ORIGINAL ARTICLE

Two-Year Outcomes with a Magnetically Levitated Cardiac Pump in Heart Failure

M.R. Mehra, D.J. Goldstein, N. Uriel, J.C. Cleveland, Jr., M. Yuzefpolskaya, C. Salerno, M.N. Walsh, C.A. Milano, C.B. Patel, G.A. Ewald, A. Itoh, D. Dean, A. Krishnamoorthy, W.G. Cotts, A.J. Tatooles, U.P. Jorde, B.A. Bruckner, J.D. Estep, V. Jeevanandam, G. Sayer, D. Horstmanshof, J.W. Long, S. Gulati, E.R. Skipper, J.B. O'Connell, G. Heatley, P. Sood, and Y. Naka, for the MOMENTUM 3 Investigators*

ABSTRACT

BACKGROUND

In an early analysis of this trial, use of a magnetically levitated centrifugal continuous-flow circulatory pump was found to improve clinical outcomes, as compared with a mechanical-bearing axial continuous-flow pump, at 6 months in patients with advanced heart failure.

METHODS

In a randomized noninferiority and superiority trial, we compared the centrifugal-flow pump with the axial-flow pump in patients with advanced heart failure, irrespective of the intended goal of support (bridge to transplantation or destination therapy). The composite primary end point was survival at 2 years free of disabling stroke (with disabling stroke indicated by a modified Rankin score of >3; scores range from 0 to 6, with higher scores indicating more severe disability) or survival free of reoperation to replace or remove a malfunctioning device. The noninferiority margin for the risk difference (centrifugal-flow pump group minus axial-flow pump group) was –10 percentage points.

RESULTS

Of 366 patients, 190 were assigned to the centrifugal-flow pump group and 176 to the axial-flow pump group. In the intention-to-treat population, the primary end point occurred in 151 patients (79.5%) in the centrifugal-flow pump group, as compared with 106 (60.2%) in the axial-flow pump group (absolute difference, 19.2 percentage points; 95% lower confidence boundary, 9.8 percentage points [P<0.001 for noninferiority]; hazard ratio, 0.46; 95% confidence interval [CI], 0.31 to 0.69 [P<0.001 for superiority]). Reoperation for pump malfunction was less frequent in the centrifugal-flow pump group than in the axial-flow pump group (3 patients [1.6%] vs. 30 patients [17.0%]; hazard ratio, 0.08; 95% CI, 0.03 to 0.27; P<0.001). The rates of death and disabling stroke were similar in the two groups, but the overall rate of stroke was lower in the centrifugal-flow pump group than in the axial-flow pump group (10.1% vs. 19.2%; hazard ratio, 0.47; 95% CI, 0.27 to 0.84, P=0.02).

CONCLUSIONS

In patients with advanced heart failure, a fully magnetically levitated centrifugal-flow pump was superior to a mechanical-bearing axial-flow pump with regard to survival free of disabling stroke or reoperation to replace or remove a malfunctioning device. (Funded by Abbott; MOMENTUM 3 ClinicalTrials.gov number, NCT02224755.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Mehra at the Brigham and Women's Hospital Heart and Vascular Center, Center for Advanced Heart Disease, 75 Francis St., Boston, MA 02115, or at mmehra@bwh.harvard.edu.

*A complete list of the investigators in the MOMENTUM 3 trial is provided in the Supplementary Appendix, available at NEJM.org.

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Left ventricular assist systems are increasingly used in patients with advanced heart failure, and concerns about device durability due to pump thrombosis have emerged.[1] An intrathoracic, fully magnetically levitated centrifugal-flow pump that was designed to prevent pump thrombosis has been engineered with wide blood-flow paths and intrinsic pulsatility.[2] In the 6-month analysis from the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM 3) trial, this device was associated with an absence of pump thrombosis leading to pump malfunction, as compared with a pump-thrombosis rate of 10.1% that was observed with a mechanical-bearing axial-flow pump.[2] In an exploratory short-term analysis from the same trial, we also found lower rates of nondisabling stroke with the centrifugal-flow pump than with the axial-flow pump.[3,4]

We next sought to ascertain whether these early observed benefits of the centrifugal-flow pump would persist into the longer term, to support patients who may wait for an extended period for heart transplantation or who may be ineligible for heart transplantation (and hence would receive a ventricular assist system as destination therapy, i.e., permanent therapy for a patient who is not a candidate for heart transplantation). We now present the 2-year prespecified analysis from the MOMENTUM 3 trial, which compared the centrifugal-flow HeartMate 3 with the axial-flow HeartMate II in patients with advanced heart failure.

