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A fully magnetically levitated left ventricular assist device — final report

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ORIGINAL ARTICLE

A Fully Magnetically Levitated Left Ventricular Assist Device — Final Report

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ABSTRACT

BACKGROUND

In two interim analyses of this trial, patients with advanced heart failure who were treated with a fully magnetically levitated centrifugal-flow left ventricular assist device were less likely to have pump thrombosis or nondisabling stroke than were patients treated with a mechanical-bearing axial-flow left ventricular assist device.

METHODS

We randomly assigned patients with advanced heart failure to receive either the centrifugal-flow pump or the axial-flow pump irrespective of the intended goal of use (bridge to transplantation or destination therapy). The composite primary end point was survival at 2 years free of disabling stroke or reoperation to replace or remove a malfunctioning device. The principal secondary end point was pump replacement at 2 years.

RESULTS

This final analysis included 1028 enrolled patients: 516 in the centrifugal-flow pump group and 512 in the axial-flow pump group. In the analysis of the primary end point, 397 patients (76.9%) in the centrifugal-flow pump group, as compared with 332 (64.8%) in the axial-flow pump group, remained alive and free of disabling stroke or reoperation to replace or remove a malfunctioning device at 2 years (relative risk, 0.84; 95% confidence interval [CI], 0.78 to 0.91; P<0.001 for superiority). Pump replacement was less common in the centrifugal-flow pump group than in the axial-flow pump group (12 patients [2.3%] vs. 57 patients [11.3%]; relative risk, 0.21; 95% CI, 0.11 to 0.38; P<0.001). The numbers of events per patient-year for stroke of any severity, major bleeding, and gastrointestinal hemorrhage were lower in the centrifugal-flow pump group than in the axial-flow pump group.

CONCLUSIONS

Among patients with advanced heart failure, a fully magnetically levitated centrifugal-flow left ventricular assist device was associated with less frequent need for pump replacement than an axial-flow device and was superior with respect to survival free of disabling stroke or reoperation to replace or remove a malfunctioning device. (Funded by Abbott; MOMENTUM 3 ClinicalTrials.gov number, NCT02224755.)

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*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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The use of left ventricular assist devices in patients with advanced-stage heart failure is beleaguered by hemocompatibility-related complications of thrombosis, stroke, and bleeding, which are consequences of adverse interactions between the pump and circulating blood elements.[1] Advances in bioengineering have led to the introduction of durable continuous-flow left ventricular assist devices, but concerns have been raised about the risk of pump thrombosis causing device malfunction.[2] The shear stress created by continuous-flow pumps also leads to degradation of high-molecular-weight multimers of von Willebrand factor, a phenomenon that has been implicated in the development of mucosal arteriovenous malformations and bleeding.[3,4] In addition, a high frequency of stroke remains a serious concern for patients who receive a left ventricular assist device.[5]

The most widely implanted left ventricular assist device, the Heartmate II (Abbott), is an axial continuous-flow pump, which requires thoracoabdominal placement.[6] An intrapericardial centrifugal-flow pump, the HVAD (Medtronic), was found to be noninferior to the HeartMate II device with regard to survival but was associated with a higher incidence of stroke.[7] A fully magnetically levitated centrifugal-flow intrathoracic left ventricular assist device, the HeartMate 3 (Abbott), has been engineered with wide blood-flow pathways, friction-free movement, and intrinsic pulsatility to reduce shear stress and stasis of blood.[8]

In the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM 3), the HeartMate 3 centrifugal-flow left ventricular assist device was compared with the HeartMate II axial-flow device, either as a bridge to transplantation or as destination therapy, in 1028 patients with advanced-stage heart failure.[9] We previously reported prespecified 6-month and 2-year interim outcomes in smaller trial cohorts from MOMENTUM 3 (294 and 366 patients, respectively).[9-11] These analyses showed a lower incidence of pump thrombosis leading to malfunction with the centrifugal-flow pump than with the axial-flow device. The 2-year interim analysis also suggested a lower incidence of nondisabling stroke with the centrifugal-flow pump.[11] We now provide the final report of efficacy and safety end points in the full trial population (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Methods

Trial Design

In this randomized trial, we compared a centrifugal-flow left ventricular assist device with an axial-flow device in patients with advanced-stage heart failure. Details of the trial design have been published previously.[9-11] The protocol was approved by each institutional review board at 69 participating centers in the United States. The trial was sponsored by Abbott, which provided the devices, selected the sites, and analyzed the data (as indicated in the Supplementary Appendix), with verification performed by an independent statistician. The authors vouch for the completeness and accuracy of all the data and analyses and for fidelity of the trial to the protocol, which is available at NEJM.org.

