plus–minus values are means ±SD. Additional data on baseline characteristics are given in the Supplementary Appendix. To convert values for creatinine to micromoles per liter, multiply by 88.4. ACE denotes angiotensin-converting enzyme, IABP intraaortic balloon pump, ICD implantable cardioverter–defibrillator, and LVAD left ventricular assist device.
† The destination therapy risk score was calculated according to the methods of Lietz et al.[17] Possible scores range from 0 to 31, with higher scores indicating an increased risk of death at 90 days.

was 1.7 years (range, 0.0 to 3.7) and 0.6 years (range, 0.0 to 2.1) for the continuous-flow left ventricular assist device and the pulsatile-flow device, respectively, with a cumulative follow-up of 211 and 41 patient-years, respectively. Cardiac transplantation was performed in 17 patients randomly assigned to the continuous-flow left ventricular assist device and 9 patients randomly assigned to the pulsatile-flow left ventricular assist device, after contraindications to transplantation resolved while the device was providing support.

The mean (±SD) cardiac index increased from 2.0±0.6 liters per minute per square meter of body-surface area preoperatively to 2.9±0.7 liters per minute per square meter by 24 hours after implantation of the continuous-flow left ventricular as-

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Table 2. Primary End Point and Hazard Ratios, According to Treatment Group.*

End Point	Continuous-Flow LVAD (N=134)	Pulsatile-Flow LVAD (N=66)	Hazard Ratio (95% CI)	P Value
	no. (% [95% CI])			
Survival free from disabling stroke and reoperation to repair or replace LVAD at 2 yr (primary composite end point)	62 (46 [38–55])	7 (11 [3–18])		<0.001
First event that prevented patient from reaching the primary end point				
Disabling stroke†	15 (11 [6–17])	8 (12 [4–20])	0.78 (0.33–1.82)	0.56
Reoperation to repair or replace pump‡	13 (10 [5–15])	24 (36 [25–48])	0.18 (0.09–0.37)	<0.001
Death within 2 yr after implantation	44 (33 [25–41])	27 (41 [29–53])	0.59 (0.35–0.99)	0.048
Any	72 (54 [45–62])	59 (89 [82–97])	0.38 (0.27–0.54)	<0.001

* Hazard ratios were calculated with the use of Cox regression, and the P value for the primary end point with the use of Fisher's exact test. CI denotes confidence interval, and LVAD left ventricular assist device.
† Disabling stroke was defined as stroke with a Rankin score of more than 3.
‡ Reoperation to repair or replace pump included urgent heart transplantation or device explantation.

sist device (P<0.001) and from 2.1±0.6 to 2.9±0.7 liters per minute per square meter after implantation of the pulsatile-flow left ventricular assist device (P<0.001). At the same time points, the pulmonary-capillary wedge pressure decreased from 24±8 to 17±7 mm Hg (P<0.001) with the continuous-flow left ventricular assist device and from 24±9 to 16±6 mm Hg (P<0.001) with the pulsatile-flow left ventricular assist device.

A total of 114 of the 133 patients (86%) with the continuous-flow left ventricular assist device and 45 of the 59 (76%) with the pulsatile-flow left ventricular assist device were discharged from the hospital with the device in place. The median length of stay after surgery was 27 days in the continuous-flow device group and 28 days in the pulsatile-flow device group. The percentage of total time spent out of the hospital after device implantation was 88% with the continuous-flow left ventricular assist device, as compared with 74% with the pulsatile-flow device (P=0.02).

PRIMARY END POINT

All 200 patients were followed for at least 2 years or until death, transplantation, or device explantation. The primary composite end point was achieved in more patients assigned to receive a continuous-flow left ventricular assist device than in those assigned to receive a pulsatile-flow left ventricular assist device (46% vs. 11%; hazard ratio, 0.38; 95% confidence interval [CI], 0.27 to 0.54; P<0.001) (Table 2). Failure to reach the primary end point was influenced by reoperation to repair or replace the left ventricular assist device and death within 2 years after device implantation, the rates of which were reduced with the continuous-flow device.

