

Hemocompatibility-Related Outcomes in the MOMENTUM 3 Trial at 6 Months

A Randomized Controlled Study of a Fully Magnetically Levitated Pump in Advanced Heart Failure

BACKGROUND: The HeartMate 3 (HM3) Left Ventricular Assist System (LVAS) (Abbott) is a centrifugal, fully magnetically levitated, continuous-flow blood pump engineered to enhance hemocompatibility and reduce shear stress on blood components. The MOMENTUM 3 trial (Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3) compares the HM3 LVAS with the HeartMate II (HMII) LVAS (Abbott) in advanced heart failure refractory to medical management, irrespective of therapeutic intention (bridge to transplant versus destination therapy). This investigation reported its primary outcome in the short-term cohort (n=294; 6-month follow-up), demonstrating superiority of the HM3 for the trial primary end point (survival free of a disabling stroke or reoperation to replace the pump for malfunction), driven by a reduced need for reoperations. The aim of this analysis was to evaluate the aggregate of hemocompatibility-related clinical adverse events (HRAEs) between the 2 LVAS.

METHODS: We conducted a secondary end point evaluation of HRAE (survival free of any nonsurgical bleeding, thromboembolic event, pump thrombosis, or neurological event) in the short-term cohort (as-treated cohort n=289) at 6 months. The net burden of HRAE was also assessed by using a previously described hemocompatibility score, which uses 4 escalating tiers of hierarchical severity to derive a total score for events encountered during the entire follow-up experience for each patient.

RESULTS: In 289 patients in the as-treated group (151 the HM3 and 138 the HMII), survival free of any HRAE was achieved in 69% of the HM3 group and in 55% of the HMII group (hazard ratio, 0.62; confidence interval, 0.42–0.91; $P=0.012$). Using the hemocompatibility score, the HM3 group demonstrated less pump thrombosis requiring reoperation (0 versus 36 points, $P<0.001$) or medically managed pump thrombosis (0 versus 5 points, $P=0.02$), and fewer nondisabling strokes (6 versus 24 points, $P=0.026$) than the control HMII LVAS. The net hemocompatibility score in the HM3 in comparison with the HMII patients was 101 (0.67 ± 1.50 points/patient) versus 137 (0.99 ± 1.79 points/patient) (odds ratio, 0.64; confidence interval, 0.39–1.03; $P=0.065$).

CONCLUSIONS: In this secondary analysis of the MOMENTUM 3 trial, the HM3 LVAS demonstrated greater freedom from HRAEs in comparison with the HMII LVAS at 6 months.

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Clinical Perspective

What Is New?

- Hemocompatibility with a left ventricular assist system refers to the constellation of bleeding and thrombosis events that often aggregate together in the same individual.
- This 6-month secondary analysis of the MOMENTUM 3 trial (Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3) compares the HeartMate 3 with the HeartMate II pump and demonstrates that the HeartMate 3 pump is superior in reducing hemocompatibility-related adverse outcomes (driven by absent pump thrombosis and decreased nondisabling strokes) at 6 months.

What Are the Clinical Implications?

- We now provide quantitative estimates of freedom from hemocompatibility-related adverse events between the 2 pumps (at 6 months) and suggest exploratory findings of clinical correlates in the hemostatic management axis that may warrant prospective confirmation.
- Importantly, we define a new score of the burden of hemocompatibility that can serve to standardize assessment of aggregate patient-level outcomes across various device platforms.

Hemocompatibility-related adverse events (HRAEs) are the Achilles heel of the interaction between a left ventricular assist system (LVAS) and its biological circulatory interface.¹ The constellation of device-related hemolysis, pump thrombosis leading to malfunction, neurological events (predominantly stroke and bleeding), and nonsurgical bleeding (particularly gastrointestinal bleeding) are the principal concerns that influence outcomes in mechanical circulatory support. These frequent complications are noted to occur with all contemporary centrifugal and axial continuous-flow devices, the HeartWare HVAD (HeartWare International Inc) and the HeartMate II (HMII) (Abbott) LVAS, respectively.^{2,3}

The HeartMate 3 (HM3) LVAS (Abbott) is a continuous-flow centrifugal pump, with a fully magnetically levitated rotor, wide blood flow passages, and an intrinsic pulse designed to avert stasis within the pump.⁴ This novel LVAS is currently being evaluated in a prospective, randomized, controlled trial comparing it with the HMII pump in patients with advanced heart failure who are refractory to optimal medical therapy (MOMENTUM 3 trial [Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3]).⁵ The primary analysis of the short-term cohort in this study (n=294 [intention-to-treat population], 6-month follow-up) was recently published.⁶ In this

analysis, the HM3 LVAS demonstrated superiority to the HMII for the primary end point of survival free of disabling stroke or reoperation for pump replacement. Although clearly focusing on the most severe complications of LVAS, such an end point may underappreciate the totality of HRAEs encountered in the experiential journey.¹

The purpose of this secondary analysis is several-fold: (1) to compare outcomes between the HM3 and HMII LVAS, when all HRAEs are evaluated as an efficacy end point, (2) to assess the aggregate net burden of HRAEs encountered within and between each device system, and (3) to explore hypothesis-generating clinical correlates predictive of HRAE that may inform further studies.