Trial Population

We enrolled patients with advanced-stage heart failure who were deemed to be candidates for therapy with a left ventricular assist device, irrespective of whether the intended goal was to provide support as a bridge to transplantation or as destination therapy. Patients were excluded from the trial if biventricular circulatory support was expected to be necessary or if irreversible end-organ dysfunction or active infection was present. Written informed consent was obtained from all patients or their authorized representatives. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix.

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 and 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 assignments. Data on end points and adverse events were collected after implantation at 1 day, 1 week, discharge, 1 month, 3 months, 6 months, and then every 6 months until 2 years of follow-up had been completed.

LEFT VENTRICULAR ASSIST SYSTEMS

The two left ventricular assist devices used were the HeartMate 3 fully magnetically levitated centrifugal continuous-flow pump and the HeartMate II mechanical-bearing axial continuous-flow pump. All the investigators were experienced in the use of the control axial-flow pump and underwent training before 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 composite primary end point was survival at 2 years free of disabling stroke or reoperation to replace or remove a malfunctioning device. In the analysis of the primary end point, disabling stroke was defined by a modified Rankin score of greater than 3 (scores range from 0 to 6, with higher scores indicating greater disability). The principal secondary end point, which the trial was separately powered to assess, was pump replacement at 2 years after implantation. Other secondary end points included actuarial survival, rehospitalization, functional status, and quality of life. Subgroup analyses were prespecified for age, sex, race, intended goal of therapy (bridge to transplantation or destination therapy), and severity of illness at baseline.

The rates of major adverse events such as stroke, bleeding, right heart failure, and infection were also evaluated (definitions are provided in the Supplementary Appendix). An independent clinical-events committee, the members of which were unaware of the treatment assignments, adjudicated the causes of death and bleeding, infection, neurologic dysfunction, suspected device thrombosis, and hemolysis. A 6-minute walk test administered by a trained technician and New York Heart Association (NYHA) classification were used to evaluate functional status. Quality of life was assessed with 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 for the full cohort of patients who underwent randomization was calculated to test whether the centrifugal-flow left ventricular assist device was superior to the axial-flow left ventricular assist device with respect to the percentage of patients undergoing pump replacement at 2 years. We determined that, with 7% of patients in the axial-flow pump group and 3% of patients in the centrifugal-flow pump group expected to have undergone pump replacement at 2 years, 1028 patients would be required to show superiority with a power of 80% and an alpha of 0.05 (two-sided) (details are provided in the Supplementary Appendix).

The primary end point was analyzed in the intention-to-treat population, which included all patients who underwent randomization. Patients were considered to have had treatment failure with respect to the primary end point if any of the following events occurred: withdrawal from the trial before implantation (i.e., the patient underwent randomization but did not undergo implantation of the assigned device), withdrawal from the trial after implantation, death, disabling stroke, any pump replacement, urgent transplantation for device malfunction, or pump explantation or permanent deactivation for a reason other than myocardial recovery. If a patient had more than one of these events, the event that occurred first was noted as the treatment-failure event in the analysis of the primary end point. Transplantation for reasons other than device malfunction and pump explantation or permanent deactivation for myocardial recovery were not considered treatment-failure events.

Noninferiority with regard to the primary end point would be shown if the lower 95% confidence boundary of the difference between the treatment groups (centrifugal-flow pump minus axial-flow pump) in the percentage of patients remaining alive and free of disabling stroke or reoperation to replace or remove a malfunctioning device at 2 years was numerically greater than –10 percentage points (i.e., closer to or greater than zero) with a two-tailed P value of less than 0.05, calculated by the Farrington–Manning risk-difference approach. If noninferiority was met, then superiority was evaluated with the z test of proportions, with the use of the normal approximation to the binomial distribution. Relative risks and 95% confidence intervals for the primary end point and its component events are shown, and actuarial event-free survival was calculated by the Kaplan–Meier method.