Methods

Trial Design

We conducted a nonblinded, randomized trial comparing a centrifugal-flow pump with an axial-flow pump in patients with advanced-stage heart failure.[5] Details of the trial design have been published previously.[2] The trial was sponsored by Abbott, which provided the devices. The complete protocol, which was designed by the sponsor in consultation with clinical advisors, is available with the full text of this article at NEJM.org.

The trial was conducted in the United States at 69 centers that had experience in the implantation and management of left ventricular assist systems. The trial sites were selected and staff were trained by the sponsor. The protocol was approved by the institutional review board at each participating center. The data were analyzed by the sponsor, with verification by an independent statistician (see the Supplementary Appendix, available at NEJM.org). The authors had access to the data and vouch for the completeness and accuracy of all the data and analyses, as well as for fidelity of the trial to the protocol.

Trial Population

Patients with advanced heart failure that was refractory to guideline-mandated medical management were enrolled. Patients were eligible regardless of whether the intended goal was to provide mechanical circulatory support as a bridge to transplantation or as destination therapy. Exclusion criteria were active infection, irreversible end-organ dysfunction, or expected use of biventricular circulatory support. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix. Written informed consent was obtained from all the patients or their authorized representatives.

Randomization and Data Collection

Patients were randomly assigned in a 1:1 ratio to receive either the centrifugal-flow pump or the axial-flow pump. Randomization was performed with the use of permuted blocks, with stratification according to study center, and was implemented with the use of an electronic data-capture system (eClinicalOS, Merge Healthcare). The investigators and patients were aware of the treatment assignment. Data were collected at baseline, at 1 day and at 1 week after implantation, at discharge, at 1 month and at 3 months after implantation, and then every 6 months until 2 years of follow-up. Outcomes and adverse events were recorded throughout the trial (definitions are provided in the Supplementary Appendix).

Left Ventricular Assist Systems

The two circulatory pumps used were the HeartMate 3 fully magnetically levitated centrifugal continuous-flow pump and the HeartMate II mechanical-bearing axial continuous-flow pump (both from Abbott).[1,2,5] A detailed description of the centrifugal-flow pump is provided in the Supplementary Appendix. All the investigators underwent surgical training before they performed their first implantation of a centrifugal-flow pump. The recommended antithrombotic treatment in

each group included aspirin at a dose of 81 to 325 mg daily and warfarin (target range for the international normalized ratio, 2.0 to 3.0).

END POINTS

The primary end point was a composite of survival at 2 years free of disabling stroke (with disabling stroke indicated by a modified Rankin score of >3; scores range from 0 to 6, with higher scores indicating more severe disability) or survival free of reoperation to replace or remove a malfunctioning device. Patients who underwent urgent heart transplantation because of device malfunction were considered to have had treatment failure with respect to the primary end point, whereas patients who underwent elective transplantation for other reasons were considered to have had treatment success.

Secondary end points included the frequency of adverse events such as stroke, bleeding, right heart failure, and infection; actuarial survival; functional status; and quality of life. An independent clinical-events committee, whose members were unaware of the treatment assignments, adjudicated causes of death and all the adverse events. The New York Heart Association (NYHA) classification and the 6-minute walk test performed by a trained technician were used to evaluate functional status. Quality of life was assessed with the use of the European Quality of Life–5 Dimensions (EQ-5D) 5-Level questionnaire (EQ-5D-5L), the EQ-5D visual-analogue scale (EQ-5D VAS), and the Kansas City Cardiomyopathy Questionnaire (KCCQ).

STATISTICAL ANALYSIS

The sample-size calculation for the 2-year analysis is described in the Supplementary Appendix. We calculated that the enrollment of 366 patients would be required for the trial to show noninferiority for the primary end point; this necessitated the enrollment of a further 72 patients in addition to the 294 patients who had been enrolled for the 6-month analysis. We determined that noninferiority at 2 years would be shown 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 was greater than –10 percentage points, at a one-sided alpha of 0.025 or a two-tailed P value of less than 0.05, with the use of the Farrington–Manning risk-difference approach.

