ORIGINAL ARTICLE

A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure

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ABSTRACT

BACKGROUND

Continuous-flow left ventricular assist systems increase the rate of survival among patients with advanced heart failure but are associated with the development of pump thrombosis. We investigated the effects of a new magnetically levitated centrifugal continuous-flow pump that was engineered to avert thrombosis.

METHODS

We randomly assigned patients with advanced heart failure to receive either the new centrifugal continuous-flow pump or a commercially available axial continuous-flow pump. Patients could be enrolled irrespective of the intended goal of pump support (bridge to transplantation or destination therapy). The primary end point was a composite of survival free of disabling stroke (with disabling stroke indicated by a modified Rankin score >3; scores range from 0 to 6, with higher scores indicating more severe disability) or survival free of reoperation to replace or remove the device at 6 months after implantation. The trial was powered for noninferiority testing of the primary end point (noninferiority margin, –10 percentage points).

RESULTS

Of 294 patients, 152 were assigned to the centrifugal-flow pump group and 142 to the axial-flow pump group. In the intention-to-treat population, the primary end point occurred in 131 patients (86.2%) in the centrifugal-flow pump group and in 109 (76.8%) in the axial-flow pump group (absolute difference, 9.4 percentage points; 95% lower confidence boundary, –2.1 [P<0.001 for noninferiority]; hazard ratio, 0.55; 95% confidence interval [CI], 0.32 to 0.95 [two-tailed P=0.04 for superiority]). There were no significant between-group differences in the rates of death or disabling stroke, but reoperation for pump malfunction was less frequent in the centrifugal-flow pump group than in the axial-flow pump group (1 [0.7%] vs. 11 [7.7%]; hazard ratio, 0.08; 95% CI, 0.01 to 0.60; P=0.002). Suspected or confirmed pump thrombosis occurred in no patients in the centrifugal-flow pump group and in 14 patients (10.1%) in the axial-flow pump group.

CONCLUSIONS

Among patients with advanced heart failure, implantation of a fully magnetically levitated centrifugal-flow pump was associated with better outcomes at 6 months than was implantation of an axial-flow pump, primarily because of the lower rate of reoperation for pump malfunction. (Funded by St. Jude Medical; MOMENTUM 3 ClinicalTrials.gov number, NCT02224755.)

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*A complete list of the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM 3) Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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A scarcity of effective therapeutic options for advanced heart failure has led to the development of durable mechanical circulatory support devices. Left ventricular assist devices, more accurately known as left ventricular assist systems, increase the rate of survival and improve quality of life among patients with advanced heart failure. However, these clinical benefits are balanced by an increased risk of infection, bleeding, neurologic events, and pump malfunction that is due principally to pump thrombosis.[1,2]

As adoption of circulatory pumps has expanded, concerns about pump thrombosis have heightened. In 2013, two reports suggested that there has been an increase in the risk of pump thrombosis, beginning in 2011, associated with a currently approved axial continuous-flow pump, HeartMate II.[3,4] Pump thrombosis has also been associated with an approved centrifugal continuous-flow pump, HeartWare.[5,6] The need for surgical pump exchange due to pump thrombosis results in substantial complications and increased cost of care.[7] These concerns have lowered enthusiasm for expansion of this therapy to patients who are less severely ill and have even led to the premature discontinuation of a clinical trial.[7,8]

A new fully magnetically levitated centrifugal continuous-flow circulatory pump, HeartMate 3, has been engineered to reduce shear stress on blood elements and avert pump thrombosis.[9,10] This pump has wide blood-flow passages and no mechanical bearings, is frictionless, and is programmed to facilitate rapid changes in rotor speed to create an intrinsic artificial pulse. This fixed pulse, which is asynchronous with the native heartbeat, reduces stasis in the pump.

We conducted a trial to compare clinical outcomes with the centrifugal-flow pump HeartMate 3 with outcomes with the axial-flow pump HeartMate II in patients with advanced heart failure that is refractory to standard medical therapy. In this report, we present the results of the first prespecified analysis of the trial.

Methods

Trial Design and Oversight

The Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM 3) was a nonblinded randomized trial that compared the centrifugal-flow pump HeartMate 3 with the axial-flow pump HeartMate II in patients with advanced heart failure.[10] The trial was sponsored by St. Jude Medical, which provided the trial devices. The trial protocol, which is available with the full text of this article at NEJM.org, was designed by the sponsor in consultation with clinical advisors and the study oversight committee (a list of members is provided in the Supplementary Appendix, available at NEJM.org).