Of the 59 patients who underwent implantation with a pulsatile-flow left ventricular assist device, 20 required 21 pump replacements (3 replaced with another pulsatile-flow device and 18 with a continuous-flow device) — and an additional 1 patient required urgent transplantation and 3 additional patients required device explantation — owing to bearing wear, valve malfunction, or infection. In the 133 patients who underwent implantation with a continuous-flow left ventricular assist device, 12 required 13 pump replacements with a continuous-flow device owing to breakage of the percutaneous lead (in 10 of the 13 replacements), pump thrombosis (in 2), or outflow elbow disconnection (in 1). One additional patient required device explantation because of a broken lead.

ACTUARIAL SURVIVAL

On the basis of the as-treated analysis, the Kaplan–Meier estimate of actuarial survival was significantly better for patients who had a continuous-flow left ventricular assist device as compared with those with a pulsatile-flow left ventricular assist device (relative risk, 0.54; 95% CI, 0.34 to 0.86; P=0.008) (Fig. 2). Estimates of the 1- and 2-year survival rates were 68% (95% CI, 60 to 76) and 58% (95% CI, 49 to 67), respectively, with the continuous-flow device and 55% (95% CI, 42 to 69)

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and 24% (95% CI, 1 to 46%) with the pulsatile-flow device. Eighteen of the pulsatile-flow left ventricular assist devices were replaced with a continuous-flow device during the follow-up period, leaving only two patients with a pulsatile-flow device (which had been replaced) at 2 years.

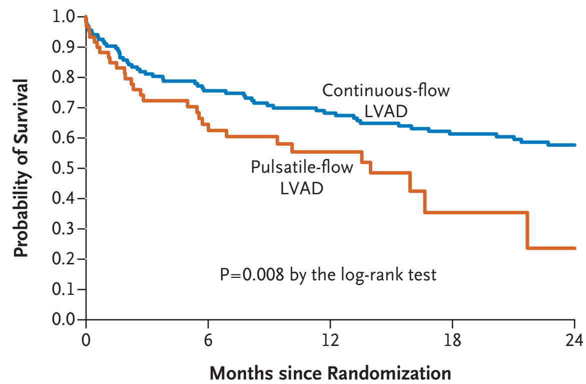
FUNCTIONAL STATUS AND QUALITY OF LIFE

Early and sustained improvements in functional capacity were seen in both groups. A total of 80% of patients with a continuous-flow left ventricular assist device had NYHA functional class I or II symptoms at 24 months, with a doubling of the mean distance on the 6-minute walk test (vs. the distance at baseline) (Table 3). Similar trends were seen with quality-of-life metrics. As compared with the baseline scores, scores on the Minnesota Living with Heart Failure questionnaire and the Kansas City Cardiomyopathy questionnaires improved by over 30 points in both groups at each time point (except the 24-month point in the single patient tested who had a pulsatile-flow device) (P<0.001).

ADVERSE EVENTS

The adverse-event data are shown in Figure 3 (with details in the Supplementary Appendix). As compared with patients with a pulsatile-flow left ventricular device, there were significant reductions in the rates of major adverse events among patients with a continuous-flow left ventricular assist device — including device-related infection (relating to the percutaneous lead, pump, or pump pocket), non–device-related infection, right heart failure, respiratory failure, renal failure, and cardiac arrhythmia. The incidence of stroke did not differ significantly between the continuous-flow group (which had 0.13 events per patient-year [stroke in 17% of patients]) and the pulsatile-flow group (which had 0.22 events per patient-year [stroke in 14% of patients]). There was a 38% relative reduction in the rate of rehospitalization among patients with a continuous-flow left ventricular assist device as compared with those with a pulsatile-flow device.

The leading causes of death among the patients with a continuous-flow left ventricular assist device were hemorrhagic stroke (in 9% who underwent device implantation), right heart failure (in 5%), sepsis (in 4%), external power interruption (in 4%), respiratory failure (in 3%), cardiac arrest (in 3%), and bleeding (in 3%). Among the patients with a pulsatile-flow left ventricular assist device, the leading causes of death were hemorrhagic stroke (in 10% who underwent device implantation), right heart failure (in 8%), multisystem organ failure (in 7%), and ischemic stroke (in 5%).



No. at Risk	0	6	12	18	24
Continuous-flow LVAD	133	95	82	69	62
Pulsatile-flow LVAD	59	32	19	5	2

Figure 2. Kaplan–Meier Estimates of Survival from the As-Treated Analysis, According to Treatment Group.