All secondary end points were analyzed in the per-protocol population, which included all patients who underwent randomization and received the assigned device. The principal secondary end point was analyzed with Fisher's exact test. Poisson regression was used to compare the rates of major adverse events between the two treatment groups as numbers of events per patient-year. The rate differences are described as relative risks with the corresponding 95% confidence intervals. The incidence of rehospitalization in discharged patients was evaluated with the Andersen–Gill model. Overall survival was analyzed by the Kaplan–Meier method, with data censored for nonfatal outcomes, such as transplantation. Hazard ratios were calculated from Cox proportional-hazards models. Longitudinal changes in functional status and quality of life were analyzed by means of linear mixed-effects modeling.

The reported P values for the primary and principal secondary end point are two-tailed. The 95% confidence intervals have not been adjusted for multiplicity, and therefore inferences drawn from these intervals may not be reproducible. Statistical analyses were performed with the use of SAS software, version 9.4 or higher (SAS Institute).

RESULTS

PATIENTS AND DEVICE IMPLANTATION

From September 2014 through August 2016, a total of 1028 patients underwent randomization (516 patients to the centrifugal-flow pump group and 512 patients to the axial-flow pump group) (Fig. S2 in the Supplementary Appendix). The baseline characteristics of the patients are shown in Table 1, and in Table S1 in the Supplementary Appendix.

One patient who had been assigned to receive the centrifugal-flow pump and 7 who had been assigned to receive the axial-flow pump did not undergo implantation per protocol. The remaining patients (per-protocol population) included 515 who underwent implantation of a centrifugal-flow pump and 505 who underwent implantation of an axial-flow pump. A total of 126 surgeons performed 1020 implantations at 69 sites.

END POINTS

All patients were followed for 2 years, and no end-point data were missing. In the analysis of the primary end point, a larger percentage of patients in the centrifugal-flow pump group than in the axial-flow pump group remained alive and free of disabling stroke or reoperation to replace or remove a malfunctioning device at 2 years (397 patients [76.9%] vs. 332 patients [64.8%]). The noninferiority criterion (absolute between-group difference, 12.1 percentage points; 95% confidence interval [CI], 6.0 to 18.2; P<0.001) and superiority criterion (relative risk, 0.84; 95% CI, 0.78 to 0.91; P<0.001) were met. Details of the primary end-point components according to the first treatment-failure event that occurred are shown in Table 2, and in Table S2 in the Supplementary Appendix.

In a worst-case sensitivity analysis, patients in the axial-flow pump group who withdrew from the trial before or after implantation or who underwent urgent heart transplantation for device malfunction were considered to have had treatment success, whereas such patients in the centrifugal-flow pump group were still considered to have had treatment failure (Table S3 in the Supplementary Appendix). The result of this analysis was similar to that of the primary end-point analysis (relative risk, 0.91; 95% CI, 0.84 to 0.98). The Kaplan–Meier estimates of actuarial event-free survival at 2 years (primary end point) in the intention-to-treat population were 74.7% in the centrifugal-flow pump group and 60.6% in the axial-flow pump group (Fig. 1).

The principal secondary end point of pump replacement at 2 years occurred less frequently in the centrifugal-flow pump group than in the axial-flow pump group (12 patients [2.3%] vs. 57 patients [11.3%]; relative risk, 0.21; 95% CI, 0.11 to 0.38; P<0.001) (Table 2). A list of the specific reasons for pump replacement in each group is provided in Table S4 in the Supplementary Appendix.

CLINICAL COURSE

Discharge from the hospital with the device in place occurred in 485 of 515 patients (94.2%) in the centrifugal-flow pump group and 471 of 505 (93.3%) in the axial-flow pump group. The median length of stay during the hospitalization for implantation was 19 days in the centrifugal-flow pump group and 17 days in the axial-flow pump group. The median number of days of rehospitalization, days spent outside the hospital receiving left ventricular assist device support, and all-cause rehospitalization rates are shown in Table 3.