The trial was conducted at 69 centers in the United States at which there were surgeons who had experience in the implantation of left ventricular assist systems; the protocol was approved by the institutional review board at each participating center. Data were collected by trial coordinators at the participating centers, verified by principal investigators at each site, and analyzed and audited by the sponsor. An independent data and safety monitoring board (see the Supplementary Appendix) monitored the trial and reviewed adherence to the protocol, device malfunction, and outcomes. All the authors had access to the data and vouch for the completeness and accuracy of the data and analyses and for the fidelity of the study to the trial protocol. An independent statistician confirmed all analyses. The manuscript was written by the first author, and all the authors had input into its drafting and content; the trial publication committee (see the Supplementary Appendix) made the decision to submit the article for publication.

Patients

Patients with advanced heart failure that was refractory to standard medical therapy were enrolled. Patients were eligible irrespective of whether the intended goal of pump support was a bridge to transplantation or destination therapy (i.e., permanent therapy for a patient who is not a candidate for heart transplantation). Main exclusion criteria were planned biventricular support, irreversible end-organ dysfunction, and active infection. A detailed list of inclusion and exclusion criteria is provided in the Supplementary Appendix. All patients or their authorized representatives provided written informed consent.

Randomization and Data Collection

Patients were randomly assigned, in a 1:1 ratio, to receive the centrifugal-flow pump or the axial-flow pump. Randomization was performed with the use of permuted blocks and with stratification according to trial center and was implemented

through an electronic data-capture system (eClinicalOS, Merge Healthcare). The investigators and patients were aware of the treatment assignments. Data were collected at baseline, 1 day after implantation, 1 week after implantation, at discharge, and 1, 3, and 6 months after implantation. Outcome events and adverse events were recorded throughout the trial.[10]

LEFT VENTRICULAR ASSIST SYSTEMS

The two circulatory pumps used in the trial were the fully magnetically levitated centrifugal continuous-flow pump HeartMate 3 and the mechanical-bearing axial continuous-flow pump HeartMate II (both manufactured by St. Jude Medical) (Fig. 1). Details about the circulatory pumps and their differences and similarities are provided in the Pump Characteristics section, Figure S1, and Table S1 in the Supplementary Appendix. All investigators underwent surgical training before performing their first implantation of a centrifugal-flow pump. Recommended antithrombotic management in both groups included aspirin (at a dose of 81 to 100 mg daily for all patients) and warfarin (with dose adjustment to achieve a target international normalized ratio [INR] of 2.0 to 3.0).

OUTCOMES

The primary end point was a composite of survival free of disabling stroke (with disabling stroke indicated by a modified Rankin score >3; scores range from 0 to 6, with higher scores indicating more severe disability) or survival free of reoperation to replace or remove the device (for reasons other than recovery) at 6 months after implantation. Patients who underwent urgent heart transplantation for pump malfunction were considered to have had treatment failure with respect to the primary end point, whereas patients who underwent transplantation for other reasons were considered to have had treatment success. Secondary end points included the frequency of adverse events; actuarial survival; functional status, as assessed with the New York Heart Association (NYHA) classification and with the 6-minute walk test performed by a trained technician; and quality of life, as assessed with the European Quality of Life–5 Dimensions (EQ-5D) questionnaire (EQ-5D-5L), the EQ-5D visual-analogue scale (EQ-5D VAS), and the Kansas City Cardiomyopathy Questionnaire (KCCQ). An independent clinical events committee, whose members were unaware of the treatment assignments, adjudicated the causes of death and all adverse events; definitions of events and a list of the committee members are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The primary objective of the trial was to show the noninferiority of the centrifugal-flow pump to the axial-flow pump with respect to the primary end-point measure at 6 months after implantation. We estimated that 138 patients in each group would be required for the study to have 80% power to show the noninferiority of the centrifugal-flow pump to the axial-flow pump. We determined that noninferiority would be demonstrated if the 95% lower confidence boundary for the difference between treatment groups (centrifugal-flow pump group minus axial-flow pump group) in the occurrence of the primary end point would be greater than –10 percentage points, at a one-sided alpha level of 0.025 or a two-tailed P value of less than 0.05. To account for transplantation or explantation for recovery before 6 months, 9 additional patients were included in each group. A total of 294 patients was required for analysis.