METHODS

MOMENTUM 3 is a prospective, multicenter, randomized, non-blinded, pivotal clinical trial comparing the HM3 with the HMII LVAS in patients who have advanced-stage heart failure, and its design has been previously described.⁵ Eligible patients (bridge to transplant or destination therapy) were randomly assigned 1:1 to receive either the HM3 or the HMII LVAS. The primary end point of the trial was survival free of disabling stroke, and reoperation to repair or replace the device, assessed at 6 months and 2 years postimplantation. This adaptive design trial has completed enrollment (n=1028 patients) at 69 US sites, and comprises 3 specific patient cohorts:

1. Short-Term Cohort: The first 294 patients enrolled into the trial, where the primary end point (powered for non-inferiority) was compared between the 2 devices at 6-months follow-up by intention-to-treat. The primary outcomes, which demonstrated noninferiority and superiority, as well, of the HM3 LVAS, have been reported.⁶
2. Long-Term Cohort: The first 366 patients (including the 294 in the Short-Term Cohort), where the primary end point (powered for noninferiority) will be (still ongoing) compared between the 2 devices at 2 years.
3. Extended Long-Term Cohort: The full cohort of 1028 patients (including the Long-Term Cohort), where the primary goal is to demonstrate superiority of the HM3 on the secondary end point of pump malfunction requiring replacement (ongoing).

Each participating center's institutional review board approved the protocol and all patients or their authorized representative provided written informed consent. Predefined adverse events, reoperations, readmissions to the hospital, and device malfunctions were reported as they occurred. Centers entered data into a validated Internet-based electronic data capture system that is compliant with Title 21 Code of Federal Regulations Part 11 (21 CFR Part 11). Site users were permitted only data entry rights to use the system, and only after database training was completed. An independent clinical events committee blinded to the randomization adjudicated all key events. They also adjudicated the severity and device relationship of these adverse events. An independent data safety and monitoring board performed regular review of the clinical safety data. Antithrombotic management included anticoagulation with warfarin (with a targeted international normalized ratio [INR] of 2.0–3.0) and aspirin therapy (81–325 mg daily) for both groups.

Hemocompatibility-Related Adverse Event

In this secondary analysis, clinical adverse events attributable to LVAS-related bleeding or thrombosis abnormalities were classified as an HRAE. These events were:

- Nonsurgical bleeding: Gastrointestinal or other nonsurgical bleeding episodes >30 days postimplant
- Neurological events: Stroke (hemorrhagic or ischemic, disabling or nondisabling) or other neurological events (eg, transient ischemic attack, seizures) at any time
- Thromboembolic events: Suspected or confirmed pump thrombosis, arterial thromboembolism with or without organ involvement at any time

A patient experiencing any of these events was deemed to have experienced an HRAE.

Hemocompatibility Score

To determine the aggregate net burden of HRAE in each patient, a tiered hierarchical score (hemocompatibility score [HCS]) that weights each event by its escalating clinical relevance was calculated for each patient as previously described.¹ The methodology for calculating the score is provided in Table 1. In brief, mild events (eg, ≤ 2 nonsurgical

bleeding episodes) contributed a single point to the HCS, whereas serious events (eg, disabling stroke) contributed a higher grade to the HCS (eg, disabling stroke contributes 4 points). The HCS was calculated for each patient by summing up all the points associated with each HRAE experienced by the patient for the duration of available follow-up. The HCS served as the net burden of all HRAEs experienced by the patient for the duration of 6-month follow-up. For example, a patient who has 3 gastrointestinal bleeds (score 2) followed by a nondisabling stroke (score 2) and then a reoperation to replace the device (score 3) would contribute a total score of 7 to the HCS end point.

Statistical Analysis

Patients implanted as randomly assigned constituted the as-treated cohort of the MOMENTUM 3 Short-Term Cohort for the present secondary analysis. Categorical variables are reported as percentages and were compared between the groups using the Fisher exact test. Continuous variables are presented as median (interquartile range) and were compared between groups using the Wilcoxon rank sum test. Statistical significance was set at $P < 0.05$. Hazard ratios and their corresponding 95% confidence intervals (CIs) were evaluated by using Cox proportional-hazard models. Time-to-event analysis was performed by using the Kaplan-Meier method with P values reported using the log-rank test. Three separate analyses were conducted.

Table 1. Calculation of Hemocompatibility Score

Intensity	Clinical Components	Score
Tier I (mild)	≤ 2 gastrointestinal or other bleeding episodes (>30 days postimplant)*	1 point each
	Suspected pump thrombosis (successfully medically treated)	
	Nonstroke-related neurological events (hemocompatibility etiology or inconclusive)	
	Arterial thromboembolism not resulting in organ loss	
Tier II (moderate)	>2 gastrointestinal or other bleeding*	2 points each
	Nondisabling stroke (hemorrhagic or ischemic)	
	Arterial thromboembolism resulting in organ loss	
Tier III		
IIIA (moderate to severe)	Pump malfunction attributable to pump thrombosis leading to reoperation for removal or replacement	3 points each
IIIB (severe)	Disabling stroke	4 points each
	Death attributable to a hemocompatibility etiology or inconclusive (unknown or multiple causes)	

Assessment of net hemocompatibility burden by calculation of hemocompatibility score (HCS).

*Score for the bleeding episodes should be based on total number of events per patient as opposed to per event. (This table is adapted from ref. 1).

