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Akinobu Itoh
Washington University School of Medicine in St. Louis
et al

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CLINICAL TRIALS

Impact of age, sex, therapeutic intent, race and severity of advanced heart failure on short-term principal outcomes in the MOMENTUM 3 trial

Daniel J. Goldstein, MD,[a] Mandeep R. Mehra, MD,[b] Yoshifumi Naka, MD,[c] Christopher Salerno, MD,[d] Nir Uriel, MD,[e] David Dean, MD,[f] Akinobu Itoh, MD,[g] Francis D. Pagani, MD,[h] Eric R. Skipper, MD,[i] Geetha Bhat, MD,[j] Nirav Raval, MD,[k] Brian A. Bruckner, MD,[l] Jerry D. Estep, MD,[l] Rebecca Cogswell, MD,[m] Carmelo Milano, MD,[n] Lahn Fendelander, MD,[o] John B. O'Connell, MD,[o] Joseph Cleveland, MD[p] and for the MOMENTUM 3 Investigators

From the [a]Department of Cardiothoracic Surgery, Montefiore Medical Center, Bronx, New York, USA; [b]Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston, Massachusetts, USA; [c]Division of Cardiothoracic Surgery, Columbia University College of Physicians & Surgeons, New York, New York, USA; [d]Department of Cardiothoracic Surgery, St. Vincent Heart Center, Indianapolis, Indiana, USA; [e]Section of Cardiology, University of Chicago School of Medicine and Medical Center, Chicago, Illinois, USA; [f]Division of Cardiothoracic Surgery, Piedmont Heart Institute, Atlanta, Georgia, USA; [g]Division of Cardiothoracic Surgery, Washington University School of Medicine, St. Louis, Missouri, USA; [h]Department of Cardiac Surgery, University of Michigan Health System, Ann Arbor, Michigan, USA; [i]Department of Thoracic and Cardiovascular Surgery, Danger Heart and Vascular Institute, Carolinas Medical Center, Charlotte, North Carolina, USA; [j]Division of Cardiology, Advocate Christ Medical Center, Oak Lawn, Illinois, USA; [k]Cardiology Department, Florida Hospital, Orlando, Florida, USA; [l]Department of Cardiology, Houston Methodist Hospital, Houston, Texas, USA; [m]Division of Cardiology, University of Minnesota, Minneapolis, Minnesota, USA; [n]Department of Surgery, Duke Heart Center, Duke University, Durham, North Carolina, USA; [o]Abbott, Chicago, Illinois, USA; and the [p]Division of Cardiothoracic Surgery, University of Colorado School of Medicine, Aurora, Colorado, USA.

KEYWORDS:
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mechanical circulatory support;
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ventricular assist devices

BACKGROUND: Primary outcomes analysis of the Multicenter Study of MagLev Technology in Patients Undergoing MCS Therapy With HeartMate 3 (MOMENTUM 3) trial short-term cohort demonstrated a higher survival rate free of debilitating stroke and reoperation to replace/remove the device (primary end-point) in patients receiving the HeartMate 3 (HM3) compared with the HeartMate (HMII). In this study we sought to evaluate the individual and interactive effects of pre-specified patient subgroups (age, sex, race, therapeutic intent [bridge to transplant/bridge to candidacy/destination therapy] and severity of illness) on primary end-point outcomes in MOMENTUM 3 patients implanted with HM3 and HMII devices.

METHODS: Cox proportional hazard models were used to analyze patients enrolled in the "as-treated cohort" ($n = 289$) of the MOMENTUM 3 trial to: (1) determine interaction of various subgroups on primary end-point outcomes; and (2) identify independent variables associated with primary end-point success.

Reprint requests: Mandeep R. Mehra, MD, Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, 75 Francis Street, Boston, MA 02115. Telephone: +617 732 8534.
E-mail address: mmehra@bwh.harvard.edu

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RESULTS: Baseline characteristics were well balanced among HM3 ($n = 151$) and HMII ($n = 138$) cohorts. No significant interaction between the sub-groups on primary end-point outcomes was observed. Cox multivariable modeling identified age (≤65 years vs >65 years, hazard ratio 0.42 [95% confidence interval 0.22 to 0.78], $p = 0.006$]) and pump type (HM3 vs HMII, hazard ratio 0.53 [95% confidence interval 0.30 to 0.96], $p = 0.034$) to be independent predictors of primary outcomes success. After adjusting for age, no significant impact of sex, race, therapeutic intent and INTERMACS profiles on primary outcomes were observed.