The data shown are for the 192 patients who received a left ventricular assist device (LVAD). Of the 59 patients who had a pulsatile-flow LVAD, 20 had the device replaced during the study period, with 18 (31%) receiving a continuous-flow LVAD instead of another pulsatile-flow LVAD. By 2 years, only 2 patients had a pulsatile-flow LVAD, both of whom had replacement devices.

DISCUSSION

Our study shows that implantation of a continuous-flow left ventricular assist device, as compared with a pulsatile-flow device, significantly improved the probability of survival free of stroke and reoperation for device repair or replacement at 2 years in patients with advanced heart failure in whom current therapy had failed and who were ineligible for transplantation. In addition, the actuarial survival over a 2-year period of support by a left ventricular assist device was significantly better with the continuous-flow device than with the pulsatile-flow device in a population of patients whose 2-year survival rate while receiving medical therapy has been shown to be approximately 10%.[12,13] The continuous-flow left ventricular assist device was also associated with significant reductions in the frequency of adverse events and the rate of repeat hospitalization, as well as

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Table 3. Functional Status and Quality-of-Life Secondary End Points, Based on the As-Treated Analysis, According to Time Point.*

End Point	Continuous-Flow LVAD					Pulsatile-Flow LVAD					P Value between Treatments at 12 mo
	Baseline	3 Mo	12 Mo	24 Mo	P Value for Treatment over Time†	Baseline	3 Mo	12 Mo	24 Mo	P Value for Treatment over Time†	
NYHA class											
No. of patients tested	126	91	72	50		55	38	18	1		
Class I — no. (%)	0	30 (33)	30 (42)	21 (42)		0	10 (26)	6 (33)	1 (100)		
Class II — no. (%)	0	38 (42)	25 (35)	19 (38)		0	16 (42)	5 (28)	0		
Class IIIA — no. (%)	4 (3)	16 (18)	13 (18)	6 (12)		1 (2)	10 (26)	4 (22)	0		
Class IIIB — no. (%)	27 (21)	5 (5)	4 (6)	1 (2)		11 (20)	1 (3)	2 (11)	0		
Class IV — no. (%)	95 (75)	2 (2)	0	3 (6)		43 (78)	1 (3)	1 (6)	0		
Patients with class I or II — no. (%)	0	68 (75)	55 (76)	40 (80)	<0.001	0	26 (68)	11 (61)	1 (100)	<0.001	0.22
6-Minute walk test											
No. of patients tested	50	77	61	36		19	29	12	1		
Distance walked — m	182±140	319±191	318±164	372±191	<0.001	172±108	291±134	306±145	277	<0.001	0.62
Minnesota Living with Heart Failure questionnaire											
No. of patients tested	116	89	76	44		49	36	19	1		
Score	75.4±17.7	37.4±22.2	34.1±22.4	29.6±22.4	<0.001	76.1±18.0	42.1±23.3	44.4±23.2	61.0	<0.001	0.03
Kansas City Cardiomyopathy questionnaire											
No. of patients tested	115	89	76	47		47	36	18	1		
Overall summary score	27.4±16.3	63.4±18.5	65.9±20.0	69.9±18.7	<0.001	26.5±17.4	56.7±21.1	59.1±20.3	33.3	<0.001	0.06
Clinical summary score	35.1±18.5	67.2±17.4	68.6±21.8	72.9±19.3	<0.001	31.6±18.4	64.0±19.8	60.8±20.2	63.5	<0.001	0.12

* Plus–minus values are means ±SD. Scores on the 21-question Minnesota Living with Heart Failure questionnaire range from 0 to 105, with higher scores indicating a worse quality of life. Scores on the Kansas City Cardiomyopathy questionnaire range from 0 to 100, with higher scores indicating a better quality of life. The number of patients tested at each time point varied as a result of ability to complete the test and unavailability owing to death or transplantation. LVAD denotes left ventricular assist device, and NYHA New York Heart Association.

† P values for the effect of the treatment over time were calculated with the use of linear mixed-effects modeling.