Analysis 1: Comparison of HRAEs Between HM3 and HMII LVAS

Outcome measures assessed and compared between the 2 groups were: (1) Survival free of any HRAE at 6 months (analyzed using the Kaplan-Meier and Cox proportional-hazard models), and (2) the incidence of any HRAE at 6 months (odds ratios and 95% CIs were evaluated from the associated 2×2 contingency table, and the statistical significance was tested using the Fisher exact test). The analysis was stratified by age >65 and ≤ 65 , because age has previously been shown to be a risk factor associated with HRAEs, and this age cutoff is clinically meaningful in distinguishing destination therapy indications.^{7,8} Additionally, days spent in the hospital after the patient had been readmitted for an HRAE were compared between the HM3 and HMII using the Wilcoxon rank sum test.

Analysis 2: Comparison of the Net Burden of HRAEs (Assessed by the HCS) Between the HM3 and HMII

The distribution of HCS was compared between the HM3 and the HMII by using a proportional odds regression model. HCS was modeled as an ordinal outcome variable for each patient with values of 0, 1, 2, 3, 4, or ≥ 5 , for a total of 6 ordinal levels. The proportional odds assumption was tested and was found to be satisfied.

Analysis 3: Exploratory Determination of Clinical Correlates Predictive of HRAEs (Based on a HCS>0)

This analysis was performed for the full cohort by comparing those patients alive with a HCS=0 in comparison with those with a HCS>0 or death. The clinical correlates analyzed included baseline characteristics (eg, age, sex, therapeutic intent), anticoagulation level (INR), and the use of aspirin therapy and mean arterial pressures at 30 days postimplant. These include variables that have been found to be

risk factors impacting bleeding and thrombotic events with LVAS.^{9,10} A multivariable logistic regression analysis was used for identifying factors that were independently predictive of any HRAEs (HCS>0) or death in the full cohort of patients, with device type included as a covariate. Variables with *P* values<0.1 on univariable analysis were incorporated into the multivariable regression analysis.

RESULTS

Two hundred eighty-nine patients (of the 294 intention-to-treat population) constituted the as-treated cohort of MOMENTUM 3 (HM3=151 patients; HMII=138 patients). The baseline characteristics of the 2 treatment groups are reported in Table 2.

Analysis 1: Comparison of HRAEs Between HM3 and HMII

Survival free of any HRAEs at 6 months was significantly higher for the HM3 than for the HMII (69±4% versus 55±4%; hazard ratio, 0.62; 95% CI, 0.42–0.91; *P*=0.012) (Figure 1A). When stratified by age, the HM3 group had a greater absolute difference relative to HMII LVAS for patients ≤65 years of age (76±5% versus 58±5%; hazard ratio, 0.51; 95% CI, 0.30–0.87; *P*=0.01). For patients >65 years of age, the results remained numerically better for the HM3 group, although *P* values exceeded 0.05 (Figure 1B). In the HM3 group, 43 patients (28%) experienced at least 1 HRAE (mild, moderate, or severe), versus 53 HMII patients (38%) (*P*=0.08). Table 3 shows the breakdown of patients who experienced bleeding, thrombosis, or both bleeding and thrombotic complications. HM3 patients had predominantly bleeding events, whereas bleeding and thromboembolic events were equally distributed in the HMII group. The total number of days spent in the hospital because of readmission for HRAE for HM3 versus HMII was 578 days versus 617 days, respectively, translating into a 6.3% reduction in favor of the HM3 group (*P*=0.079). Most events required hospitalization for <10 days.

Analysis 2: Assessment of Net HRAE Burden Assessed Using HCS

The HCS for HM3 versus HMII patients was 101 points (0.67±1.50 points/patient; median [range]: 0 [0–10] points/patient) versus 137 (0.99±1.79 points/patient; median [range]: 0 [0–9] points/patient; odds ratio, 0.64; CI, 0.39–1.03; *P*=0.065), respectively. Further analysis of the HCS breakdown between the devices is presented in Table 4. Figure 2 outlines the proportional contribution of tiered events to the HCS. Figure 3 shows a distribution of the cumulative score experienced by each patient in both the HM3 and HMII groups, respectively.

Table 2. Baseline Characteristics Comparing the HM3 and HMII LVAS

Characteristic	HeartMate 3 (n=151)	HeartMate II (n=138)	<i>P</i> Value
Age, y	64 (53–69)	61 (52–69)	0.18
Male sex, n (%)	120 (79)	111 (80)	0.88
Race, n (%)			0.26
White	103 (68)	105 (76)	
Black	37 (25)	23 (17)	
Other	11 (7)	10 (7)	
Body surface area, m ²	2.0 (1.9–2.2)	2.0 (1.9–2.2)	0.65
Ischemic cause of heart failure, n (%)	68 (45)	68 (49)	0.48
History of stroke, n (%)	12 (8)	14 (10)	0.54
Concomitant therapies or intervention, n (%)			
Intravenous inotropic agents	131 (87)	118 (86)	0.86
CRT/CRT-D	59 (39)	50 (36)	0.63
ICD/CRT-D	100 (66)	97 (70)	0.53
IABP	18 (12)	18 (13)	0.86
Serum sodium, mmol/L	136 (134–138)	136 (132–138)	0.16
Serum creatinine, mg/mL	1.3 (1.0–1.6)	1.3 (1.1–1.6)	0.79
INTERMACS Profile, n (%)			1.00
1	1 (1)	2 (1)	
2	50 (33)	43 (31)	
3	76 (50)	69 (50)	
4	22 (15)	22 (16)	
5–7	2 (1)	2 (1)	
Intended use of device at implant, n (%)			1.00
Bridge to transplant (BTT)	40 (26)	36 (26)	
Bridge to candidacy	27 (18)	24 (17)	
Destination therapy (DT)	84 (56)	78 (57)	