Enrollment in the trial continued after the proposed sample of 294 patients was reached, to provide sufficient power for two prespecified subsequent analyses. These include the occurrence of the primary end-point measure at 24 months after implantation (366 patients) and the occurrence of the prespecified secondary end-point measure of pump replacement at 24 months after implantation (1028 patients). These additional populations and analyses are not discussed in this report.

The primary end-point analysis was based on data from the intention-to-treat population, which included all patients who underwent randomization. For patients who had more than one event during follow-up that resulted in failure to reach the primary end point, the event that occurred first is the one included in the analysis. Patients who underwent randomization but not implantation were considered to have treatment failure at the time of randomization. If noninferiority was proved, the primary end point was then analyzed for superiority with the use of a z test of proportions, performed according to the normal approxi-

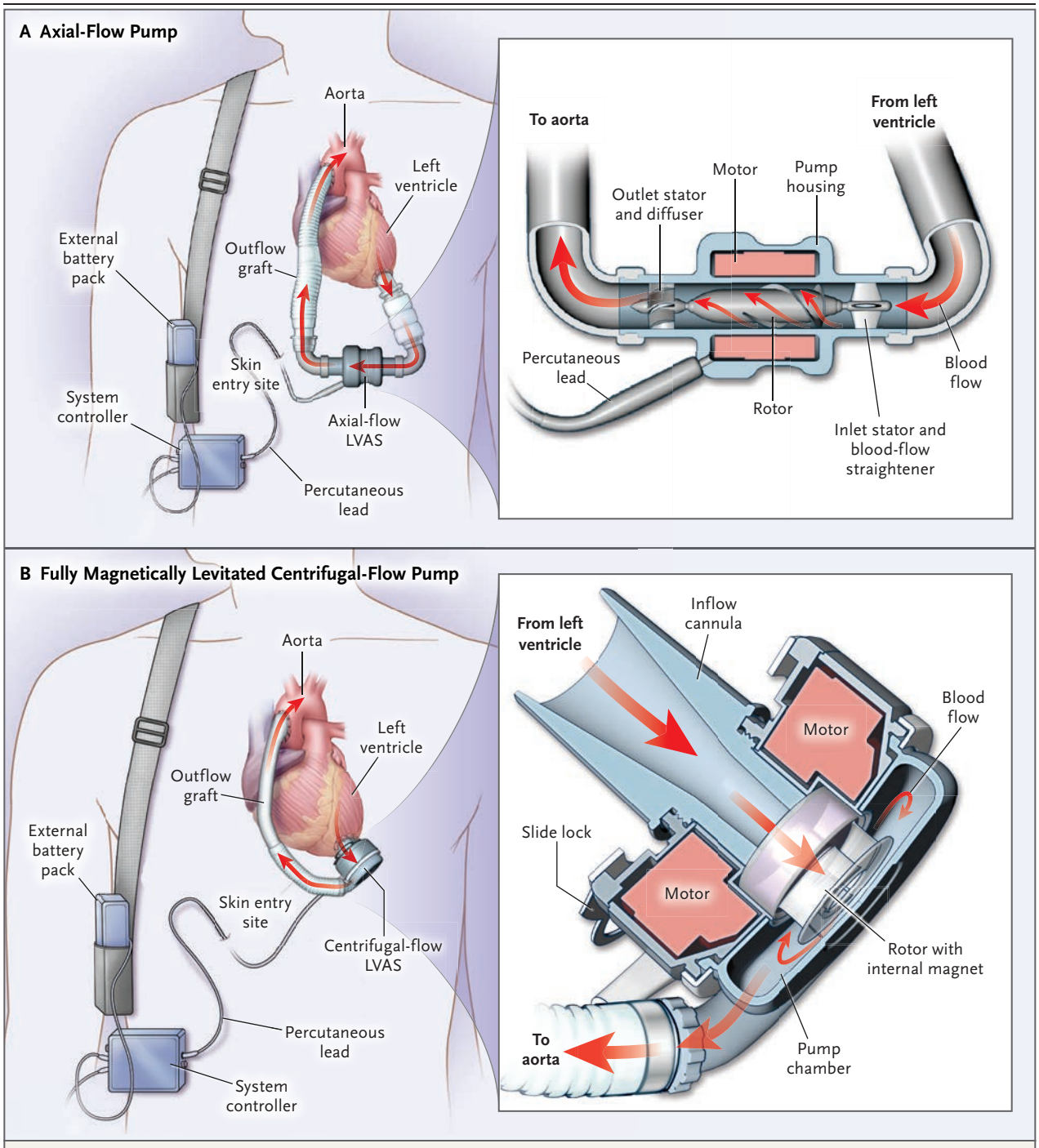

Figure 1. Diagrams of the Axial-Flow Pump and the Centrifugal-Flow Pump.

