The MOMENTUM 3 Trial

Multicenter Study Of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3

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HARVARD MEDICAL SCHOOL

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*Drs. Mehra and Naka contributed equally to this study

#Drs. Mehra, Uriel, Goldstein, Cleveland served as Study Oversight Committee and contributed equally to the trial conduct and oversight

Background

- **Advanced heart failure patients treated with continuous-flow Left Ventricular Assist Systems benefit from improved survival and quality of life[1]**

- **However, clinical outcomes are limited by infection, bleeding, neurological events, and pump malfunction (principally due to *pump thrombosis*)**

- **Pump thrombosis, a complication noted with the available axial[2,3] and centrifugal-flow pumps[4] is a principal component of the constellation of *"hemocompatibility related outcomes"***

[1]Slaughter et al. Advanced Heart Failure treated with Continuous Flow Left Ventricular Assist Device. *N Engl J Med*. 2009 Dec 16;361(23):2241-2251.
[2]Starling RC et al. Unexpected abrupt increase in left ventricular assist device thrombosis. *N Engl J Med*. 2014 Jan 2;370(1):33-40.
[3]Kirklin JK et al. INTERMACS analysis of pump thrombosis in the HeartMate II left ventricular assist device. *J Heart Lung Transplant*. 2014 Jan;33(1):12-22.
[4]Najjar SS. An analysis of pump thrombus events in patients in the HeartWare ADVANCE bridge to transplant and continued access protocol trial. *J Heart Lung Transplant.* 2014 Jan;33(1):23-34.

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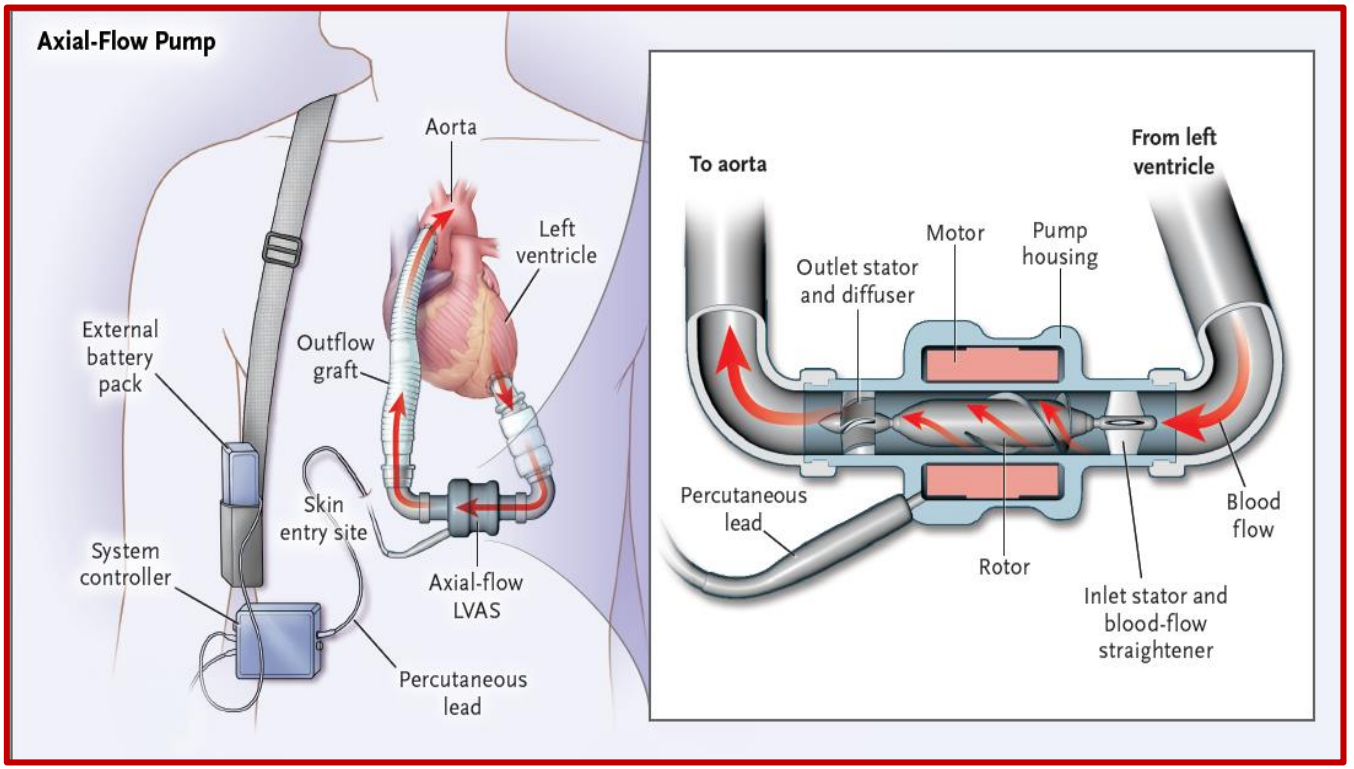
HeartMate II LVAS