Baseline characteristics from the as-treated cohort. There were no clinically meaningful differences in any of the baseline characteristics between patients implanted with HM3 and HMII. CRT indicates cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator; HM3, HeartMate 3; HMII, HeartMate II; IABP, intra-aortic balloon pump; ICD, implantable cardioverter defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; and LVAS, left ventricular assist system.

Analysis 3: Clinical Correlates for HRAEs

Analysis of exploratory clinical correlates associated with patients experiencing any HRAEs (HCS>0) for the

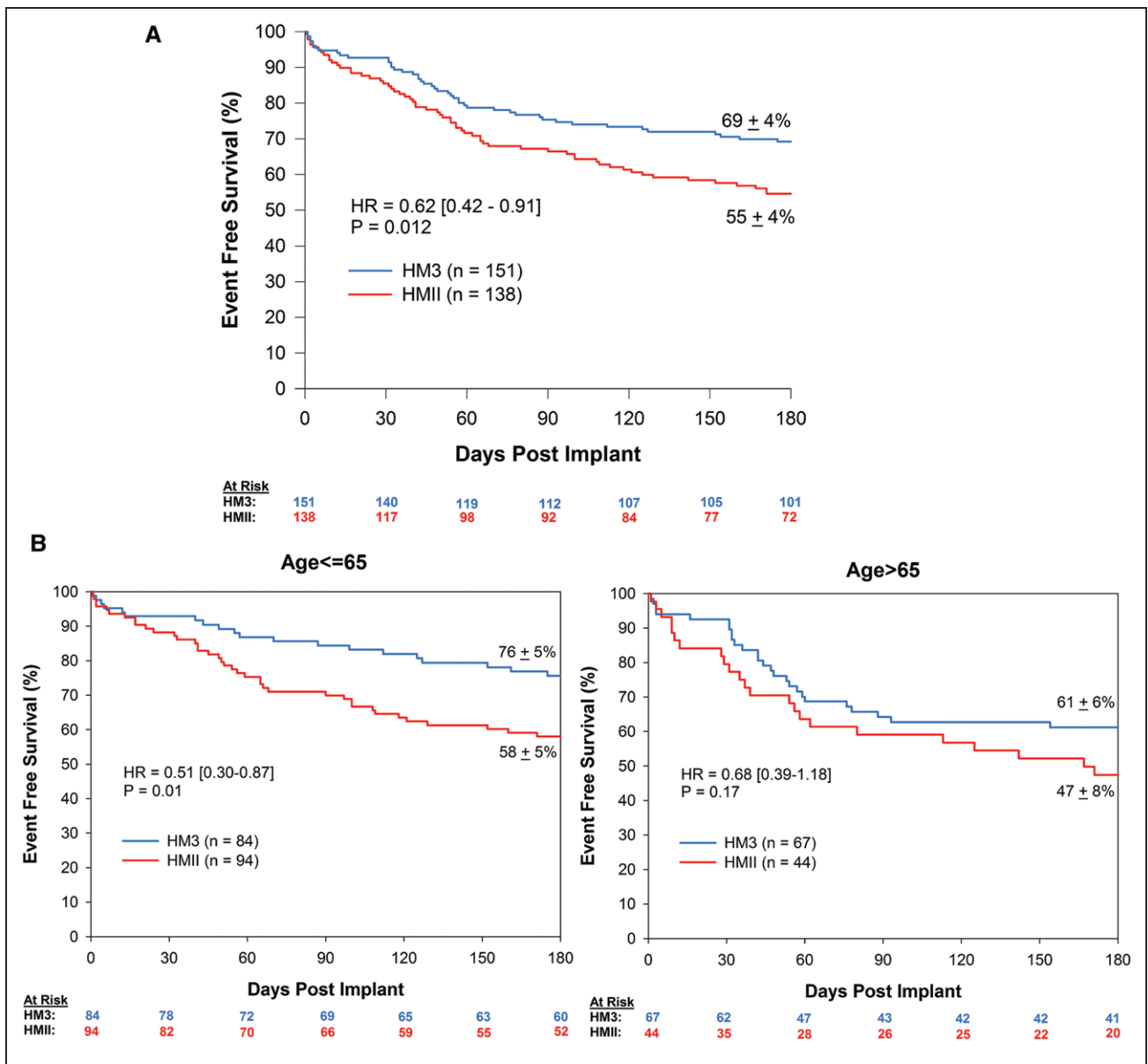


Figure 1. Survival free of HRAE for both HM3 and HMII patients.