CONCLUSIONS: This analysis of MOMENTUM 3 suggests that younger age (≤65 years) at implant and pump choice are associated with a greater likelihood of primary end-point success. These findings further suggest that characterization of therapeutic intent into discrete bridge-to-transplant and destination therapy categories offers no clear clinical advantage, and should ideally be abandoned.

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The HeartMate 3 left ventricular assist system (HM3 LVAS), an intrathoracic centrifugal continuous-flow pump, has been introduced for the treatment of advanced heart failure and is uniquely engineered to enhance hemocompatibility of the blood–device interface.[1–3] In a 6-month analysis of the largest comparative effectiveness trial of LVAS to date (i.e., the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3 [MOMENTUM 3]), the HM3 was shown to be superior to the HeartMate II (HMII) LVAS in achieving the primary end-point of survival freedom from disabling stroke or reoperation to replace the device.[3] The superiority was largely defined by the absence of suspected or established pump thrombosis in this short-term analysis. Further scrutiny is required to determine whether the principal outcomes observed are similarly noted across various demographic and clinical subgroups.

Among others, there are 5 fundamental sub-groups of interest in determining LVAS outcomes, including age, sex, race, therapeutic intent (bridge to transplant [BTT] or destination therapy [DT]) and disease severity, as adjudicated by the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) clinical profiles. *Age* has been the best studied risk factor and has been shown to be a strong predictor of adverse outcome,[4,5] but its importance has been controversial in the literature.[6–8] Studies on the impact of *sex* on current generation LVASs have suggested a higher risk of neurologic complications in women, although its conclusive effect on survival has not been forthcoming.[9–14] The influence of *race* or ethnicity has received considerable attention in the general cardiovascular realm, but the data remain scarce in the context of mechanical circulatory support.[13,15,16] Greater *disease severity* (based on INTERMACS profile) and DT as *therapeutic intent* have both been associated with a heightened early hazard for death in the most recent INTERMACS annual report.[17]

The primary objectives of this current study were as follows: (1) to determine whether the primary results from the MOMENTUM 3 trial were disparately influenced by any of the 5 pre-specified subgroup variables; (2) to define differences in the key components of various observed outcomes within the subgroups; and (3) to evaluate interactions, if any, between these discrete demographic and clinical variables.

Methods

MOMENTUM 3 clinical trial

The MOMENTUM 3 trial is a prospective, randomized, multicenter clinical investigation comparing the HM3 with the HMII LVAS for the treatment of advanced heart failure in patients refractory to optimal medical therapy.[18] The trial includes 69 participating centers in the United States wherein eligible BTT and DT LVAS candidates were randomly assigned to receive either the HM3 or the HMII, with the primary end-point being survival free of disabling stroke and reoperation to replace or remove the device, assessed at 6 and 24 months post-implantation. The trial details have been reported previously.[6,18] The short-term cohort includes the first 294 patients (with 289 comprising the "as-treated cohort") of 1,028 enrolled in the full trial, wherein the primary end-point was powered to demonstrate non-inferiority of the HM3 to the HMII at 6 months post-implantation.

Subgroup analysis

The MOMENTUM 3 clinical trial protocol pre-specified an analysis of 5 patient subgroups stratified by age, sex, race, therapeutic intent (BTT/DT) and severity of illness (INTERMACS profiles). Age was analyzed as a continuous variable as well as a categorical variable dichotomized at a cut-off age of 65 years. This cut-off is commonly used by transplant programs as the age limit for transplant candidacy, and to make pivotal decisions regarding the therapeutic intent of device implantation as (BTT or DT). The patients in this secondary pre-specified analysis included the 289 patients implanted with the HM3 and HMII LVAS in the "as-treated" population within the MOMENTUM 3 short-term cohort (Figure 1).