The HeartMate II LVAS (St. Jude Medical, Inc.) is a mechanical bearing axial continuous-flow blood pump;
only device in the US approved for *both* Bridge-To-Transplant (BTT) and Destination Therapy (DT) patients

[1]Slaughter et al. Advanced Heart Failure treated with Continuous Flow Left Ventricular Assist Device. *N Engl J Med*. 2009 Dec 16;361(23):2241-2251.

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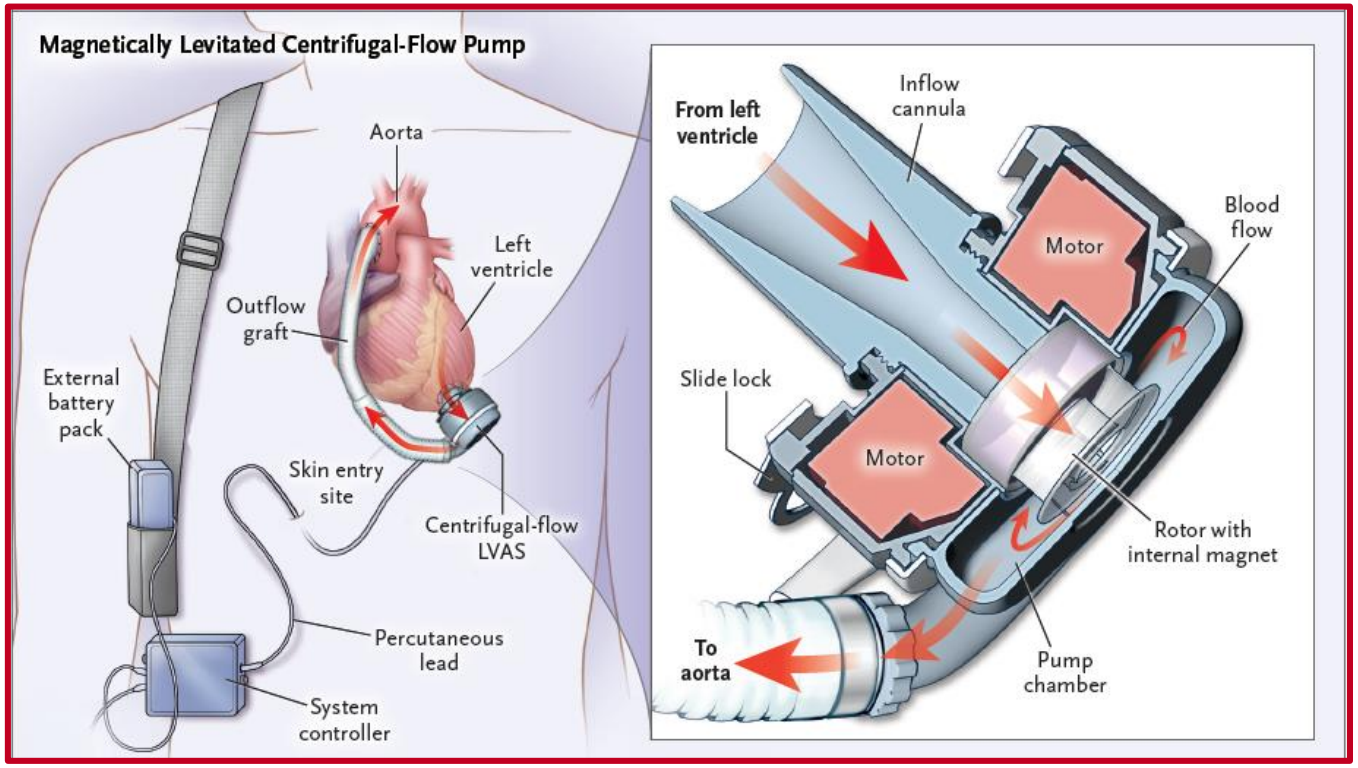
HeartMate 3 LVAS