Table 1. Baseline Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	Centrifugal-Flow Pump Group (N=516)	Axial-Flow Pump Group (N=512)
Age — yr		
Mean	59±12	60±12
Median (range)	62 (18–83)	63 (21–84)
Male sex — no. (%)	411 (79.7)	419 (81.8)
Race or ethnic group — no. (%)†		
White	342 (66.3)	367 (71.7)
Black	145 (28.1)	120 (23.4)
Asian	8 (1.6)	3 (0.6)
Native Hawaiian or Pacific Islander	0	4 (0.8)
Other	21 (4.1)	18 (3.5)
Body-surface area — m^2	2.1±0.3	2.1±0.3
Ischemic cause of heart failure — no. (%)	216 (41.9)	240 (46.9)
History of atrial fibrillation — no. (%)	215 (41.7)	238 (46.5)
History of stroke — no. (%)	50 (9.7)	56 (10.9)
Previous cardiac surgical procedures — no. (%)		
Coronary-artery bypass	102 (19.8)	114 (22.3)
Valve replacement or repair	36 (7.0)	31 (6.1)
Left ventricular ejection fraction — %	17.3±5.1	17.2±5.0
Arterial blood pressure — mm Hg		
Systolic	108.4±14.7	106.5±14.5
Diastolic	66.8±10.6	65.7±10.2
Mean arterial pressure — mm Hg	79.2±10.4	79.2±10.1
Pulmonary-capillary wedge pressure — mm Hg	23.1±8.6	22.9±9.2
Cardiac index — liters/min/m^2	2.0±0.5	2.0±0.6
Pulmonary vascular resistance — Wood units	3.1±1.7	3.0±1.7
Right atrial pressure — mm Hg	10.8±6.5	10.7±6.8
Serum sodium level — mmol/liter	135.4±4.1	135.5±4.2
Serum creatinine level — mg/dl	1.4±0.4	1.4±0.4
Estimated glomerular filtration rate — ml/min/1.73 m^2	61.3±23.7	59.5±22.0
Intended goal of pump support — no. (%)		
Bridge to transplantation	113 (21.9)	121 (23.6)
Bridge to candidacy for transplantation	86 (16.7)	81 (15.8)
Destination therapy	317 (61.4)	310 (60.5)

* Plus–minus values are means ±SD. There were no significant differences between the groups in any characteristic except for race (P=0.04) and systolic blood pressure (P=0.03). The intention-to-treat population included all patients who underwent randomization. Data on Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles and concomitant medications and cardiac interventions are provided in Table S1 in the Supplementary Appendix. Percentages may not total 100 because of rounding. To convert the serum creatinine level to micromoles per liter, multiply by 88.4.

† Race or ethnic group was reported by the patient.

Table 2. Primary and Principal Secondary End Points.*

End Point	Centrifugal-Flow Pump Group (N=516)		Axial-Flow Pump Group (N=512)		Absolute Difference	Relative Risk (95% CI)	P Value
	no. of patients	*% (95% CI)*	*no. of patients*	*% (95% CI)*	*percentage points (95% LCB)*		
Primary end point†							
Noninferiority analysis	397	76.9 (73.1–80.5)	332	64.8 (60.5–69.0)	12.1 (6.0)		<0.001‡
Superiority analysis	397	76.9 (73.1–80.5)	332	64.8 (60.5–69.0)		0.84 (0.78–0.91)	<0.001‡
First event that resulted in treatment failure with respect to the primary end point§							
Withdrew before implantation	1	0.2 (0.0–1.1)	7	1.4 (0.6–2.8)		0.14 (0.02–1.15)	
Withdrew after implantation	4	0.8 (0.2–2.0)	3	0.6 (0.1–1.7)		1.32 (0.30–5.88)	
Underwent reoperation to replace or remove pump¶	14	2.7 (1.5–4.5)	73	14.3 (11.4–17.6)		0.19 (0.11–0.33)	
Had disabling stroke‖	20	3.9 (2.4–5.9)	30	5.9 (4.0–8.3)		0.66 (0.38–1.15)	
Died within 24 months after implant**	80	15.5 (12.5–18.9)	67	13.1 (10.3–16.3)		1.18 (0.88–1.60)	
Principal secondary end point††							
Pump replacement within 24 months after implantation	12	2.3 (1.2–4.0)	57	11.3 (8.7–14.4)		0.21 (0.11–0.38)	<0.001‡‡

* The 95% confidence intervals have not been adjusted for multiplicity, and therefore inferences drawn from these intervals may not be reproducible. LCB denotes lower confidence boundary.

† The primary end point was a composite of survival free of disabling stroke or reoperation to replace or remove a malfunctioning device at 24 months after implantation. Disabling stroke was defined by a modified Rankin score of greater than 3 (scores range from 0 to 6, with higher scores indicating more severe disability). The intention-to-treat population included all patients who underwent randomization.

‡ P values for the primary end-point analyses are from Farrington–Manning risk difference (in the noninferiority analysis) or the z test of proportions with normal approximation to the binomial distribution (in the superiority analysis).