Panel A shows a diagram of the axial-flow pump; blood enters at one end of the rotor and is driven along the axis of the rotor to the outflow of the pump. Panel B shows a diagram of the fully magnetically levitated centrifugal-flow pump; blood enters at the central axis of the rotor and is driven outward centrifugally to the outflow of the pump. Both pumps are considered to be continuous-flow pumps (rather than pulsatile-flow pumps) because blood flow is continuous and not interrupted, although the centrifugal-flow pump incorporates rapid changes in rotor speed to create an intrinsic artificial pulse. Panel A is adapted from Slaughter et al.[1] LVAS denotes left ventricular assist system.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Centrifugal-Flow Pump Group (N=152)	Axial-Flow Pump Group (N=142)
Age — yr		
Mean	60.3±12.3	58.9±12.0
Median (range)	64.0 (19–81)	61.0 (24–78)
Male sex — no. (%)	121 (79.6)	114 (80.3)
Race or ethnic group — no. (%)†		
White	104 (68.4)	107 (75.4)
Black	37 (24.3)	24 (16.9)
Asian	2 (1.3)	1 (0.7)
Native Hawaiian or Pacific Islander	0	2 (1.4)
Other	8 (5.3)	8 (5.6)
Not provided	1 (0.7)	0
Body-surface area — m^2	2.1±0.3	2.1±0.3
Ischemic cause of heart failure — no. (%)	68 (44.7)	72 (50.7)
History of stroke — no. (%)	12 (7.9)	14 (9.9)
Left ventricular ejection fraction — %	17.1±5.0	17.3±4.9
Arterial blood pressure — mm Hg		
Systolic	110.4±15.7	105.8±11.7
Diastolic	66.9±10.4	65.6±10.3
Mean arterial pressure — mm Hg	81.4±10.4	79.0±9.4
Pulmonary-capillary wedge pressure — mm Hg	23.4±8.5	22.0±9.4
Cardiac index — liters/min/m^2 of body-surface area	1.9±0.5	2.0±0.7
Pulmonary vascular resistance — Wood units	3.3±1.7	3.0±1.6
Right atrial pressure — mm Hg	10.3±5.8	10.6±6.8
Serum sodium — mmol/liter	135.6±3.9	134.9±4.2
Serum creatinine — mg/ml	1.4±0.4	1.4±0.4
Estimated glomerular filtration rate — ml/min/1.73 m^2	60.5±24.1	58.5±21.8
Concomitant medication or intervention — no. (%)		
Intravenous inotropic agents	132 (86.8)	121 (85.2)
Diuretic	134 (88.2)	136 (95.8)
Angiotensin-converting–enzyme inhibitor	37 (24.3)	38 (26.8)
Angiotensin II–receptor antagonist	10 (6.6)	18 (12.7)
Beta-blocker	91 (59.9)	79 (55.6)
Cardiac resynchronization therapy with or without defibrillator	59 (38.8)	51 (35.9)
Implantable cardioverter–defibrillator with or without cardiac resynchronization therapy	101 (66.4)	100 (70.4)
Intraaortic balloon pump	18 (11.8)	21 (14.8)
Intended goal of pump support — no. (%)		
Bridge to transplantation	41 (27.0)	37 (26.1)
Bridge to candidacy for transplantation	27 (17.8)	27 (19.0)
Destination therapy	84 (55.3)	78 (54.9)

Table 1. (Continued.)