- **Wide** blood-flow passages to reduce shear stress
- **Frictionless** with absence of mechanical bearings
- **Intrinsic Pulse** designed to reduce stasis and avert thrombosis

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Target Population

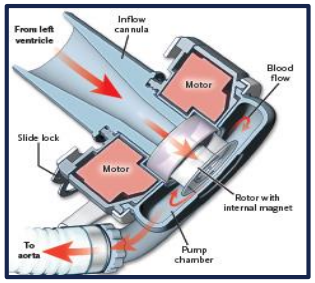
- **Patients with advanced heart failure and severe limitations (NYHA IIIB or IV),** refractory to standard medical therapy and *deemed as necessary candidates for left ventricular assist device implantation*, irrespective of the intended goal of pump support (BTT or DT)

- **Key exclusion criteria** included planned biventricular support, irreversible end-organ dysfunction, or active infection

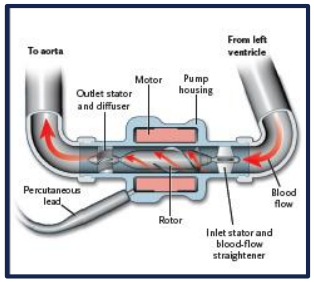
Heatley et al. Clinical trial design and rationale of the multicenter study of MagLev technology in Patients undergoing mechanical circulatory support therapy with the HeartMate 3 (MOMENTUM 3) IDE clinical study protocol. *J Heart Lung Transplant.* 2016;35:528-36..

Study Design

HeartMate 3



Patient meets MOMENTUM 3 eligibility criteria?



HeartMate II

Randomization 1:1

Short Term (ST) Cohort
N=294
6-month follow-up

Long Term (LT) Cohort
N=366
24-month follow-up

Full Study Cohort
N=1028
24-month follow-up for powered secondary endpoint

Intent-to-Treat (ITT) Population
N=294

HeartMate 3
N=152

HeartMate II
N=142

Treatment failures
(not treated with study device)
N=1

Death: 1

Treatment failures
(not treated with study device)
N=4

No LVAD implant: 1
Withdrawal of consent: 1
Transplant: 1
Implanted with non-study LVAD: 1

As Treated Population
N=289

Implanted with HeartMate 3
N=151

Implanted with HeartMate II
N=138

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Study Endpoint

- **Primary Endpoint (*composite, by ITT*):**
  - Survival at 6 months free of disabling stroke (modified Rankin score >3) or reoperation to replace or remove the pump (other than for recovery)

- **Demonstration of non-inferiority of HeartMate 3 to HeartMate II**
  - If lower 95% confidence bound for difference in primary endpoint success between treatment arms is > -10%, non-inferiority is met (1-tailed P<0.025)
  - Sequential *superiority* testing conducted If non-inferiority met

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Baseline Characteristics - 1

Characteristic	HeartMate 3 (n=152)	HeartMate II (n=142)
Age - years		
Mean	60 ± 12	59 ± 12
Median (range)	64 (19 - 81)	61 (24 - 78)
Male sex - no. (%)	121 (80)	114 (80)
Race – no. (%)		
White	104 (68)	107 (75)
Black or African American	37 (24)	24 (17)
Other*	11 (8)	11 (8)
Body surface area - m^2	2.1 ± 0.3	2.1 ± 0.3
Ischemic cause of heart failure - no. (%)	68 (45)	72 (51)
History of stroke - no. (%)	12 (8)	14 (10)
Concomitant medication or intervention - no (%)		
Intravenous inotropic agents	132 (87)	121 (85)
Diuretics**	134 (88)	136 (96)
ACE inhibitor	37 (24)	38 (27)
Angiotensin II -receptor antagonist	10 (7)	18 (13)
Beta blocker	91 (60)	79 (56)
CRT/CRT-D	59 (39)	51 (36)
ICD/CRT-D	101 (66)	100 (70)
IABP	18 (12)	21 (15)