§ The event that occurred first was noted as the treatment-failure event in this component analysis. Patients could have multiple events after the first event leading to treatment failure with regard to the primary end point (e.g., disabling stroke after a pump exchange), which are not accounted for in the primary analysis. Table S2 in the Supplementary Appendix shows this in the context of disabling strokes and deaths as first events or recurrent events.

¶ For the component analysis, this category includes pump replacement (12 patients in the centrifugal-flow pump group and 56 in the axial-flow pump group), urgent heart transplantation for device malfunction (2 patients in the centrifugal-flow pump group and 15 in the axial-flow pump group), or explantation or permanent deactivation of the device for a reason other than myocardial recovery (2 patients in the axial-flow pump group). There were 57 patients in the axial-flow pump group who underwent pump replacement; 56 pump replacements in the axial-flow pump group were first events that led to treatment failure in a patient with regard to the primary end point.

‖ There were 26 patients in the centrifugal-flow pump group and 38 patients in the axial-flow pump group who had a disabling stroke; the corresponding rates of disabling stroke for the treatment groups were 0.04 events per patient-year and 0.07 events per patient-year. Among all the disabling stroke events, 20 in the centrifugal-flow pump group and 30 in the axial-flow pump group were first events that led to treatment failure in a patient with regard to the primary end point.

** A total of 98 patients in the centrifugal-flow pump group and 103 patients in the axial-flow pump group had died at 2 years; 80 deaths in the centrifugal-flow pump group and 67 deaths in the axial-flow pump group were first events that led to treatment failure in a patient with regard to the primary end point.

†† The secondary end point was evaluated in the per-protocol population (515 patients in the centrifugal-flow pump group and 505 patients in the axial-flow pump group) for the first event of pump replacement.

‡‡ The P value for the principal secondary end point was calculated with Fisher's exact test.

Table 3. Postdischarge End Points among Patients Discharged while Receiving Left Ventricular Assist Device Support (Per-Protocol Population).*

End Point	Centrifugal-Flow Pump Group (N=485)	Axial-Flow Pump Group (N=471)	Difference or Hazard Ratio (95% CI)
Median duration of rehospitalization (interquartile range) — days	13 (4 to 37)	18 (6 to 40)	−5 (−8.7 to −1.3)
Median duration receiving left ventricular assist device support outside hospital (interquartile range) — days	653 (333 to 696)	605 (259 to 690)	48 (−0.8 to 96.8)
Rate of rehospitalization for any cause — events per patient-yr	2.26	2.47	0.92 (0.86 to 0.99)†

* The per-protocol population included all patients who underwent randomization and received the assigned device. The 95% confidence intervals have not been adjusted for multiplicity, and therefore inferences drawn from these intervals may not be reproducible.
† The hazard ratio was derived from the Andersen–Gill model for the comparison of all-cause readmissions between the groups.

There were 98 deaths in the centrifugal-flow pump group and 103 in the axial-flow pump group after implantation, with no significant difference in overall survival between the groups (Fig. S3 in the Supplementary Appendix). The most common causes of death among the patients with either device were right heart failure, stroke, and infection (Table S5 in the Supplementary Appendix).

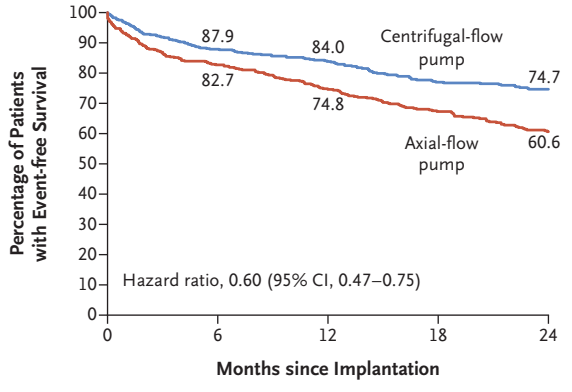

Figure 1. Kaplan–Meier Estimates of the Primary End Point in the Intention-to-Treat Population.

The intention-to-treat population included all patients who underwent randomization. The primary end point was a composite of survival free of disabling stroke or reoperation to replace or remove a malfunctioning device at 24 months after implantation. Disabling stroke was defined by a modified Rankin score of greater than 3 (scores range from 0 to 6, with higher scores indicating more severe disability). Kaplan–Meier estimates for the primary end point at 6, 12, and 24 months are shown. The 95% confidence intervals have not been adjusted for multiplicity, and therefore inferences drawn from these intervals may not be reproducible.