Characteristic	Centrifugal-Flow Pump Group (N=152)	Axial-Flow Pump Group (N=142)
INTERMACS profile — no. (%)‡		
1	1 (0.7)	4 (2.8)
2	50 (32.9)	44 (31.0)
3	76 (50.0)	69 (48.6)
4	22 (14.5)	23 (16.2)
5	2 (1.3)	2 (1.4)
6 or 7	0	0
Not provided	1 (0.7)	0

* Plus–minus values are means ±SD. There were no significant differences between the groups except for systolic blood pressure (P=0.01), mean arterial pressure (P=0.04), and diuretic use (P=0.02). Additional data on baseline characteristics are provided in the Supplementary Appendix.
† Race or ethnic group was self-reported. One patient did not wish to provide data.
‡ Interagency Registry for Mechanical Circulatory Support (INTERMACS) profiles range from 1 to 7; a profile of 1 represents the most severe illness and a profile of 7 the least severe illness. For more details, see Table S2 in the Supplementary Appendix. One patient died before the INTERMACS assessment was performed.

mation of the binomial distribution. Cox proportional-hazards analyses, with data stratification according to treatment, were used to calculate hazard ratios and 95% confidence intervals for the primary end point and its individual component events.

All secondary end-point analyses were based on data from the per-protocol population, which included only patients who underwent implantation of the assigned device. Longitudinal changes in functional status and quality of life were analyzed by means of linear mixed-effects modeling. Adverse events were compared between the two treatment groups with the use of Fisher's exact test. Analysis of actuarial survival was performed by means of the Kaplan–Meier method, and the results were compared between groups with the use of log-rank analysis. All reported P values are two-tailed, and P values of less than 0.05 were considered to indicate statistical significance. Statistical analysis was performed with the use of SAS software, version 9.3 (SAS Institute).

RESULTS

PATIENTS AND DEVICE IMPLANTATION

From September 2014 through October 2015, a total of 294 patients underwent randomization; 152 patients were assigned to the centrifugal-flow pump group and 142 to the axial-flow pump group. The baseline characteristics of the patients in the two treatment groups are shown in Table 1 and in Table S2 in the Supplementary Appendix.

One patient in the centrifugal-flow pump group and 4 in the axial-flow pump group did not undergo implantation in accordance with the protocol (Fig. S2 in the Supplementary Appendix). The remaining patients — 151 who underwent implantation of the centrifugal-flow pump and 138 who underwent implantation of the axial-flow pump — were included in the per-protocol population; 69 surgeons at 47 sites performed 289 implantations.

CLINICAL COURSE

A total of 140 patients (92.7%) in the centrifugal-flow pump group and 126 (91.3%) in the axial-flow pump group were discharged from the hospital with the device in place. Among patients who were discharged, the median length of hospital stay was 19.5 days in the centrifugal-flow pump group and 17.5 days in the axial-flow pump group (P=0.23 by the Wilcoxon rank-sum test). At 6 months, the percentage of time spent out of the hospital after device implantation did not differ significantly between the two groups (79% in the centrifugal-flow pump group vs. 81% in the axial-flow pump group).

Table 2. Noninferiority and Superiority Analyses in the Intention-to-Treat Population.*

Variable	Centrifugal-Flow Pump Group (N=152)		Axial-Flow Pump Group (N=142)		Absolute Difference	Hazard Ratio (95% CI)	P Value†
	no. of patients	*% (95% CI)*	*no. of patients*	*% (95% CI)*	*percentage points (95% LCB)*		
Noninferiority analysis							
Primary end point	131	86.2 (79.7–91.2)	109	76.8 (68.9–83.4)	9.4 (−2.1)		<0.001
Superiority analyses							
Primary end point	131	86.2 (79.7–91.2)	109	76.8 (68.9–83.4)		0.55 (0.32–0.95)	0.04
First event that resulted in failure to reach the primary end point							
Did not receive the assigned implant	1	0.7 (0–3.6)	4	2.8 (0.8–7.1)		0.23 (0.03–2.09)	0.15
Had disabling stroke	6	3.9 (1.5–8.4)	4	2.8 (0.8–7.1)		1.31 (0.37–4.64)	0.59
Underwent reoperation to replace or remove pump‡	1	0.7 (0–3.6)	11	7.7 (3.9–13.4)		0.08 (0.01–0.60)	0.002
Died within 6 months after implantation	13	8.6 (4.6–14.2)	14	9.9 (5.5–16.0)		0.82 (0.38–1.73)	0.70

* The primary end point was a composite of survival free of disabling stroke (with disabling stroke indicated by a modified Rankin score >3; scores range from 0 to 6, with higher scores indicating more severe disability) or survival free of reoperation to replace or remove the device at 6 months after implantation. The intention-to-treat population included all patients who underwent randomization. Hazard ratios and 95% confidence intervals (CIs) were calculated with the use of Cox proportional-hazards analyses. LCB denotes lower confidence boundary.
† P values for the superiority analyses are two-tailed.
‡ Data for the axial-flow pump group included two cases of urgent heart transplantation due to device malfunction.