*Other: includes Asian, Native Hawaiian or Pacific Islanders and patient who refused to provide race
**Diuretic use was statistically significant (P=0.02)

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Baseline Characteristics - 2

Characteristic	HeartMate 3 (n=152)	HeartMate II (n=142)
Left ventricular ejection fraction - %	17.1 ± 5.0	17.3 ± 4.9
Arterial blood pressure - mmHg		
Systolic*	110 ± 16	106 ± 12
Diastolic	67 ± 10	66 ± 10
Mean arterial pressure* - mmHg	81 ± 10	79 ± 9
PCWP - mmHg	23 ± 9	22 ± 9
Cardiac index - liters/min/m^2 of body surface area	1.9 ± 0.5	2.0 ± 0.7
PVR - Wood Units	3.3 ± 1.7	3.0 ± 1.6
Right atrial pressure - mmHg	10 ± 6	11 ± 7
Serum sodium - mmol/liter	135.6 ± 3.9	134.9 ± 4.2
Serum creatinine - mg/ml	1.4 ± 0.4	1.4 ± 0.4
INTERMACS Profile** – no (%)		
1	1 (1)	4 (3)
2	50 (33)	44 (31)
3	76 (50)	69 (49)
4	22 (14)	23 (16)
5-7†	2 (1)	2 (1)
Intended Use of device at implant – no (%)		
Bridge to Transplant (BTT)	41 (27)	37 (26)
Bridge to Candidacy	27 (18)	27 (18)
Destination Therapy (DT)	84 (55)	78 (55)

* Systolic blood pressure (P= 0.01) and Mean arterial pressure (P=0.04) were statistically significantly;
** one subject in HM3 group expired prior to INTERMACS Assessment;
† There were no subjects with INTERMACS 6 and 7 in either groups; PCWP denotes pulmonary capillary wedge pressure and PVR pulmonary vascular resistance

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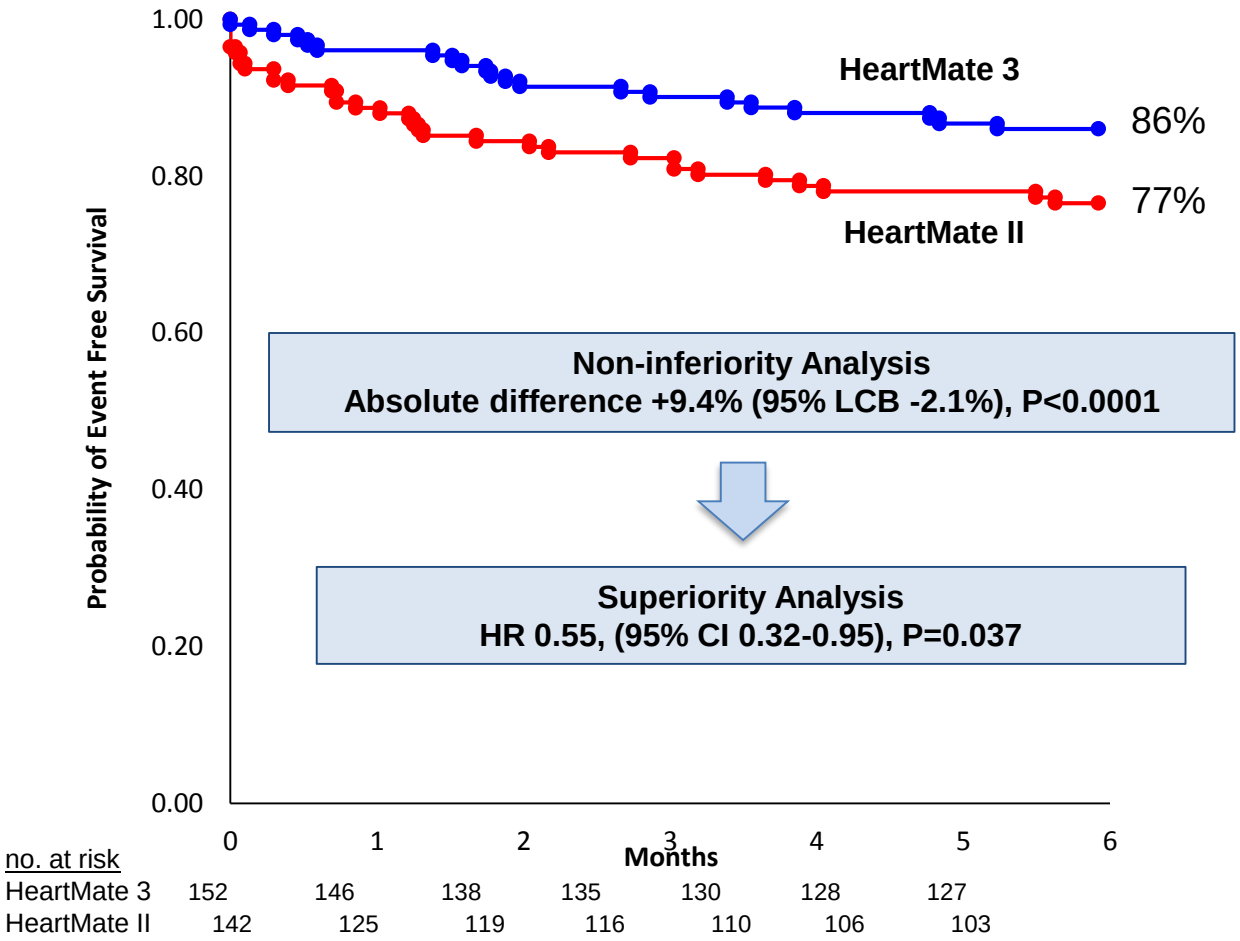
Primary End Point Analysis (ITT)