The primary end-point analysis was based on data from the intention-to-treat population, which included all the patients who underwent randomization. For patients who had more than one end-point event during follow-up, the event that occurred first was the treatment-failure event noted. Patients who underwent randomization but did not receive an implant were considered to have had treatment failure at the time of randomization. If noninferiority was proved, the primary end point and the individual component events were analyzed for superiority with the use of the z test of proportions, with the normal approximation to the binomial distribution. Cox proportional-hazards analyses, with data stratified according to treatment group, were used to calculate hazard ratios and 95% confidence intervals for the primary end point and component events.

All the secondary end points were analyzed in the per-protocol population, which excluded patients who did not receive the assigned device implant. 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. The analysis of actuarial survival was performed by the Kaplan–Meier method, and the results were compared between groups with the log-rank test. All the reported P values are two-tailed, and P values of less than 0.05 are considered to indicate statistical significance. Statistical analysis was performed with the use of SAS software, version 9.4 or higher (SAS Institute).

RESULTS

PATIENTS AND DEVICE IMPLANTATION

From September 2014 through November 2015, a total of 366 patients underwent randomization (190 patients to the centrifugal-flow pump group and 176 patients to the axial-flow pump group). The baseline characteristics of the patients in the two treatment groups are presented in Table 1, and in Tables S1 and S2 in the Supplementary Appendix.

One patient who had been assigned to receive the centrifugal-flow pump and 4 who had been

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Centrifugal-Flow Pump Group (N=190)	Axial-Flow Pump Group (N=176)
Age — yr		
Mean	61±12	59±12
Median (range)	65 (19–81)	61 (24–84)
Male sex — no. (%)	150 (78.9)	143 (81.2)
Race or ethnic group — no. (%)†		
White	127 (66.8)	131 (74.4)
Black	52 (27.4)	32 (18.2)
Asian	2 (1.1)	2 (1.1)
Native Hawaiian or Pacific Islander	0	2 (1.1)
Other	9 (4.7)	9 (5.1)
Body-surface area — m^2	2.1±0.3	2.1±0.3
Ischemic cause of heart failure — no. (%)	80 (42.1)	88 (50.0)
History of atrial fibrillation — no. (%)	81 (42.6)	83 (47.2)
History of stroke — no. (%)	16 (8.4)	20 (11.4)
Previous cardiac surgical procedure — no. (%)		
Coronary-artery bypass	44 (23.2)	41 (23.3)
History of valve replacement or repair	18 (9.5)	7 (4.0)
Left ventricular ejection fraction — %	17.2±4.9	17.4±5.0
Arterial blood pressure — mm Hg		
Systolic	110.2±15.6	106.3±12.9
Diastolic	67.0±10.8	65.4±10.4
Mean arterial pressure — mm Hg	79.5±10.1	78.4±9.8
Pulmonary-capillary wedge pressure — mm Hg	23.9±8.6	22.2±9.2
Cardiac index — liters/min/m^2 of body-surface area	2.0±0.5	2.0±0.7
Pulmonary vascular resistance — Wood units	3.2±1.7	3.0±1.6
Right atrial pressure — mm Hg	11.0±6.5	10.5±6.7
Serum sodium — mmol/liter	135.5±3.8	135.2±4.1
Serum creatinine — mg/dl‡	1.4±0.4	1.4±0.4
Estimated glomerular filtration rate — ml/min/1.73 m^2	60.2±23.2	59.6±21.5
Intended goal of pump support — no. (%)		
Bridge to transplantation	49 (25.8)	42 (23.9)
Bridge to candidacy for transplantation§	30 (15.8)	28 (15.9)
Destination therapy	111 (58.4)	106 (60.2)

* Plus–minus values are means ±SD. There were no significant differences between the groups except for history of valve replacement or repair (P=0.04) and systolic blood pressure (P=0.01). Percentages may not total 100 because of rounding. Data on the patients' Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles and concomitant medications and cardiac interventions are provided in Table S1 in the Supplementary Appendix.

† Race and ethnic group were reported by the patient.