There were no significant between-group differences in hepatic and renal function. Rates of aspirin use and anticoagulation use did not differ significantly between the two groups; a similar percentage of patients in each group had an INR within the therapeutic range[2,3] at all time points. Lactate dehydrogenase levels returned to baseline 1 month after implantation in the centrifugal-flow pump group but remained elevated at all time points through 6 months in the axial-flow pump group (P<0.001) (Tables S3, S4, and S5 in the Supplementary Appendix).

PRIMARY END POINT

All patients were followed for 6 months or until death, and no data on outcomes were missing. The primary end point of event-free survival at 6 months was achieved in a higher percentage of patients in the centrifugal-flow pump group than in the axial-flow pump group (86.2% vs. 76.8%). These results established both the noninferiority of the centrifugal-flow pump to the axial-flow pump (absolute difference, 9.4 percentage points; 95% lower confidence boundary, −2.1; P<0.001 for noninferiority) and its superiority (hazard ratio, 0.55; 95% confidence interval [CI], 0.32 to 0.95; two-tailed P=0.04 for superiority) (Table 2).

The rate of reoperation for pump malfunction was significantly lower in the centrifugal-flow pump group than in the axial-flow pump group, and this difference is the primary reason for the difference between the groups in the failure to reach the primary end point. Only 1 patient (0.7%; 95% CI, 0 to 3.6) in the centrifugal-flow pump group underwent pump replacement (because of a drive-line communication fault resulting from moisture ingress that caused electrical failure), whereas 11 patients (7.7%, 95% CI, 3.9 to 13.4) in the axial-flow pump group underwent either a device exchange (9 patients) or device removal with urgent transplantation (2 patients) (P=0.002). There were no significant differences between the two groups in the rates of death or disabling stroke. The Kaplan–Meier estimate of the rate of actuarial event-free survival (as defined for the primary end point) was significantly higher in the centrifugal-flow pump group (86%; 95% CI, 80 to 92) than in the axial-flow pump group (77%; 95% CI, 70 to 84; two-tailed P=0.03 by the log-rank test) (Fig. 2).

FUNCTIONAL STATUS AND QUALITY OF LIFE

Functional status, which was assessed with the NYHA classification and with performance on the 6-minute walk test, improved equally in the two groups. As compared with baseline scores, the scores on the EQ-5D-5L, EQ-5D VAS, and KCCQ improved in both groups at 3 months and at 6 months. No significant differences in improvement were observed between the treatment groups (Fig. S3 in the Supplementary Appendix). In post hoc sensitivity analyses for functional status and quality of life, patients with missing data were assigned the worst possible score for each test; there were again no significant differences between the treatment groups.

ADVERSE EVENTS AND SUBGROUP ANALYSIS

No patients in the centrifugal-flow pump group had suspected or confirmed pump thrombosis, but 14 patients (10.1%) in the axial-flow pump group had 18 such events (P<0.001). Individual narratives for each case of suspected or confirmed pump thrombosis and event tabulations are provided in the Pump Thrombosis Narratives section and Table S6, respectively, in the Supplementary Appendix. The incidence of other adverse events did not differ significantly between the groups (Table 3, and Fig. S4 and S5 and Table S7 in the Supplementary Appendix).

The most common causes of death among patients in either group were right heart failure, stroke, and sepsis (Table S8 in the Supplementary Appendix). There were 17 deaths in the centrifugal-flow pump group and 18 in the axial-flow pump group. Results of analyses of actuarial survival and survival with competing risks are shown in Figures S6 and S7 in the Supplementary Appendix.