Statistical analysis

Continuous variables are depicted as mean ± standard deviation or median (range), and categorical variables are depicted as percent. Comparison of continuous data between groups was performed

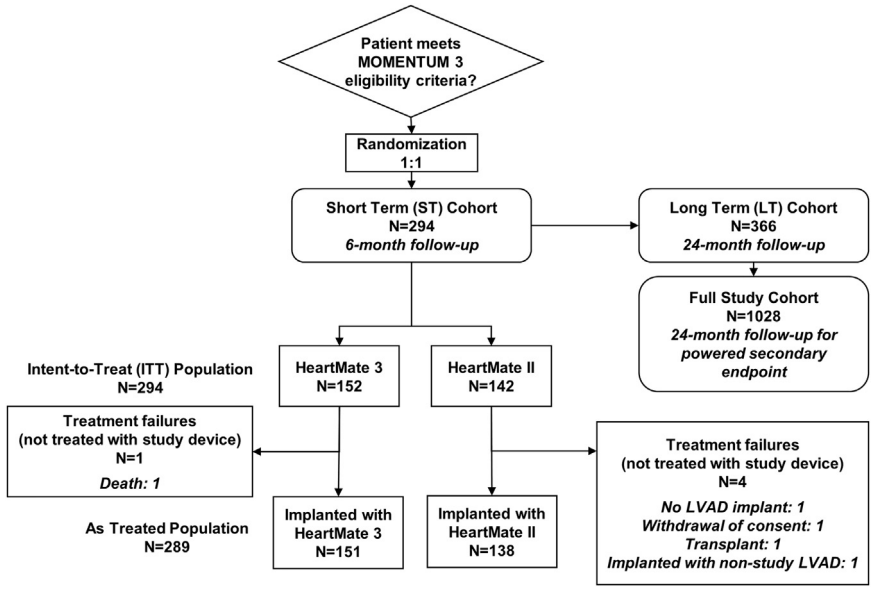

Figure 1 Study cohort.

using Wilcoxon's rank sum test. Comparison of categorical data between groups was performed using Fisher's exact test. The time-to-event analysis was performed using the Kaplan–Meier method.

Two specific analyses were performed using Cox proportional-hazard models in order to:

1. Compare primary end-point (survival free of disabling stroke and reoperation to remove or replace the device) outcomes between HM3 and HMII *within* each of the 5 pre-specified subgroups and to test for significant interactions that may exist between the pre-specified subgroups.
2. Determine independent predictors of primary end-point success in the combined "as-treated" cohort of both HM3 and HMII patients. Pump type and the 5 pre-specified subgroups were entered simultaneously as covariates into the multivariable model. This approach was also utilized to evaluate the relationship between age (as continuous variable), pump type and the other 4 pre-specified subgroups (therapeutic intent, sex, INTERMACS profile and race) on primary end-point outcomes in the combined cohort. Two-sided $p < 0.05$ was considered significant.

Lastly, an analysis comparing baseline characteristics and adverse events was performed in the patient subgroups identified as having statistically significant independent predictors of primary end-point outcomes. All events occurring within 6 months post-implant (not just the first end-point event encountered) are reported.

Results

Baseline characteristics

Two hundred eighty-nine patients (151 with HM3, 138 with HMII) formed the "as-treated" cohort for this analysis. Baseline characteristics are depicted in Table 1. More than 85% of the patients in both cohorts were receiving intravenous inotropic support and >10% were on an intra-aortic balloon pump at the time of randomization. The majority of patients were classified as INTERMACS Profile 2 or 3, and a majority of the patients in both groups were implanted with DT as the therapeutic intent.

Primary end-point

A total of 49 patients in the "as-treated" cohort failed the primary end-point. Table S1 (refer to Supplementary Material online at www.jhltonline.org/) depicts the first event that contributed to primary end-point failure and the total number of disabling strokes, reoperations for device malfunction and deaths for HM3 and HMII patients.

Analysis 1: Comparison of outcomes (HM3 vs HMII) within patient subgroups

Figure 2 depicts comparison of hazard ratios and their interaction p-values for each of the 5 pre-specified subgroups. No significant interaction in primary end-point outcomes was observed between patient subgroups.