Competing-risk curves that reflect the cumulative percentages of patients in each group who had an outcome of ongoing device support, transplantation, device explantation or deactivation, or death through 2 years are shown in Figure S4 in the Supplementary Appendix.

SAFETY OUTCOMES

Between-group comparisons of event rates for hemocompatibility-related adverse events (including pump thrombosis, stroke, and bleeding) and other major events are shown in Figure 2. Instantaneous hazard risk curves are shown in Figure S5 in the Supplementary Appendix. There were 70 cases of suspected or confirmed pump thrombosis with the axial-flow pump and 7 cases with the centrifugal-flow pump; narratives of these events with the centrifugal-flow pump are provided in the Supplementary Appendix. Data on other major adverse events are shown in Figure S6 and Tables S6 and S7 in the Supplementary Appendix. Ventricular arrhythmias were less frequent with the centrifugal-flow pump than with the axial-flow device.

There were no significant differences between the groups with respect to clinical factors associated with stroke risk, including history of atrial fibrillation, history of stroke, maintenance of mean arterial blood pressure at or below 90 mm Hg, or receipt of antithrombotic therapy during the trial. Lactate dehydrogenase levels were lower in the centrifugal-flow pump group than in the axial-flow pump group. Details of these analyses and data regarding hepatic and renal function are provided in Table 1, and in Tables S8 through S10 and Figure S7 in the Supplementary Appendix.

Adverse Event	Centrifugal-Flow Pump	Axial-Flow Pump	Centrifugal-Flow Pump	Axial-Flow Pump	Relative Risk (95% CI)	P Value
	no. of patients with events (%)		*events per patient-yr*			
Suspected or confirmed pump thrombosis	7 (1.4)	70 (13.9)	0.01	0.12	0.08 (0.04–0.16)	<0.001
Any stroke	51 (9.9)	98 (19.4)	0.08	0.18	0.42 (0.30–0.57)	<0.001
Disabling stroke	26 (5.0)	38 (7.5)	0.04	0.07	0.54 (0.34–0.85)	0.008
Any bleeding	225 (43.7)	278 (55.0)	0.61	0.95	0.64 (0.57–0.72)	<0.001
Gastrointestinal bleeding	126 (24.5)	156 (30.9)	0.31	0.49	0.64 (0.54–0.75)	<0.001
Other neurologic event	59 (11.5)	47 (9.3)	0.09	0.08	1.25 (0.88–1.79)	0.21
Any major infection	300 (58.3)	285 (56.4)	0.82	0.82	1.00 (0.89–1.12)	0.96
Right heart failure	176 (34.2)	143 (28.3)	0.27	0.23	1.15 (0.94–1.42)	0.18
Cardiac arrhythmia	185 (35.9)	207 (41.0)	0.37	0.45	0.82 (0.70–0.97)	0.02
Respiratory failure	111 (21.6)	98 (19.4)	0.19	0.17	1.10 (0.86–1.40)	0.44
Renal dysfunction	73 (14.2)	56 (11.1)	0.11	0.08	1.36 (0.98–1.89)	0.07
Hepatic dysfunction	25 (4.9)	27 (5.3)	0.03	0.04	0.78 (0.46–1.34)	0.38

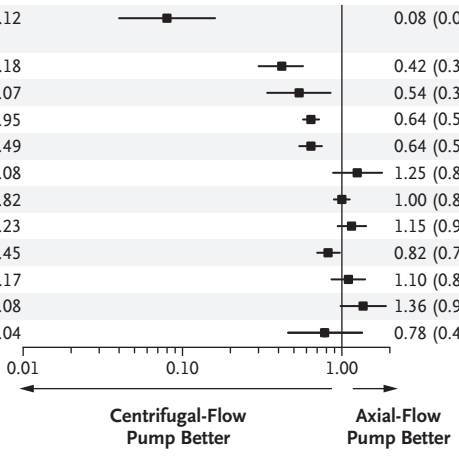

Figure 2. Principal Safety Outcomes in the Per-Protocol Population.