Subgroup analyses showed no significant interaction with respect to the primary end point between treatment group and age, sex, race, intended goal of pump support (bridge to transplantation or destination therapy), or Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile. However, in both groups, an age of 70 years or older was associated with lower all-cause survival than an age of younger than 70 years (Impact of Age on Survival section and Fig. S8 in the Supplementary Appendix). An analysis of the surgeons' learning curves was performed with data from centers at which 3 or more patients underwent implantation of the centrifugal-flow pump; data for the first 2 patients implanted with this device were compared with data for all later recipients of the same device. No differences with respect to the primary end point, adverse events, or mortality were seen.

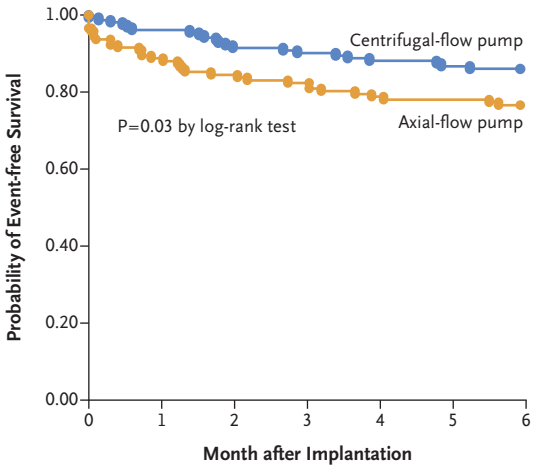

Figure 2. Kaplan–Meier Estimates of Event-free Survival in the Intention-to-Treat Population.

Event-free survival is survival free of disabling stroke (with disabling stroke indicated by a modified Rankin score >3; scores range from 0 to 6, with higher scores indicating more severe disability) or survival free of reoperation to replace or remove the device at 6 months after implantation. The intention-to-treat population included all patients who underwent randomization.

DISCUSSION

In the MOMENTUM 3 trial, we found that implantation of the fully magnetically levitated centrifugal continuous-flow pump HeartMate 3 was associated with a higher rate of survival free of disabling stroke or survival free of reoperation to replace or remove the device at 6 months after implantation than was implantation of the mechanical-bearing axial continuous-flow pump HeartMate II among patients with advanced heart failure, irrespective of their eligibility for transplantation. The incremental benefits associated with the centrifugal-flow pump observed in this 6-month analysis were due to the absence of suspected or confirmed pump thrombosis leading to surgical pump exchange or urgent transplantation.

Table 3. Major Adverse Events in the Per-Protocol Population.*

Event	Centrifugal-Flow Pump Group (N=151)		Axial-Flow Pump Group (N=138)		Relative Risk (95% CI)	P Value
	no. of patients with events (%)	*no. of events*	*no. of patients with events (%)*	*no. of events*		
Suspected or confirmed pump thrombosis	0	0	14 (10.1)	18	NA	<0.001
Stroke						
Any stroke	12 (7.9)	12	15 (10.9)	17	0.73 (0.35–1.51)	0.39
Hemorrhagic stroke	4 (2.6)	4	8 (5.8)	8	0.46 (0.14–1.48)	0.18
Ischemic stroke	8 (5.3)	8	9 (6.5)	9	0.81 (0.32–2.05)	0.66
Disabling stroke	9 (6.0)	9	5 (3.6)	5	1.65 (0.57–4.79)	0.36
Other neurologic event†	9 (6.0)	9	8 (5.8)	8	1.03 (0.41–2.59)	0.95
Bleeding						
Any bleeding	50 (33.1)	100	54 (39.1)	98	0.85 (0.62–1.15)	0.29
Bleeding requiring surgery	15 (9.9)	15	19 (13.8)	21	0.72 (0.38–1.36)	0.31
Gastrointestinal bleeding	24 (15.9)	47	21 (15.2)	36	1.04 (0.61–1.79)	0.87
Sepsis	14 (9.3)	19	9 (6.5)	10	1.42 (0.64–3.18)	0.39
LVAS drive-line infection	18 (11.9)	21	9 (6.5)	11	1.83 (0.85–3.93)	0.12
Local infection not associated with LVAS	46 (30.5)	57	36 (26.1)	58	1.17 (0.81–1.69)	0.41
Right heart failure						
Any right heart failure	45 (29.8)	49	34 (24.6)	36	1.21 (0.83–1.77)	0.33
Right heart failure managed with RVAS	4 (2.6)	4	8 (5.8)	8	0.46 (0.14–1.48)	0.18
Cardiac arrhythmia						
Any cardiac arrhythmia	47 (31.1)	61	52 (37.7)	68	0.83 (0.60–1.14)	0.24
Ventricular arrhythmia	27 (17.9)	33	27 (19.6)	37	0.91 (0.57–1.48)	0.71
Supraventricular arrhythmia	23 (15.2)	27	30 (21.7)	31	0.70 (0.43–1.15)	0.15
Respiratory failure	33 (21.9)	44	24 (17.4)	27	1.26 (0.78–2.02)	0.34
Renal dysfunction	17 (11.3)	18	12 (8.7)	12	1.29 (0.64–2.61)	0.47
Hepatic dysfunction	7 (4.6)	7	3 (2.2)	3	2.13 (0.56–8.08)	0.34
Hemolysis not associated with pump thrombosis	1 (0.7)	1	2 (1.4)	2	0.46 (0.04–4.98)	0.61