A, More patients implanted with HM3 were alive free of HRAE at 6 months compared to patients supported with the HMII. This was associated with a statistically significant 38% reduction in the Hazard Ratio in favor of the HM 3. These numbers correspond to survival probability estimates \pm standard error obtained from the Kaplan-Meier analysis. Hazard ratios were obtained from Cox Proportional Hazards modeling. There were 46 events in the HM3 group, and 62 events in the HMII group. **B**, Survival Free of HRAEs stratified by age. Overall improvement in survival free of HRAEs with the HM3 is more pronounced in patients ≤ 65 years of age. In the Age ≤ 65 subgroup, there were 20 events in the HM3 group and 39 events in the HMII group. In the Age > 65 subgroup, there were 26 events in the HM3 group, and 23 events in the HMII group. There was no interaction of age with device-type ($P=0.49$). HM3 indicates HeartMate 3; HMII, HeartMate II; HR, hazard ratio; and HRAE, hemocompatibility-related clinical adverse event.

total cohort (HMII+HM3) are shown in Table 5. In this univariable analysis, patients who experienced any HRAE or death were more often implanted with the HMII, were older, received the device as destination therapy, were more likely to have a lower INR (<1.5), and were not on aspirin at 30 days postimplant. Figure 4 shows the result of the multivariable analysis of the full cohort of patients. The HMII LVAS, older age, absence of aspirin at 30 days, and a lower INR (<1.5) at 30 days were independently

associated with development of any HRAE or death at 6 months postimplantation. Mean arterial pressure and therapeutic intent were not significant in the final multivariable model.

DISCUSSION

The findings of this investigation demonstrate that the fully magnetically levitated centrifugal flow pump, the

Table 3. Proportion of Patients Who Experienced Either a Hemorrhagic Event, a Thrombotic Event, or Both

Event Type	HM3 (n=151)	HMII (n=138)
Hemorrhagic or thrombotic event, n (%)	43 (28.4)	53 (38.4)
Hemorrhagic only, n (%)	23 (15.2)	25 (18.1)
Thrombotic only, n (%)	11 (7.3)	23 (16.7)
Hemorrhagic and thrombotic, n (%)	9 (6.0)	5 (3.6)

Proportionally, HM3 patients experienced more hemorrhagic events than thrombotic events, whereas HMII patients evenly experienced both hemorrhagic and thrombotic events. HM3 indicates HeartMate 3; and HMII, HeartMate II.

HM3, is associated with a significant increase in freedom from HRAE in comparison with the HMII LVAS at 6 months, driven predominantly by a reduction in nondisabling strokes and any pump thrombosis. Importantly, as previously described,⁶ no evidence of pump thrombosis was noted with the HM3 pump. Furthermore, the HCS, which assesses net burden of events per patient, is nu-

merically lower in those implanted with the HM3 LVAS, although this comparison did not meet conventional levels of statistical significance ($P=0.065$).

Hemocompatibility represents the interaction between the LVAS interface and intrinsic pathophysiology of activation or destruction of circulating blood elements.¹ Clinically, the overall interaction manifests itself as nonsurgical bleeding (predominantly gastrointestinal or nasal) and thromboembolic events (stroke, pump thrombosis, and other systemic embolic events). Importantly, the relationship between events is closely intertwined, because the management to ameliorate one may directly influence the other. Historically, in LVAS trials, these events are reported separately, some counting as efficacy end points and most as adverse events; understanding their interplay, and the accumulation of events in each patient, as well, has therefore been obscured. As in the recent opinion piece, we evaluated hemocompatibility, for the first time, as an aggregate-consolidated end point.¹ Similarly, we used the proposed HCS to allow a closer appreciation of the totality of these complications encountered by the patient.

Table 4. Points Associated With Events Contributing to HCS

HCS	HM3 Cumulative Score	HM3 Patients With Events (Events)	HM3 Score / Patient Median [Max]	HMII Cumulative Score	HMII Patients With Events (Events)	HMII Score / Patient Median [Max]	Odds Ratio (95% CI)	P
Total score	101	43 (55)	0 [10]	137	53 (70)	0 [9]	0.64 [0.39–1.04]	0.08
Tier I	31	27 (31)	0 [2]	33	30 (33)	0 [2]	0.78 [0.44–1.40]	0.46
Bleeding >30D (≤ 2 events)	21	21 (21)	0 [1]	19	19 (19)	0 [1]	1.01 [0.52–1.97]	1.00
Medically managed PT	0	0 (0)	0 [0]	5	5 (5)	0 [1]	-	0.02
Nonstroke neurological event	9	9 (9)	0 [1]	8	8 (8)	0 [1]	1.03 [0.39–2.75]	1.00
Arterial TE with no organ loss	1	1 (1)	0 [1]	1	1 (1)	0 [1]	0.91 [0.06–14.74]	1.00
Tier II	26	12 (13)	0 [4]	32	14 (16)	0 [4]	0.76 [0.34–1.72]	0.54
Bleeding >30D (>2 events)	16	8 (8)	0 [2]	8	4 (4)	0 [2]	1.87 [0.55–6.37]	0.38
Nondisabling stroke	6	3 (3)	0 [2]	24	11 (12)	0 [4]	0.23 [0.06–0.86]	0.026
Arterial TE with organ loss	4	2 (2)	0 [2]	0	0 (0)	0 [0]	-	0.50
Tier IIIA: surgically managed PT	0	0 (0)	0 [0]	36	10 (12)	0 [6]	-	<0.001
Tier IIIB	44	10 (11)	0 [8]	36	9 (9)	0 [4]	1.02 [0.40–2.58]	1.00
Disabling stroke*	36	9 (9)	0 [4]	20	5 (5)	0 [4]	1.69 [0.55–5.16]	0.42
HC-related or inconclusive death	8	2 (2)	0 [4]	16	4 (4)	0 [4]	0.45 [0.08–2.49]	0.43

CI indicates confidence interval; D, days; HC, hemocompatibility; HCS, hemocompatibility score; HM3, HeartMate 3; HMII, HeartMate II; PT, pump thrombosis; and TE, thromboembolic event.