Relative risks of key adverse events, calculated on the basis of the number of events per patient-year in the centrifugal-flow pump group as compared with the axial-flow pump group, are shown. The per-protocol population included all patients who underwent randomization and received the assigned device. The relative risk of an adverse event favors the centrifugal-flow pump when the upper boundary of the 95% confidence interval is less than 1.0. Neither pump is favored when the 95% confidence interval spans the line of unity. The 95% confidence intervals have not been adjusted for multiplicity, and therefore inferences drawn from these intervals may not be reproducible. Narratives for suspected pump-thrombosis events in the centrifugal-flow pump group are provided in the Supplementary Appendix. P values for relative risk are derived from Poisson regression. Other neurologic events included transient ischemic attack, seizure, encephalopathy, and neurologic events other than stroke.

FUNCTIONAL STATUS AND QUALITY OF LIFE

For both groups, there were sustained improvements from baseline in the 6-minute walk test, NYHA functional class, KCCQ overall summary score, EQ-5D-5L total score, and the EQ-5D VAS (Fig. S8 in the Supplementary Appendix). There were no significant differences in functional-status test results or quality-of-life measures between the treatment groups. Sensitivity analyses accounting for missing values favored the centrifugal-flow pump group over the axial-flow pump group with regard to the NYHA classification and the EQ-5D VAS.

SUBGROUP ANALYSES

No interaction between the groups 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 with regard to the primary end point. Details are provided in Figure S9 in the Supplementary Appendix.

DISCUSSION

In this final report of the MOMENTUM 3 trial, we showed that the HeartMate 3 fully magnetically levitated centrifugal-flow pump was superior to the HeartMate II axial-flow left ventricular assist system with respect to survival free of disabling stroke or reoperation to replace or remove a malfunctioning device. In addition to reducing the need for pump replacement (mostly for pump thrombosis), the centrifugal-flow pump was associated with a lower incidence of either ischemic or hemorrhagic strokes of any severity and fewer bleeding events. We calculate that for every 10 patients who received the centrifugal-flow pump rather than the axial-flow pump, 2.2 pump-thrombosis events, 2 strokes, and 6.8 bleeding events (3.6 gastrointestinal bleeds) were averted over a 2-year period. These findings were accompanied

by fewer days spent in the hospital at 2 years among patients who received the magnetically levitated left ventricular assist device.

Reports of lower stroke rates with the centrifugal pump that were noted in earlier analyses of this trial were interpreted cautiously, since only the rates of nondisabling strokes were favorably influenced.[11-14] In the population in the current analysis, which was 3 times as large, we found lower rates of both hemorrhagic and ischemic strokes and a lower rate of disabling strokes. Stroke rates were not influenced by differences in baseline rates of atrial fibrillation, anticoagulation regimens, or blood pressure control in our current or previous analyses.[14]

The magnetically levitated centrifugal pump does not degrade high-molecular-weight multimers of Von Willebrand factor to the extent observed with other devices.[15] This finding is consistent with the lower lactate dehydrogenase levels that were found in patients with this pump, which suggests that less hemolysis was occurring. However, in previous analyses of the MOMENTUM 3 trial, no discernible benefit with regard to the incidence of mucosal bleeding was noted.[10,11] In this final analysis involving the full trial population, we noted that the centrifugal pump was associated with lower rates of bleeding, including gastrointestinal bleeding, which is linked with the unique physiological features of continuous-flow left ventricular assist devices.[16,17] However, a significant residual risk of bleeding persists, which suggests the need to investigate whether a reduction in the exposure of patients with these pumps to antiplatelet or anticoagulation therapy would be beneficial.[2,18]

In our trial, infections affecting the drive line exit site and in other locations occurred frequently, with no significant differences between left ventricular assist devices. Studies have made note of aberrant T-cell activation and compromised cellular immunity in patients with older pumps.[19,20] Efforts to eliminate the drive line by developing internally powered durable heart pumps are likely to be an important advance in this regard. However, vigilance in preventing generalized infections will remain important.[21,22] Late-onset right heart failure, a leading cause of death, also needs further study.[23,24] Outflow-graft twist occlusion, a unique adverse event with the centrifugal pump, has been noted previously.[25-27] Recognition of this insidious complication is important, since it compromises pump flow and may mimic pump thrombosis. A surgical clip to fix the pump outflow graft to the connector is now available to help prevent outflow-graft rotation.

In summary, in this final analysis from the MOMENTUM 3 trial, the centrifugal-flow HeartMate 3 left ventricular assist device was associated with a less frequent need for pump replacement than the axial-flow HeartMate II left ventricular assist device and was superior to the axial-flow pump with respect to survival free of disabling stroke or reoperation to replace or remove a malfunctioning device.

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APPENDIX

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