Survival at 6 months free of disabling stroke or reoperation to replace or remove the pump



LCB, lower confidence boundary, HR, hazard ratio, and CI, confidence interval

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Primary Endpoint (ITT)
Superiority Analysis (Components)

Superiority Analysis	HeartMate 3 (n=152) n (% [95%CI])	HeartMate II (n=142) n (% [95%CI])	Hazard Ratio†	P value
Survival free from disabling stroke and reoperation to repair or replace the LVAD at 6 months	131 (86.2 [80 - 91])	109 (76.8 [69 - 83])	0.55 (0.32 - 0.95)	0.037
First event that prevented patient from reaching the primary endpoint				
Did not receive assigned pump	1(1[0-4])	4 (3 [1 - 7])	0.23 (0.03 – 2.09)	0.15
Disabling stroke (Rankin Score > 3)	6 (4 [1 - 8])	4 (3 [1 - 7])	1.31 (0.37 - 4.64)	0.59
Reoperation to repair or replace pump*	**1 (1 [0 - 4])**	**11 (8 [4 - 13])**	**0.08 (0.01 - 0.60)**	**0.002**
Death within 180 days after implant	13 (9 [5 - 14])	14 (10 [6 - 16])	0.82 (0.38 - 1.73)	0.70

†Hazard ratios were calculated with the use of Cox regression.
* includes two cases of urgent heart transplant due to device malfunction in the axial-flow pump group
CI denotes confidence interval and LVAD left ventricular assist device

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Key Adverse Events: Pump Thrombosis, Neurological Events, Bleeding

	HeartMate 3 (n=151)		HeartMate II (n=138)				
	n (%)	no. of Events	n (%)	no. of Events	RR	95% CI for RR	P Value
Suspected or Confirmed Pump Thrombosis	**0 (0)**	**0**	**14 (10)**	**18**	**N/A**	**N/A**	**< 0.0001**
All Stroke	12 (7)	12	15 (10)	17	0.73	0.35-1.51	0.39
Hemorrhagic Stroke	4 (2)	4	8 (5)	8	0.46	0.14-1.48	0.18
Ischemic Stroke	8 (5)	8	9 (6)	9	0.81	0.32-2.05	0.66
Disabling Stroke	9(6)	9	5(3)	5	1.65	0.57-4.79	0.36
Other Neurologic Events*	9 (6)	9	8 (5)	8	1.03	0.41-2.59	0.95
Bleeding	50 (33)	100	54 (39)	98	0.85	0.62-1.15	0.29
Bleeding Requiring Surgery	15 (9)	15	19 (13)	21	0.72	0.38-1.36	0.31
Gastrointestinal Bleeding	**24 (15)**	**47**	**21 (15)**	**36**	**1.04**	**0.61-1.79**	**0.87**