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

§ Bridge to candidacy for transplantation refers to patients who were not immediately acceptable as candidates for transplantation but who, with device support, might become suitable candidates for such therapy; others in this category would revert to the destination-therapy group over time. Destination therapy is permanent therapy for a patient who is not a candidate for heart transplantation.

assigned to receive the axial-flow pump did not undergo implantation per protocol (Fig. S1 in the Supplementary Appendix). The remaining patients (per-protocol population) included 189 who underwent implantation of a centrifugal-flow pump and 172 who underwent implantation of an axial-flow pump. A total of 78 surgeons performed 361 implantations at 52 sites.

CLINICAL COURSE

A total of 177 of 189 patients (93.7%) in the centrifugal-flow pump group and 160 of 172 (93.0%) in the axial-flow pump group were discharged from the hospital with the device in place. The median length of stay during the hospitalization for implantation was 20 days in the centrifugal-flow pump group and 18 days in the axial-flow pump group (P=0.12 by the Wilcoxon rank-sum test). The percentage of time spent out of the hospital after device implantation did not differ significantly between groups (91.4% in the centrifugal-flow pump group and 90.3% in the axial-flow pump group). The number of rehospitalization days after discharge was nonsignificantly lower in the centrifugal-flow pump group than in the axial-flow pump group (median, 11 and 17 days per discharged patient, respectively; P=0.07).

PRIMARY END POINT

All the patients were followed for 2 years or until death, and no end-point data were missing. The primary end point occurred in more patients assigned to receive the centrifugal-flow pump than those assigned to receive the axial-flow pump (79.5% vs. 60.2%). The noninferiority criterion was met (absolute difference, 19.2 percentage points; 95% lower confidence boundary, 9.8 percentage points; P<0.001 for noninferiority), as was superiority (hazard ratio, 0.46; 95% confidence interval [CI], 0.31 to 0.69; two-tailed P<0.001 for superiority) (Table 2).

The difference between groups was primarily driven by reoperation or device removal for pump malfunction, the rates of which were significantly lower in the centrifugal-flow pump group than in the axial-flow pump group. Among the patients who had been assigned to the centrifugal-flow pump group, 3 (1.6%) underwent pump replacement (1 for a drive-line communication fault causing electrical failure, 1 because of a drive-line infection, and 1 because of persistent low pump flow that was due to an obstructive outflow-graft twist), whereas 30 patients (17.0%) who had been assigned to the axial-flow pump group underwent either a device exchange or device explantation, most often (in 67% of the patients) for pump thrombosis or severe hemolysis (hazard ratio, 0.08; 95% CI, 0.03 to 0.27; P<0.001) (Fig. S2 and Table S3 in the Supplementary Appendix). There were no significant between-group differences in the rates of death or disabling stroke.

ACTUARIAL SURVIVAL

The Kaplan–Meier estimate of actuarial event-free survival (primary end point) in the intention-to-treat population was significantly higher among patients assigned to the centrifugal-flow pump group than among those assigned to the axial-flow pump group (77.9% vs. 56.4%, P<0.001 by the log-rank test) (Fig. 1). Individual components of the primary end point, including overall survival, freedom from disabling strokes, and freedom from pump reoperations or removal, are shown in Figures S3 through S5 in the Supplementary Appendix.

In a worst-case sensitivity analysis, patients who had undergone randomization but had not received an implant were considered to have had treatment failure for the centrifugal-flow pump and treatment success for the axial-flow pump. In this analysis, the centrifugal-flow pump was again superior to the axial-flow pump with regard to the primary end point (hazard ratio, 0.51; 95% CI, 0.34 to 0.75; P<0.001) (Table S4 in the Supplementary Appendix). We also reanalyzed urgent heart transplantations that had been performed for the indication of device malfunction as a treatment success (rather than treatment failure), and the result was similar to what was observed in the primary end-point analysis (hazard ratio, 0.53; 95% CI, 0.35 to 0.78; P=0.002).