Analysis 2: Multivariable analysis of primary end-point outcomes

Figure 3 shows the results of the multivariable analysis of subgroups impacting primary end-point success in the full cohort (HMII+HM3) of patients. All covariates were entered simultaneously into the Cox proportional hazards model. Age and device type were the 2 primary independent predictors of primary end-point success. When device type and age are accounted for, neither sex, gender, therapeutic intent nor severity of illness were predictive of primary outcome success. Furthermore, when age was analyzed as a continuous variable, the HM3 retained a lower estimated risk of primary end-point failure compared with the HMII over the entire age range of patients of 20 to 80 years (Figure 4). A similar analysis of primary end-point outcomes as a function of age, but stratified by therapeutic

Table 1 Baseline Characteristics

Characteristic	HeartMate 3 ($n = 151$)	HeartMate II ($n = 138$)
Age (years)	64 (19 to 81)	61 (24 to 78)
Male sex	120 (79)	111 (80)
Race		
White	103 (68)	105 (76)
Black	37 (25)	23 (17)
Other[a]	11 (7)	10 (7)
Body surface area (m^2)	2.1 ± 0.3	2.1 ± 0.3
Ischemic cause of heart failure	68 (45)	68 (49)
History of stroke	12 (8)	14 (10)
Concomitant medication or intervention		
Intravenous inotropic agents	131 (87)	118 (86)
Diuretics[b]	133 (88)	133 (96)
ACE inhibitor	37 (25)	37 (27)
Angiotensin II receptor antagonist	10 (7)	18 (13)
β-blocker	91 (60)	77 (56)
CRT/CRT-D	59 (39)	50 (36)
ICD/CRT-D	100 (66)	97 (70)
IABP	18 (12)	18 (13)
LVEF (%)	17.1 ± 5.0	17.4 ± 4.9
Arterial blood pressure (mm Hg)		
Systolic[c]	110 ± 16	106 ± 12
Diastolic	67 ± 10	66 ± 10
Mean	81 ± 11	79 ± 10
PCWP (mm Hg)	23 ± 9	22 ± 9
Cardiac index (liters/min/m^2)	1.9 ± 0.5	2.0 ± 0.7
PVR (Wood units)	3.2 ± 1.7	3.1 ± 1.6
RAP (mm Hg)	10 ± 6	11 ± 7
Serum sodium (mmol/liter)	135.6 ± 3.9	135.0 ± 4.2
Serum creatinine (mg/ml)	1.4 ± 0.4	1.4 ± 0.4
INTERMACS profile		
1	1 (1)	2 (1)
2	50 (33)	43 (31)
3	76 (50)	69 (50)
4	22 (15)	22 (16)
5 to 7[d]	2 (1)	2 (1)
Intended use of device at implant		
Bridge to transplant	40 (26)	36 (26)
Bridge to candidacy	27 (18)	24 (17)
Destination therapy	84 (56)	78 (57)

Data are expressed as median (range), number (%) or mean ± standard deviation. ACE, angiotensin-converting enzyme; CRT-D, cardiac resynchronization therapy-defibrillator; IABP, intra-aortic balloon pump; ICD, implantable cardioverter-defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

[a]Includes Asian, Native Hawaiian or Pacific Islanders.
[b]Diuretic use was statistically significant ($p = 0.01$).
[c]Systolic blood pressure was statistically significant (p = 0.008).
[d]There were no subjects with INTERMACS Profiles 6 or 7 in either group.

intent, level of illness, sex and race for both HM3 and HMII, are shown in Figure 5A–D. There were minimal differences in outcomes between these subgroups over the entire age range for both the HM3 and HMII patient cohorts.