No Pump Thrombosis in the HeartMate 3 group

Similar Stroke and Bleeding rates in both groups

RR, denotes Relative Risk and CI, confidence interval
*Includes transient ischemic attacks and neurologic events other than stroke

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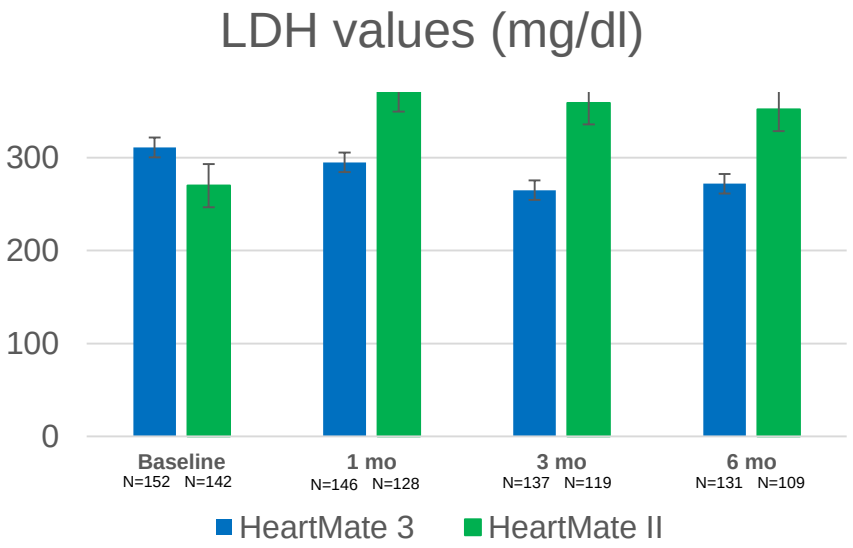
INR and LDH values

	HeartMate 3				HeartMate II				
	Baseline N=152	1 Mo N=146	3 Mo N=137	6 Mo N=131	Baseline N=142	1 Mo N=128	3 Mo N=119	6 Mo N=109*	P value**
INR	1.3±0.4	2.3±0.9	2.2±0.6	2.5±1.2	1.3±0.4	2.3±0.9	2.2±0.7	2.3±0.7	0.10
LDH (mg/dl)	**311±428**	**295±124**	**265±108**	**272±133**	**270±129**	**373±195**	**359±222**	**352±144**	**<0.001**

*no. of subjects for INR=110.
**between treatment arms
Data presented as mean ± standard deviation. Differences at 6 months between treatments compared with a two-sample t-test.
INR, international normalized ratio and LDH, lactate dehydrogenase



No differences in anti-coagulation and antiplatelet therapy

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Other Adverse Events

	HeartMate 3 (n=151)		HeartMate II (n=138)				
	n (%)	no. of Events	n (%)	no. of Events	RR	95% CI for RR	P Value
Sepsis	14 (9)	19	9 (6)	10	1.42	0.64-3.18	0.39
LVAS Driveline Infection	18 (11)	21	9 (6)	11	1.83	0.85-3.93	0.12
Local non-LVAS Infection	46 (31)	57	36 (26)	58	1.17	0.81-1.69	0.41
Right Heart Failure	45 (30)	49	34 (25)	36	1.21	0.83-1.77	0.33
Right Heart Failure managed with RVAD	4 (3)	4	8 (6)	8	0.46	0.14-1.48	0.18
Cardiac Arrhythmia	47 (31)	61	52 (38)	68	0.83	0.60-1.14	0.24
Ventricular	27 (18)	33	27 (20)	37	0.91	0.57-1.48	0.71
Supraventricular	23 (15)	27	30 (22)	31	0.7	0.43-1.15	0.15
Respiratory Failure	33 (22)	44	24 (17)	27	1.26	0.78-2.02	0.34
Renal Dysfunction	17 (11)	18	12 (9)	12	1.29	0.64-2.61	0.47
Hepatic Dysfunction	7 (5)	7	3 (2)	3	2.13	0.56-8.08	0.34
Hemolysis not associated with device thrombosis	1 (1)	1	2 (1)	2	0.46	0.04-4.98	0.61

LVAS denotes Left Ventricular Assist System, RVAD, Right Ventricular Assist Device, RR, Relative Risk and CI, confidence interval.