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Subgroup	Continuous-Flow LVAD (N=133) (211 patient-yr) no. (%)	Continuous-Flow LVAD no. of Events/Patient-Yr	Pulsatile-Flow LVAD (N=59) (41 patient-yr) no. (%)	Pulsatile-Flow LVAD no. of Events/Patient-Yr	P Value for Interaction
Pump replacement	12 (9)	0.06	20 (34)	0.51	<0.001
Stroke	24 (18)	0.13	8 (14)	0.22	0.21
Ischemic	11 (8)	0.06	4 (7)	0.10	0.38
Hemorrhagic	15 (11)	0.07	5 (8)	0.12	0.33
LVAD-related infection	47 (35)	0.48	21 (36)	0.90	0.01
Local non-LVAD infection	65 (49)	0.76	27 (46)	1.33	0.02
Sepsis	48 (36)	0.39	26 (44)	1.11	<0.001
Bleeding					
Bleeding requiring PRBC	108 (81)	1.66	45 (76)	2.45	0.06
Bleeding requiring surgery	40 (30)	0.23	9 (15)	0.29	0.57
Other neurologic event	29 (22)	0.17	10 (17)	0.29	0.14
Right heart failure					
Managed with extended use of inotropes	27 (20)	0.14	16 (27)	0.46	<0.001
Managed with RVAD	5 (4)	0.02	3 (5)	0.07	0.12
Cardiac arrhythmia	75 (56)	0.69	35 (59)	1.31	0.006
Respiratory failure	50 (38)	0.31	24 (41)	0.80	<0.001
Renal failure	21 (16)	0.10	14 (24)	0.34	<0.001
Hepatic dysfunction	3 (2)	0.01	0	0.00	
LVAD thrombosis	5 (4)	0.02	0	0.00	
Rehospitalization	107 (94)	2.64	42 (96)	4.25	0.02

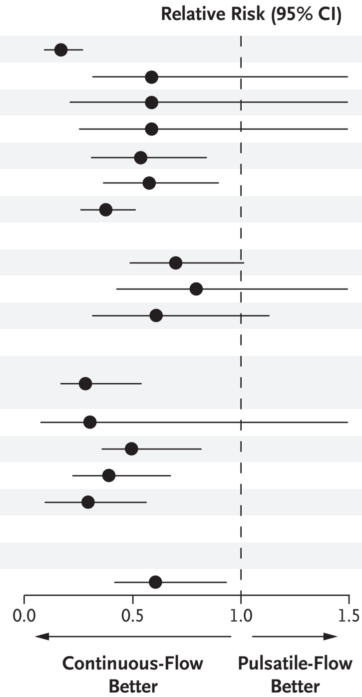

Figure 3. Adverse Events and Associated Relative Risks from the As-Treated Analysis, According to Treatment Group.
The "other neurologic event" subcategory included transient ischemic attack and neurologic events other than stroke. For the "rehospitalization" subcategory, the rates were calculated on the basis of patient-years after initial hospital discharge. LVAD denotes left ventricular assist device, PRBC packed red cells, and RVAD right ventricular assist device.

with an improved quality of life and functional capacity. The survival rate at 2 years among our patients with a pulsatile-flow left ventricular assist device was similar to that among patients with a left ventricular assist device in the REMATCH trial,[12] whereas the survival rate among our patients with a continuous-flow device was more than twice the rate among the REMATCH patients.

Device durability is an important limitation to use of the currently approved pulsatile-flow left ventricular assist device as long-term therapy, because valve or bearing failures occurred routinely by 18 months. The need for pump replacement in the continuous-flow left ventricular assist device occurred at a rate of 6 events per 100 patient-years, almost one eighth the incidence seen with the pulsatile-flow device, and was mainly required because of damage to the percutaneous lead. There were no primary-pump or bearing failures in patients with a continuous-flow left ventricular assist device, with 62 patients having functioning devices for at least 2 years (and 1 patient with ongoing device support at 4 years). Redesign of the percutaneous lead and development of modular components may further reduce the infrequent need for replacement of the continuous-flow device.

Concerns persist that left ventricular assist devices may predispose patients to an undue burden of thromboembolic and infectious events. The rate of ischemic stroke among patients with a continuous-flow left ventricular assist device (6 events per 100 patient-years) is similar to that among patients with advanced heart failure who do not have device support and have other cardiovascular conditions such as atrial fibrillation.[18,19] In our study, the rate of bleeding events associated with either type of left ventricular assist device were almost 10 times the rate of thromboembolic events. This finding was also noted in the HeartMate II bridge to transplant trial[20] and has led many centers to reduce the targeted international normalized ratio to 1.5 to 2.5 for the continuous-flow left ventricular assist device. The smaller pump and

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percutaneous lead in the continuous-flow left ventricular assist device also requires less surgical dissection for implantation, which reduces the potential for infection, as compared with the pulsatile-flow device. Patients with a continuous-flow left ventricular assist device had a rate of device-related infection nearly 50% of that among patients with a pulsatile-flow device, which contributed to their reduced need for rehospitalization.