* The per-protocol population included patients who underwent implantation of the assigned device. LVAS denotes left ventricular assist system, NA not available, and RVAS right ventricular assist system.
† Other neurologic events included transient ischemic attack and neurologic events other than stroke.

Pump thrombosis, which is manifested by elevations in hemolytic biomarkers such as lactate dehydrogenase level or in sudden transient increases in pump power, is an important limitation to the use of currently available circulatory pumps.[3,11-13] As the clinical syndrome progresses, worsening heart failure caused by the inability of the pump to unload the left ventricle becomes apparent and ultimately necessitates reoperation or urgent transplantation to replace or remove the pump. In this trial, the absence of suspected or confirmed pump thrombosis with the centrifugal-flow pump is similar to the results with the same device in the nonrandomized Conformité Européene study.[14] A recent analysis has also shown that the centrifugal-flow device does not cause loss of high-molecular-weight multimers of von Willebrand factor to the same degree that the axial-flow pump does.[15]

There were no significant differences between the two pumps in the associated rates of other major complications, including right heart failure, any stroke or disabling stroke, major infection including drive-line infections, or bleeding episodes,

particularly gastrointestinal bleeding.[16,17] We noted a numerical, but not statistically significant, trend toward a higher rate of disabling strokes with the centrifugal-flow pump than with the axial-flow pump and a higher rate of right heart failure events managed with a right ventricular assist system with the axial-flow pump than with the centrifugal-flow pump. It is unclear whether pump thrombosis would remain infrequent if anticoagulation doses were reduced in an effort to decrease rates of bleeding.

This study included patients who had advanced heart failure, irrespective of their candidacy for transplantation. Clinical discrimination of patients with advanced heart failure who receive a ventricular assist system into either a bridge-to-transplantation strategy or a destination-therapy strategy can be arbitrary and can leave a large proportion of patients in the gray zone of bridge to candidacy for transplantation (for whom a decision about transplant candidacy is made after device implantation). Furthermore, 28% of patients who are listed with the initial intention of undergoing heart transplantation continue to receive support with a left ventricular assist system for longer than 2 years, and up to 44% of patients are moved off the transplantation list over time because of complications or clinical preference.[18] In this trial, of the patients who were listed with an intended goal of bridge to transplantation, only 9.8% underwent transplantation during the 6-month follow-up period. Therefore, we believe that the decision to implant a ventricular assist system should not reflect the intended goal of eventual transplantation but rather should reflect the clinical need for the circulatory pump.

This trial has some limitations. First, it was not possible for the patients and investigators to be unaware of the treatment assignments, and this may have affected the results of patient-reported assessments such as those for functional status and quality of life. Second, the surgeons at most, if not all, of the participating centers had long-term experience in the implantantion of axial-flow pumps, and thus the surgical and medical outcomes were potentially biased against the centrifugal-flow pump, since the new pump had not been used previously in the United States. Third, the decision to remove or replace a pump for suspected or confirmed pump thrombosis was informed by the lactate dehydrogenase level or evidence of pump dysfunction but was at the discretion of the local site investigators. Finally, the trial findings should not be extrapolated to a broader population with less severe heart failure.

In conclusion, in this trial, we compared the centrifugal-flow left ventricular assist system HeartMate 3 with the axial-flow left ventricular assist system HeartMate II in patients with advanced heart failure. We found evidence of incremental improvement in clinical outcomes with the centrifugal-flow pump that was attributable to a lower rate of reoperation for pump malfunction without an apparent between-group difference in the rate of other adverse events.

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