Analysis 3: Differences in patient characteristics and outcomes stratified by age

Because age was found to be a strong predictor of outcomes, additional analyses were performed comparing baseline characteristics and adverse events between older (age >65 years) and younger (age ≤65 years) patients. Tables 2 and 3 depict differences in baseline characteristics and all major adverse events for the combined cohort of HM3 and HMII patients. Older patients were more often Caucasian, had an ischemic etiology of heart failure, had worse baseline renal function, and were more likely to have received LVAS as DT. Moreover, older patients were more likely to have a bleeding event, particularly in the gastrointestinal tract, have a higher incidence of disabling stroke, and were more likely to develop renal failure. On the other hand, the incidence of right heart failure, infection and suspected pump thrombosis was not different between groups.

Discussion

The 3 main findings of our study are as follows: First, the superiority of the HM3 device over the HMII pump for the primary outcome end-point, as noted in the MOMENTUM 3 trial publication, is not due to a performance bias within any single one the 5 pre-specified subgroups associated with age, sex, therapeutic intent or severity of illness.[3] Second, in multivariate analyses incorporating the 5 pre-specified variables and pump type, only HM3 LVAS and younger age (<65 years) emerged as independent predictors of primary end-point success. Third, when age at device implant was examined in combination with the other pre-specified variables, no discernible changes in achieving primary end-point success were noted.

The impact of age on outcomes after LVAS implantation has received considerable attention in the literature. Sandner and colleagues retrospectively reviewed their institutional experience with 3 different continuous-flow LVASs as BTT. Age >60 years emerged as the only independent predictor of post-LVAS death. Moreover, the older cohort had a lower incidence of successful bridging and a greater likelihood of post-operative renal failure. Interestingly, however, post-transplantation survival up to 5 years was similar.[5] Lushaj et al dichotomized their 128 LVAS recipients (all but 1 received the HMII pump) into those <65 and >65 years of age. The older cohort had a statistically higher incidence of post-operative cerebrovascular accident but similar survival at 2 years.[4] Kim et al[6] and Huang et al[7] both demonstrated a lack of impact of age on LVAS outcomes; however, one of these studies was an observational registry-type study that included highly experienced centers, whereas the other investigation involved an earlier generation device analysis of the now-decommissioned Novacor pump. A more contemporary study by Cowger and colleagues with the HMII LVAS demonstrated advancing age as a significant risk marker for poor outcome.[19] Similarly, our results confirm this association independent of device type and suggest that age >65 years portends a worse outcome post-LVAS, irrespective of device choice.

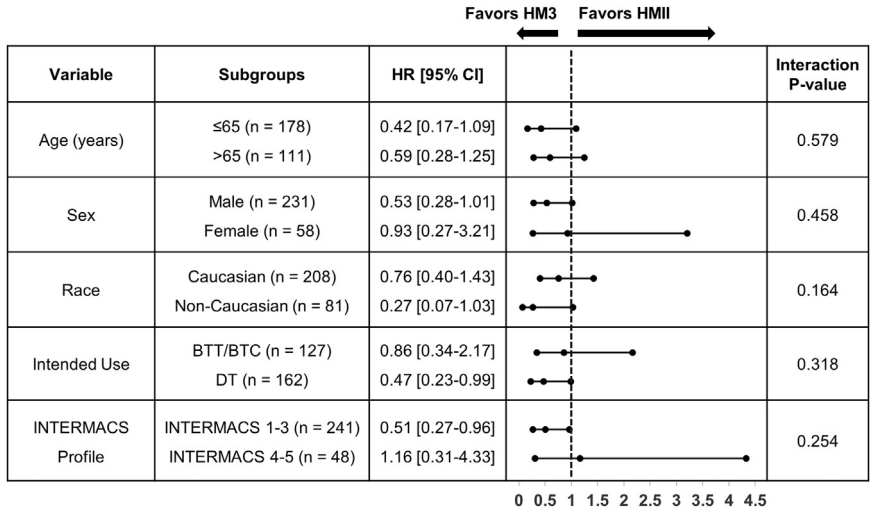

Figure 2 Hazard ratios for event-free survival in the pre-specified subgroups. Hazard ratios (HRs) are presented for HM3 vs HMII.