ADVERSE EVENTS

Suspected events of pump thrombosis occurred in 2 patients (1.1%) in the centrifugal-flow pump group, as compared with 27 patients (15.7%) who had 33 such events in the axial-flow pump group (hazard ratio, 0.06; 95% CI, 0.01 to 0.26; P<0.001). Individual case narratives for each case of suspected pump thrombosis are presented in the Supplementary Appendix, and the events are tabulated in Table S5 in the Supplementary Appendix. The Kaplan–Meier estimates of actuarial event-free

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

Variable	Centrifugal-Flow Pump Group (N = 190)		Axial-Flow Pump Group (N = 176)		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	151	79.5 (73.0–85.0)	106	60.2 (52.6–67.5)	19.2 (9.8)		<0.001
Superiority analyses							
Primary end point	151	79.5 (73.0–85.0)	106	60.2 (52.6–67.5)		0.46 (0.31–0.69)	<0.001
First event that resulted in failure to reach the primary end point							
Did not receive the assigned implant	1	0.5 (0.0–2.9)	4	2.3 (0.6–5.7)		0.23 (0.03–2.07)	0.16
Withdrawal after implantation§	2	1.1 (0.1–3.8)	3	1.7 (0.4–4.9)		0.53 (0.09–3.17)	0.59
Underwent reoperation to replace or remove pump¶	3	1.6 (0.3–4.5)	30	17.0 (11.8–23.4)		0.08 (0.03–0.27)	<0.001
Had disabling stroke	11	5.8 (2.9–10.1)	7	4.0 (1.6–8.0)		1.45 (0.56–3.75)	0.42
Died within 24 mo after implantation	22	11.6 (7.4–17.0)	26	14.8 (9.9–20.9)		0.75 (0.43–1.33)	0.37

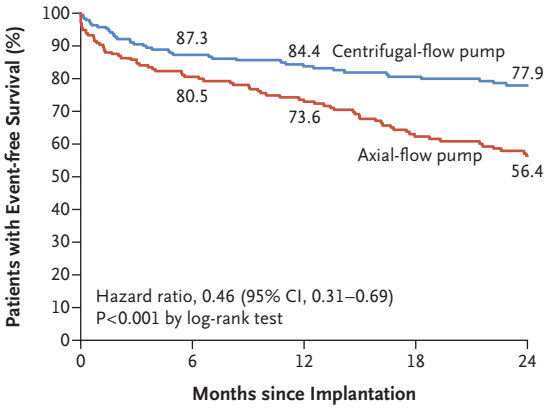
* The intention-to-treat population included all the patients who underwent randomization. The primary end point was a composite of survival free of disabling stroke (with disabling stroke indicated by a modified Rankin score of >3; scores range from 0 to 6, with higher scores indicating more severe disability) or survival free of reoperation to replace or remove the device at 24 months after implantation. LCB denotes lower confidence boundary.

† Hazard ratios and 95% confidence intervals were calculated with the use of Cox proportional-hazards analyses.

‡ P values for the superiority analyses are from a two-tailed test.

§ In the centrifugal-flow pump group, one patient was withdrawn from the trial owing to nonadherence to the protocol, and one patient underwent explantation and received a total artificial heart. In the axial-flow pump group, two patients received a pump exchange to a nonstudy device owing to infection and pump thrombosis (in one patient each), and one patient withdrew consent.

¶ Data for the axial-flow pump group include eight cases of urgent heart transplantation because of device malfunction (Table S3 in the Supplementary Appendix).

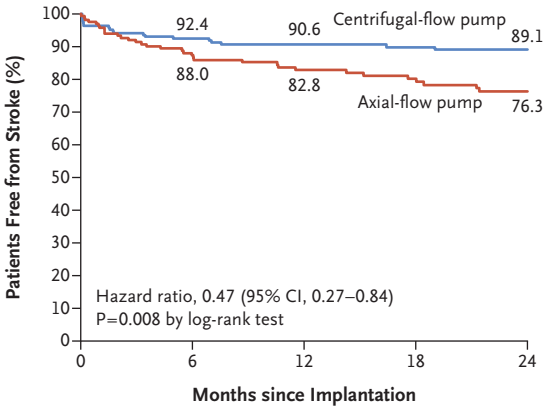


No. at Risk

Centrifugal-flow pump	190	161	141	122	111
Axial-flow pump	176	134	114	90	75

Figure 1. Kaplan–Meier Estimates of the Primary End Point in the Intention-to-Treat Population.