No differences in Infections or Right Heart Failure

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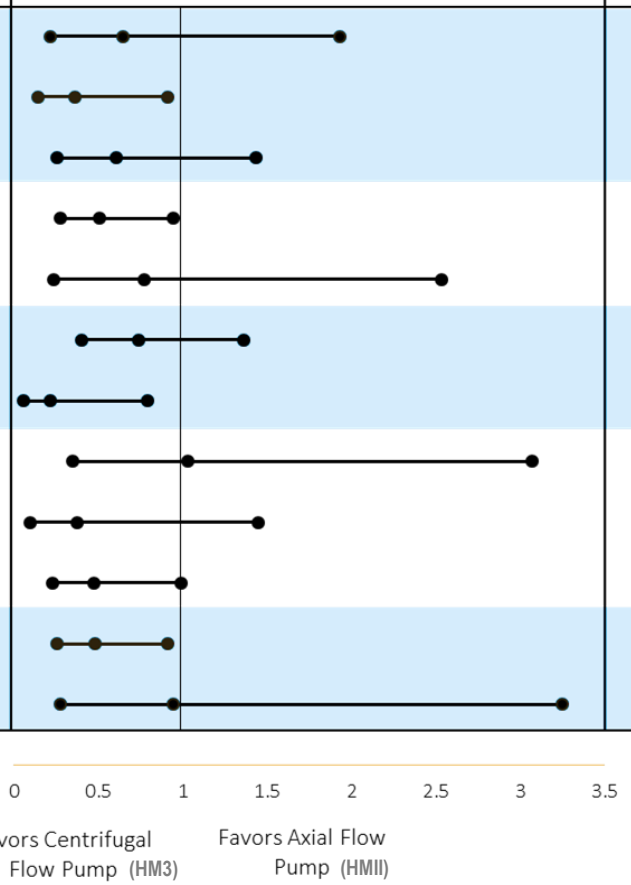
Subgroup Analysis for Primary Endpoint (ITT)

Variable	Groups	HR (95% CI)	Interaction p-value
Age (years)	18 - 59 (n=127)	0.65 (0.22-1.93)	0.67
	60 - 69 (n=102)	0.36 (0.14-0.91)	
	70+ (n=65)	0.60 (0.25-1.43)	
Gender	Men (n=235)	0.51 (0.27-0.94)	0.63
	Women (n=59)	0.77 (0.24-2.54)	
Race	Caucasian (n=211)	0.74 (0.40-1.36)	0.09
	Non-Caucasian (n=83)	0.21 (0.06-0.79)	
Intended Use	BTT (n=78)	1.03 (0.35-3.07)	0.28
	BTC (n=54)	0.37 (0.10-1.45)	
	DT (n=162)	0.47 (0.23-0.99)	
INTERMACS Profile	INTERMACS 2 or 3 (n=239)	0.48 (0.26-0.91)	0.29
	INTERMACS 4 or 5 (n=49)	0.94 (0.27-3.25)	



BTT= Bridge to Transplant, BTC=Bridge to Candidacy, DT = Destination Therapy; INTERMACS =Interagency Registry for Mechanical Circulatory Support