*Of the 9 disabling strokes in the HM3 group, 4 were hemorrhagic and 5 were ischemic strokes. Of the 5 disabling strokes in the HMII group, 3 were hemorrhagic, 1 was ischemic, and 1 was an ischemic stroke that converted to a hemorrhagic stroke. Patients supported with HM3 had significant reduction in medically (tier I) and surgically (tier IIIA) treated pump thrombosis, and in nondisabling strokes, as well (tier II). No other differences were observed. Odds ratios and the P values are based on the 2×2 contingency table associated with patients experiencing an event and patients who did not.

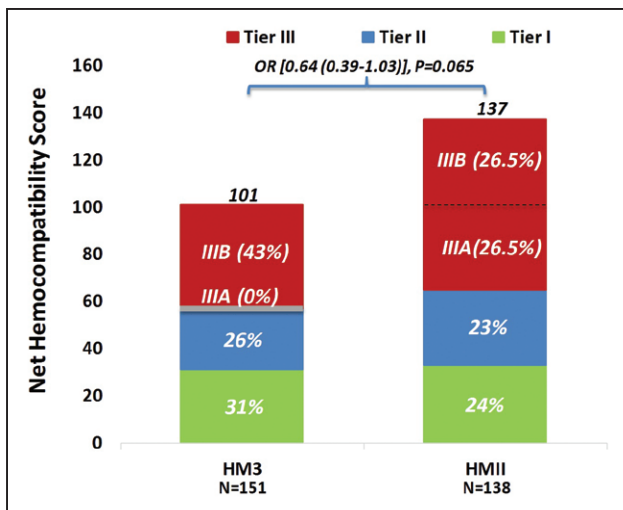


Figure 2. Proportional contribution of the tiered events to the total HCS.

The *P* value and the odds ratio correspond to the differences in the overall score distribution between HM3 and HMII. For the HM3 group, all tier III events were tier IIB, and for the HMII group, the tier III events were equally distributed between tiers IIIA and IIB. HCS indicates hemocompatibility score; HM3, HeartMate 3; HMII, HeartMate II; and OR, odds ratio.

This analysis of the MOMENTUM 3 trial demonstrates the relative frequencies between bleeding, clotting, or both as contributors to the expression of clinical hemocompatibility. We illuminate the fact that a device may predispose predominantly to varying clinical grades of

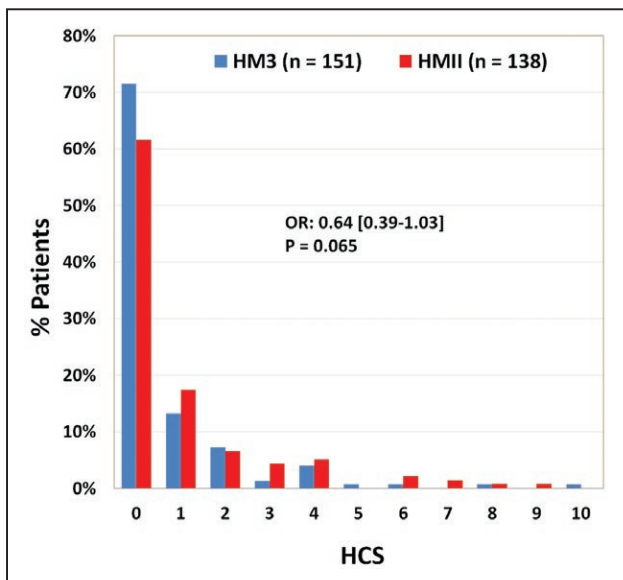


Figure 3. Comparison of HCS distribution between HM3 and HMII.

HM3 patients trended to have a reduced burden of HRAEs in comparison with the HMII. HCS indicates hemocompatibility score; HM3, HeartMate 3; HMII, HeartMate II; HRAE, hemocompatibility-related clinical adverse event; and OR, odds ratio.