The intention-to-treat population included all the patients who underwent randomization. The primary end point was a composite of survival free of disabling stroke (with disabling stroke indicated by a modified Rankin score of >3; scores range from 0 to 6, with higher scores indicating more severe disability) or survival free of reoperation to replace or remove a malfunctioning device at 24 months after implantation. Rates of the primary end point at 6, 12, and 24 months are shown.



No. at Risk

Centrifugal-flow pump	189	159	138	120	111
Axial-flow pump	172	127	104	85	73

Figure 2. Actuarial Freedom from Stroke of Any Severity in the Per-Protocol Population.

The per-protocol population included only patients who received the assigned device implant. Rates of freedom from stroke at 6, 12, and 24 months are shown.

survival for suspected pump thrombosis are shown in Figure S6 in the Supplementary Appendix.

In the centrifugal-flow pump group, 22 strokes occurred in 19 patients (10.1%), as compared with 43 strokes that occurred in 33 patients (19.2%) in the axial-flow pump group (hazard ratio, 0.47; 95% CI, 0.27 to 0.84; P=0.02). The actuarial freedom from stroke of any severity is shown in Figure 2. The between-group differences in the rates of stroke according to severity (on the basis of the modified Rankin score) are shown in Figure S7 in the Supplementary Appendix. The incidence of ischemic stroke and of hemorrhagic stroke was lower in the centrifugal-flow pump group than in the axial-flow pump group (to a similar extent), although the difference in the incidence of hemorrhagic stroke did not reach significance.

No significant differences were noted between the two groups with respect to blood-pressure control, antiplatelet therapy, anticoagulation regimens, preexisting or new atrial fibrillation, or history of stroke (Table 1, and Table S6 and Fig. S8 in the Supplementary Appendix). The rates of other adverse events, including right heart failure, surgical and nonsurgical bleeding (gastrointestinal bleeding), and infection, including driveline infection, did not differ significantly between the two groups (Table 3, and Table S7 in the Supplementary Appendix).

At 1 month, the lactate dehydrogenase levels had decreased below baseline values in the centrifugal-flow pump group, whereas they had increased in the axial-flow pump group (P<0.001). The use of aspirin (or another antiplatelet agent) and anticoagulation levels did not differ significantly between groups, with similar percentages of international normalized ratio values in the therapeutic range[2,3] at all time points. Details of these analyses and data regarding hepatic and renal function are provided in Figures S9 and S10 and in Tables S8 through S10 in the Supplementary Appendix.

There were 30 total deaths in the centrifugal-flow pump group and 36 in the axial-flow pump group. The most common causes of death among the patients with either device were right heart failure, stroke, and infection (Table S11 in the Supplementary Appendix). Competing-risk analyses are shown in Figure S11 in the Supplementary Appendix.

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

Event	Centrifugal-Flow Pump Group (N=189)		Axial-Flow Pump Group (N=172)		Hazard Ratio (95% CI)	P Value†
	no. of patients with event (%)	*no. of events*	*no. of patients with event (%)*	*no. of events*		
Suspected or confirmed pump thrombosis	2 (1.1)	2	27 (15.7)	33	0.06 (0.01–0.26)	<0.001
Pump thrombosis resulting in reoperation or removal of device	0	0	21 (12.2)	25	NA	<0.001
Stroke						
Any stroke	19 (10.1)	22	33 (19.2)	43	0.47 (0.27–0.84)	0.02
Hemorrhagic stroke	8 (4.2)	8	16 (9.3)	17	0.42 (0.18–0.98)	0.06
Ischemic stroke	12 (6.3)	14	23 (13.4)	26	0.44 (0.22–0.88)	0.03
Disabling stroke	13 (6.9)	15	9 (5.2)	11	1.25 (0.54–2.93)	0.66
Other neurologic event‡	22 (11.6)	25	15 (8.7)	16	1.27 (0.66–2.45)	0.39
Bleeding						
Any bleeding	81 (42.9)	187	90 (52.3)	206	0.71 (0.53–0.96)	0.07
Bleeding that led to surgery	23 (12.2)	29	30 (17.4)	34	0.66 (0.38–1.13)	0.18
Gastrointestinal bleeding	51 (27.0)	107	47 (27.3)	100	0.92 (0.62–1.37)	1.00
Sepsis	26 (13.8)	37	24 (14.0)	28	0.95 (0.55–1.66)	1.00
LVAS drive-line infection	45 (23.8)	68	34 (19.8)	59	1.15 (0.73–1.79)	0.37
Local infection not associated with LVAS	70 (37.0)	108	60 (34.9)	114	1.00 (0.71–1.42)	0.74
Right heart failure						
Any right heart failure	60 (31.7)	73	48 (27.9)	53	1.12 (0.77–1.64)	0.49
Right heart failure managed with RVAS	6 (3.2)	6	8 (4.7)	8	0.67 (0.23–1.94)	0.59
Cardiac arrhythmia						
Any cardiac arrhythmia	71 (37.6)	108	70 (40.7)	105	0.88 (0.63–1.23)	0.59
Ventricular arrhythmia	45 (23.8)	67	39 (22.7)	64	1.04 (0.67–1.59)	0.80
Supraventricular arrhythmia	33 (17.5)	40	36 (20.9)	37	0.79 (0.49–1.26)	0.42
Respiratory failure	45 (23.8)	61	39 (22.7)	46	1.04 (0.68–1.59)	0.80
Renal dysfunction	25 (13.2)	29	18 (10.5)	18	1.23 (0.67–2.25)	0.52
Hepatic dysfunction	8 (4.2)	8	7 (4.1)	7	0.98 (0.36–2.71)	1.00