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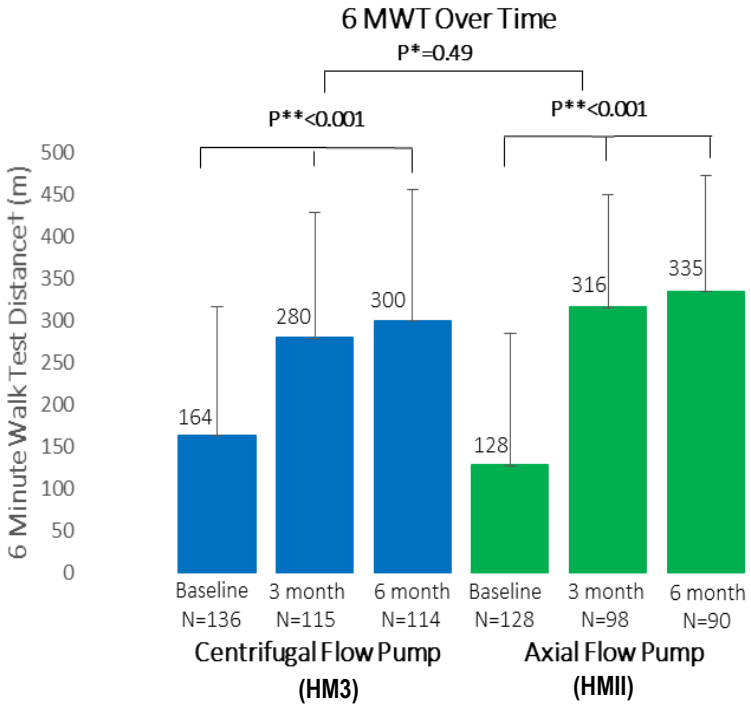
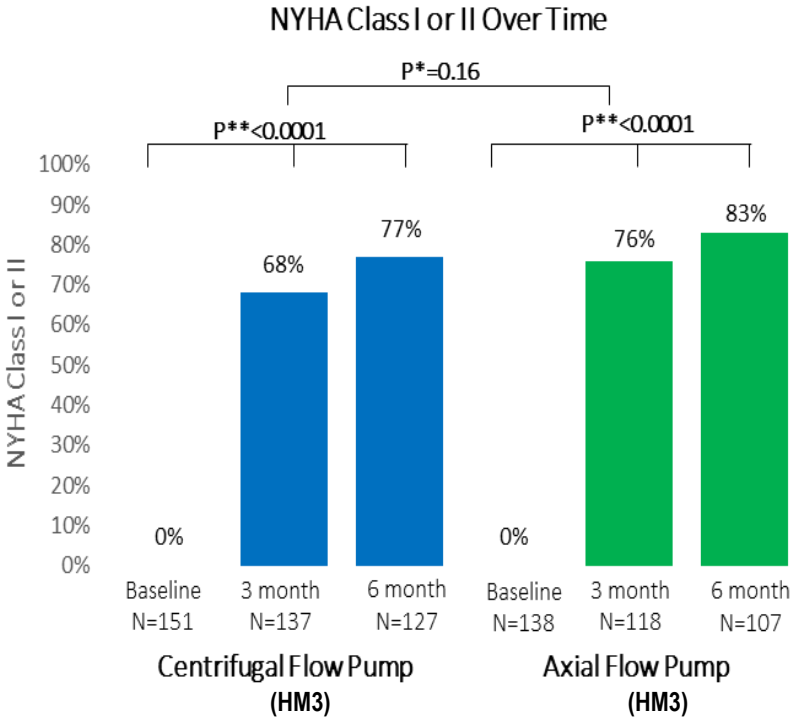
Functional Status





*p value between treatment arms over time; **p value for treatment over time

No differences in QOL parameters as well

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Conclusions

In this primary 6-month analysis of the ongoing MOMENTUM 3 Trial, we demonstrated

- Incremental improvement in outcomes driven by a reduction in the need for reoperation for pump malfunction or replacement of the HeartMate 3 LVAS

- No suspected or confirmed pump thrombosis events with the HeartMate 3 LVAS, a principal driver for pump exchange

- Similar functional and quality of life improvement in patients treated with either the HeartMate 3 or the HeartMate II LVAS with no difference between devices in the incidence of other adverse events

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure

Mandeep R. Mehra, M.D., Yoshifumi Naka, M.D., Nir Uriel, M.D., Daniel J. Goldstein, M.D., Joseph C. Cleveland, Jr., M.D., Paolo C. Colombo, M.D., Mary N. Walsh, M.D., Carmelo A. Milano, M.D., Chetan B. Patel, M.D., Ulrich P. Jorde, M.D., Francis D. Pagani, M.D., Keith D. Aaronson, M.D., David A. Dean, M.D., Kelly McCants, M.D., Akinobu Itoh, M.D., Gregory A. Ewald, M.D., Douglas Horstmanshof, M.D., James W. Long, M.D., and Christopher Salerno, M.D., for the MOMENTUM 3 Investigators*

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We THANK all the patients, our investigators, clinical nurse coordinators, and allied health personnel for their dedication to the conduct of the MOMENTUM 3 trial

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