A critical therapeutic goal in treating patients with advanced heart failure is to enhance their quality of life and functional capabilities. There are few data from medical-therapy trials involving this population of patients that highlight exercise or quality-of-life benefits.[1,8,9] A retrospective analysis of patients with NYHA class IV symptoms who were treated with cardiac-resynchronization therapy showed an increase of 45 m in the 6-minute-walk distance, a 25-point improvement in the Minnesota Living with Heart Failure score, and improvement in symptoms corresponding to a reduction by at least one NYHA functional class in 78% of the patients.[21] The exercise and quality-of-life benefits with a continuous-flow left ventricular assist device in our trial consist of a doubling of the 6-minute-walk distance, an average improvement of 35 points in the quality-of-life scores, and an increase in the number of patients whose symptoms showed improvement, to NYHA functional class I or II. Patients in both groups in our study had significant early and sustained improvements in the 6-minute-walk distance and the functional class, suggesting that the exercise benefits are related to the reduction of cardiac filling pressures and improvement in cardiac output rather than being related to the characteristics of either pulsatile or continuous flow. The patient-reported symptom burden and heart-failure–related quality-of-life scores reflected similar improvements in the two groups over the duration of the study, with a trend toward greater improvement with the continuous-flow left ventricular assist device as compared with the pulsatile-flow device.

This study was a randomized, controlled clinical trial, but it was not possible to ensure that the patients and investigators were unaware of the treatment assignments. Thus, there is potential for bias, particularly regarding patient-reported outcomes such as functional abilities and the quality of life. Several sites had limited experience with the continuous-flow device before the study began, and several enrolled a small number of patients. Previous studies have shown a link between the volume of implantations with a left ventricular assist device and outcomes.[22] In addition, most participating centers had more experience with the pulsatile-flow left ventricular assist device used in this trial than with the particular continuous-flow device, potentially biasing the analysis against the study device. Finally, the trial was performed in a select patient population, and applicability to the broader population of patients with heart failure, including those with less hemodynamic and functional compromise than our patients, would be speculative.

In conclusion, this study shows improvements in the rate of survival, quality of life, functional capacity of patients, and device durability with the continuous-flow left ventricular assist device (HeartMate II) as compared with the pulsatile-flow left ventricular assist device (HeartMate XVE). Reductions in the frequencies of adverse events related to device characteristics and strategies of care for patients favorably affected the rate of rehospitalization. Our results support the use of continuous-flow, permanent left ventricular assist device therapy in selected patients as a means to provide long-term hemodynamic support that is linked to improvements in longevity and the quality of life.

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APPENDIX

In addition to the authors, the following surgeons, cardiologists, and study coordinators participated in this study: *Advocate Christ Hospital, Oak Lawn, IL* — M. Sobieski, C. Gallagher, P. Pappas, M. Silver; *Duke University Medical Center, Durham, NC* — A. Lodge, L. Blue; *Johns Hopkins Hospital, Baltimore* — A. Shah, D. Yuh, S. Ullrich, D. Dordunoo, D. Rivard; *Texas Heart Institute, Houston* — B. Kar, B. Radovancevic, I. Gregoric, A. Civitello, E. Massin, C. Gemmato, M. Jafar, R. Bogaev, F. Smart; *Ohio State University, Columbus* — J. Sirak, S. Sudhaker, T. Yanssens; *Intermountain Medical Center (LDS Hospital), Salt Lake City* — B. Reid, S. Horton, D. Renland, J. Revenaugh, M. Eidson; *Clarian Methodist Hospital, Indianapolis* — M. Turrentine, S. Becka; *Allegheny General Hospital, Pittsburgh* — D. Dean, S. Murali, G. Magovern, S. Bailey, G. Sokos, L. Kernickey; *Barnes–Jewish Hospital, Washington University, St. Louis* — N. Moazami, G. Ewald, K. Shelton, D. Anderson,

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