* The per-protocol population included only patients who received the assigned device implant. LVAS denotes left ventricular assist system, NA not available, and RVAS right ventricular assist system.
† P values were calculated with the use of Fisher's exact test. An upper boundary of the 95% confidence interval of the hazard ratio of less than 1.0 was considered to indicate statistical significance.
‡ Other neurologic events included transient ischemic attack and neurologic events other than stroke.

SUBGROUP ANALYSES

No significant interaction between groups with regard to the primary end point was observed for the prespecified subgroups of age, sex, race or ethnic group, intended goal of pump support (bridge to transplantation or destination therapy), or Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile. Details are provided in Figure S12 in the Supplementary Appendix.

FUNCTIONAL STATUS AND QUALITY OF LIFE

Performance on the 6-minute walk test and NYHA functional class improved to a similar extent in the two groups. Scores on the KCCQ, the EQ-5D-5L, and the EQ-5D VAS improved, as compared with

baseline scores, in each group at the 3-month and 6-month time points. No significant differences in improvement were observed between the treatment groups. Sensitivity analyses to account for missing values favored the centrifugal-flow pump group over the axial-flow pump group with regard to the EQ-5D-5L and the EQ-5D VAS (Fig. S13 in the Supplementary Appendix).

DISCUSSION

In the MOMENTUM 3 trial, we found that implantation of the HeartMate 3 fully magnetically levitated continuous-flow centrifugal pump prolonged survival free of disabling stroke or reoperation to replace or remove a malfunctioning device, as compared with the HeartMate II continuous-flow axial mechanical-bearing pump, at 2 years among patients with advanced heart failure. In this trial, the centrifugal-flow pump also resulted in a lower risk of stroke than the axial-flow pump, while averting pump thrombosis–related device malfunction.

The centrifugal-flow pump is designed to mitigate against the development of thrombosis within the device itself (often termed "de novo" thrombosis). However, we observed two cases of suspected pump thrombosis with this device. These events could have been due to thrombus formation outside the pump. For example, a thrombus within the atrial appendage or ventricular cavity could be ingested and, if entrapped, propagate within the device. It may also pass unobstructed owing to wide flow paths of the pump and result in a large stroke. Cases showing this scenario have been reported.[6,7] As low-intensity anticoagulation regimens are examined with the centrifugal-flow pump, close monitoring for such events will be essential. The principal reasons for pump malfunction with the magnetically levitated centrifugal-flow pump were electrical failure or mechanical complications such as outflow-graft twist, a problem that has been described by others and that needs to be better understood.[8]

Strokes remain an important complication of left ventricular assist systems, and our understanding of this complication is still incomplete.[9] A different centrifugal-flow device (the HeartWare Ventricular Assist System, Medtronic) was associated with substantially higher rates of stroke than were observed with the axial-flow pump.[10] This finding initially raised concerns about whether centrifugal-flow pathways or the widths of blood paths predispose patients to observed increases in the severity of neurologic adverse effects. In other analyses of the HeartWare device, the use of antiplatelet agents, the adequacy of anticoagulation levels, and blood-pressure control were found to correlate with lower rates of stroke.[11] Our findings suggest that strokes are not necessarily correlated with the type of flow path (centrifugal vs. axial). We also found no correlation with preexisting stroke, atrial fibrillation (history at baseline or new), blood-pressure control, or antiplatelet or anticoagulation regimens.