Table 5. Univariable Analysis of Factors Impacting Survival Free of Any HRAE

Parameter	Alive and HCS=0 (n=181)	Deceased or HCS>0 (n=108)	<i>P</i> Value
HMII	76 (42)	62 (57)	0.01
Age	61 (51–68)	64 (56–71)	0.01
Female sex	36 (20)	22 (20)	1.00
White race	128 (71)	80 (74)	0.59
Destination therapy	92 (51)	70 (65)	0.03
INTERMACS profile 1–3	153 (85)	88 (81)	0.52
Ischemic etiology	80 (44)	56 (52)	0.22
History of diabetes mellitus	72 (40)	51 (47)	0.22
History of stroke	13 (7)	13 (12)	0.20
History of atrial fibrillation	76 (42)	51 (47)	0.39
LAA closure	18 (10)	5 (5)	0.12
INR at 30 days*	2.2 (1.8–2.8) n=180	2.2 (1.6–2.7) n=93	0.09
INR at 30 days <1.5*	14 (8)	17 (18)	0.01
INR at 30 days >3.0*	28 (16)	8 (9)	0.13
No aspirin at 30 days*	14 (8)	16 (17)	0.03
Daily aspirin dosage*			
81–162 mg	89 (54)	46 (59)	
300–325 mg	70 (42)	27 (35)	
>325 mg	7 (4)	5 (6)	
MAP at 30 days, mmHg*	86 (78–92)	82 (73–90)	0.08

The values shown are n (%), unless otherwise noted. HCS, hemocompatibility score; HM3, HeartMate 3; HMII, HeartMate II; HRAE, hemocompatibility-related clinical adverse event; INR, international normalized ratio; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LAA, left atrial appendage; MAP, mean arterial pressures;

*Sample size for this analysis was 180 patients in the alive and HCS=0 group, and 94 patients in the deceased or HCS>0 group. There was 1 patient in the alive and HCS=0 group, and 14 patients in the deceased or HCS>0 group who were excluded from the analysis. For the analysis incorporating MAP, anticoagulation, and antiplatelet data at 30 days, only patients ongoing on device support at 30 days were included. There were 15 patients who either died (n=14, 5 in HM3, 9 in HMII) or received transplants (n=1, HMII) in the first 30 days.

HRAEs in 1 domain (such as thrombosis) while showing little change in the other domain (such as bleeding). Thus, in our analysis, HM3 patients show their greatest benefit in the domain of thrombosis-related hemocompatibility outcomes as seen in the absence of medically or surgically managed pump thrombosis and marked

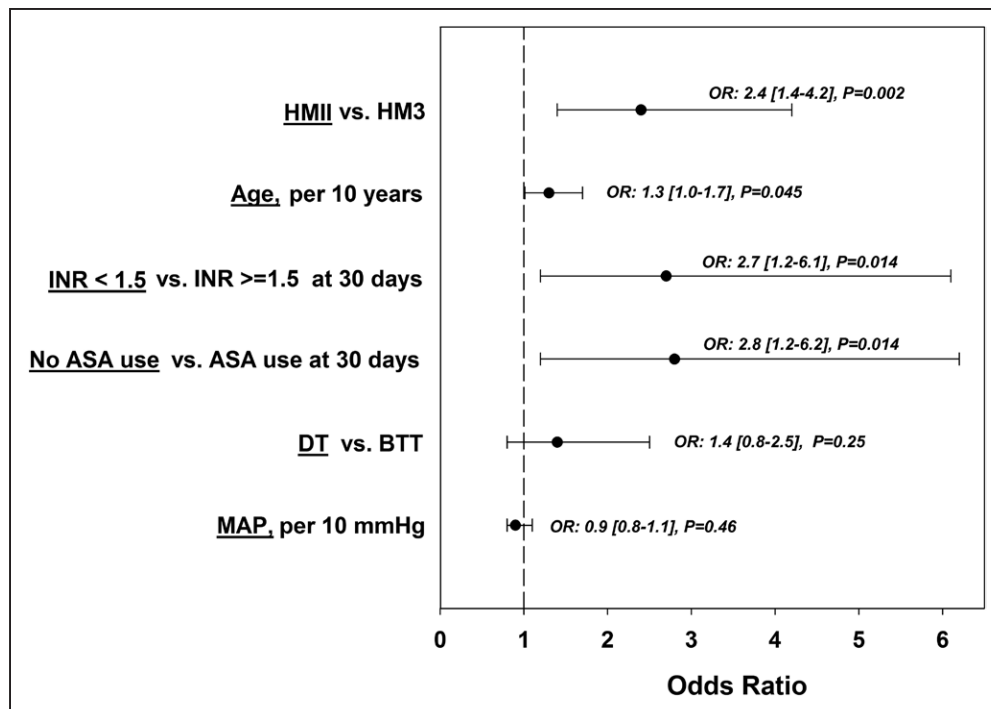


Figure 4. A forest plot of the multivariable logistic regression analysis for all treated patients examining clinical correlates for patients experiencing any HRAEs or death.

Odds ratios (ORs) are shown for each variable entered into the multivariable model. Significant correlates included the use of the HMII LVAS, older age, an INR < 1.5, or no aspirin use at 30 days postimplant. Importantly, there were no significant differences in HRAE outcomes by therapeutic intention (destination therapy [DT] or bridge to transplantation [BTT]) or mean arterial pressure at 30 days postimplant. ASA indicates aspirin; HM3, HeartMate 3; HMII, HeartMate II; HRAE, hemocompatibility-related clinical adverse event; INR, international normalized ratio; LVAS, Left Ventricular Assist System; and MAP, mean arterial pressure.

reduction in nondisabling strokes (typically ischemic in origin). We did not show a difference between the 2 LVAS in disabling strokes, which typically represent a devastating nonsurgical bleeding complication.