Previous studies have suggested a relationship between acquired von Willebrand factor deficiency and gastrointestinal bleeding with left ventricular assist systems.[12] The centrifugal-flow pump has less tendency to cause von Willebrand factor deficiency than the axial-flow pump.[13] However, no significant difference in the rate of gastrointestinal bleeding was noted between the two devices, although the cumulative bleeding events were numerically lower in the centrifugal-flow pump group. This finding suggests that other factors, including anticoagulation levels, oxidative stress, and microcirculatory factors, may play more dominant roles than acquired von Willebrand factor deficiency in determining gastrointestinal bleeding.[14-16]

Our trial has some limitations, including the lack of blinding, which may have introduced bias. However, decisions to reoperate on a malfunctioning pump are never taken lightly, and it therefore seems unlikely that this decision could be substantially influenced by knowledge of the device used. An uncontrolled, single-group trial, the Prevention of HeartMate II Pump Thrombosis through Clinical Management (PREVENT) trial, has shown that the use of standardized medical management (which was also used in our trial) and adherence to a structured surgical implantation technique of the axial-flow pump were associated with lower rates of pump thrombosis than those observed in clinical registries, but these rates fall within our observed 95% confidence interval.[17,18]

In conclusion, we compared the HeartMate 3 centrifugal-flow left ventricular assist system with the HeartMate II axial-flow left ventricular assist system in patients with advanced heart failure, irrespective of the intended goal of support. We found that, at 2 years, the centrifugal-flow pump was superior to the axial-flow pump with respect

to a composite primary end point of survival free of disabling stroke or reoperation to replace or remove a malfunctioning device.

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APPENDIX

The authors' full names and academic degrees are as follows: Mandeep R. Mehra, M.D., Daniel J. Goldstein, M.D., Nir Uriel, M.D., Joseph C. Cleveland, Jr., M.D., Melana Yuzefpolskaya, M.D., Christopher Salerno, M.D., Mary N. Walsh, M.D., Carmelo A. Milano, M.D., Chetan B. Patel, M.D., Gregory A. Ewald, M.D., Akinobu Itoh, M.D., David Dean, M.D., Arun Krishnamoorthy, M.D., William G. Cotts, M.D., Antone J. Tatooles, M.D., Ulrich P. Jorde, M.D., Brian A. Bruckner, M.D., Jerry D. Estep, M.D., Valluvan Jeevanandam, M.D., Gabriel Sayer, M.D., Douglas Horstmanshof, M.D., James W. Long, M.D., Sanjeev Gulati, M.D., Eric R. Skipper, M.D., John B. O'Connell, M.D., Gerald Heatley, M.S., Poornima Sood, M.D., and Yoshifumi Naka, M.D.

The authors' affiliations are as follows: Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston (M.R.M.); Montefiore Einstein Center for Heart and Vascular Care (D.J.G., U.P.J.) and Columbia University College of Physicians and Surgeons and New York Presbyterian Hospital (M.Y., Y.N.), New York; University of Chicago School of Medicine and Medical Center (N.U., V.J., G.S.) and Abbott (J.B.O., G.H., P.S.), Chicago, and Advocate Christ Medical Center, Oak Lawn (W.G.C., A.J.T.) — all in Illinois; University of Colorado School of Medicine, Aurora (J.C.C.); St. Vincent Heart Center, Indianapolis (C.S., M.N.W.); Duke Heart Center, Duke University, Durham (C.A.M., C.B.P.), and Carolinas Medical Center, Charlotte (S.G., E.R.S.) — both in North Carolina; Washington University School of Medicine, St. Louis (G.A.E., A.I.); Piedmont Hospital, Atlanta (D.D., A.K.); Houston Methodist Hospital, Houston (B.A.B., J.D.E.); and Integris Baptist Medical Center, Oklahoma City (D.H., J.W.L.).

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