Engineering changes in the HM3 that correlate with the observed improved outcomes in the fully magnetically levitated, continuous-flow blood pump exhibit 3 potential advantages¹: a frictionless rotor, with no mechanical bearings subject to wear and tear²; wide gaps between the rotor and casing that allow for permissive blood paths³; and an artificial intrinsic pulse that prevents pump stasis.⁵ These engineering attributes, in vitro, are associated with reduced shear stress and absence of hemolysis or thrombosis in comparison with contemporary devices.¹¹ A proposed explanation for reduced hemocompatibility-related complications with the HM3 include the absence of observed hemolysis, which is directly correlated with the impact of the LVAS on blood element destruction and the effects on high-molecular-weight multimers of von Willebrand factor. These clinical biomarkers are also known to reflect effects of the continuous-flow circulatory interface and potentially herald hemocompatibility-related adverse outcomes.¹² There is now preliminary evidence from an observational in vivo investigation that the HM3 LVAS prevents shearing of the high-molecular-weight multimers compared with the

HMII device, which results in more predictable loss of this biomarker.¹³ Whether these mechanisms directly correlate with improved hemocompatibility or merely represent an epiphenomenon, remains uncertain. However, it is very reassuring to note that, although only half of the HMII LVAS-treated patients are free of a HRAE at 6 months, over two-thirds of HM3 patients demonstrate freedom of this morbidity. Importantly, advancing age appears to influence hemocompatibility-related adverse outcomes. As noted in our investigation, those >65 years of age experience less freedom from hemocompatibility-related adverse outcomes with either LVAS, a finding that has implications for the growing population of lifetime therapy patients who are ineligible for transplantation. Thus, a significant burden of hemocompatibility-related complications remains in the elderly age group, a clinical predicament that will require continued close attention.

The vexing dilemma of hemocompatibility-related adverse outcomes has led investigators to alter management practices in the domain of device function (by driving the speed up or down), managing antiplatelet and anticoagulation regimens disparately, all in attempts to abrogate the net burden of hemocompatibility-related complications. However, experience has suggested that such attempts may be associated with improvement in 1

domain (eg, reduced anticoagulation bridging and running the pump in parallel, rather than in series, to decrease gastrointestinal bleeding) while yielding a worsening in a second critical domain (eg, a surge in pump thrombosis).^{14–17} Nevertheless, attention has shifted to the role of both antiplatelet and anticoagulation protocols in managing the LVAS. A European experience demonstrated that an aspirin-free protocol was not related to an increased rate of thromboembolic adverse events in HMII-treated patients.¹⁸ However, analyses with other devices point to the importance of full antiplatelet therapy in achieving improved neurological outcomes.¹⁹ In our exploratory multivariable analysis, we find evidence for age and antiplatelet and anticoagulation management regimens as important arbiters of HRAE. Surprisingly, blood pressure did not appear to clearly correlate with such HRAE outcomes.

Limitations

The current secondary analysis is based on the short-term cohort of the MOMENTUM 3 study and reflects a small number of patients with a short 6-month follow-up duration. Further validation of the HM3 LVAS and outcome durability will emerge from planned analyses of the ongoing larger cohorts in the trial. The hemocompatibility end point may miss some bleeding events in the perioperative phase (<30 days postimplant) and thus may not fully represent the net burden of hemocompatibility. Note should be made that we included all deaths, thrombosis-related events, and neurological events from implant to 6 months. However, the early postimplant period is typically a time of adjustment of the patient to the device and stabilization of anticoagulation regimens, and it is fraught with predominant surgical complications. Typically, patients stay in-hospital for 3 weeks postimplant, and bleeding events that occur during this time usually represent surgical events or adverse sequelae of a baseline patient predisposition (eg, a gastric ulcer that bleeds). Yet, events in this early period may drive consequences further downstream, and our exploratory findings with respect to antiplatelet and anticoagulation use point in this direction. Importantly, early deaths (within 30 days) would have reduced the opportunity for a subsequent nonsurgical bleeding event. In this regard, it should be noted, that there were 5 deaths in the HM3 group and 9 deaths in the HMII group in the first 30 days. Thus, any disadvantage in the lost opportunity for subsequent HRAE would have been levied in the HM3 group. Another important issue relates to the role of infection and its consequent inflammatory state in driving a change in the hemocompatibility milieu.²⁰ We did not specifically study the interrelationship between these variables for this analysis. This was the first attempt at using the hemocompatibility burden score and could serve to help refine its utility over time.

CONCLUSION

In this secondary analysis of the MOMENTUM 3 trial, the HM3 had a higher freedom from an aggregate of HRAEs at 6 months in comparison with the HMII LVAS, driven predominantly by a reduction in nondisabling strokes and absence of any pump thrombosis. These data provide further evidence that the HM3 LVAS has a more favorable physiological circulatory interface than does the HMII.

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DISCLOSURES

Drs Uriel, Cleveland, Goldstein, and Mehra, serve as National Principal Investigators and contributed equally to the trial conduct and oversight. Dr Mehra is chair of the presentations and publications committee of the trial. Drs Sundareswaran and Sood are employees of Abbott and serve on the publications committee of the trial. All other authors or their institutions have received research and consulting support from Abbott for participation in the trial. Additional disclosures are provided online.

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FOOTNOTES

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Hemocompatibility-Related Outcomes in the MOMENTUM 3 Trial at 6 Months: A Randomized Controlled Study of a Fully Magnetically Levitated Pump in Advanced Heart Failure

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