Greater consistency in outcomes has been reported when examining the impact of sex on outcomes after LVAD implantation. Uniformly, no difference in survival has been seen between females and males.[9–14] A higher incidence of neurologic complications, however, has been reported by some investigators,[9–11] but not others.[12–14] In the present study, and in support of the aforementioned studies, gender had no impact in primary end-point outcomes (which included survival and disabling stroke), even when adjusted for age. It remains to be seen whether this represents the shorter duration of follow-up (6 months) or lower rate of events encountered.

Race has only been meagerly studied in the durable LVAS realm. Tsiouris and colleagues compared post-LVAS survival among 32 black and 56 white patients[16]; van Meeteren and colleagues assessed survival at up to 5 years in 586 white and 112 black patients[13]; and Aggarwal et al contrasted survival differences between 34 white and 33 black patients.[15] Our study has confirmed the observation that race does not substantially alter or influence post-operative LVAS outcomes.

MOMENTUM 3 is the first clinical trial to enroll an "all-comer" population including BTT or DT, thus allowing for a comparative assessment of clinical outcomes between contemporaneous enrollees. Until now, most registry analyses suggest a gradient of outcome between BTT and DT patients such that event-free survival is lower in those receiving LVAS with a lifelong intent.[17,20] Uniquely, our analysis has demonstrated that outcomes are not disparately influenced by therapeutic intent alone, at least with regard to the use of the HM3 LVAS. The key variable influencing outcome is that of age and not the artificial boundaries created by therapeutic intent, which often are dynamic and change over time. These findings once again support the notion that use of such discrimination in discrete categories is unwise clinically and an LVAS should be used as a "therapeutic strategy in the journey of disease progression."[21]

As one would surmise, INTERMACS score as a measure of severity of illness has been shown to correlate with

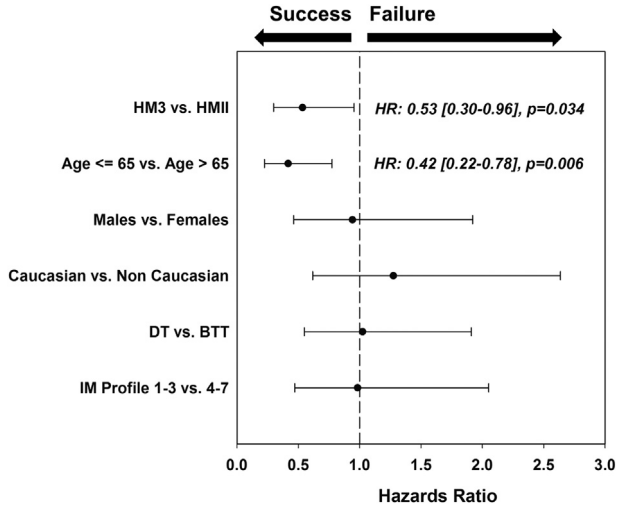

Figure 3 Multivariable analysis of impact of subgroups on primary end-point success.

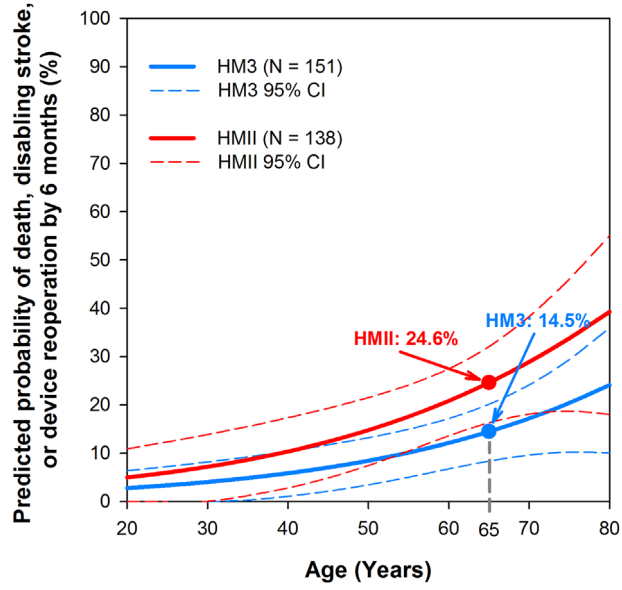

Figure 4 Estimated risk of primary end-point failure in HM3 and HMII patients over the age range of 20 to 80 years.

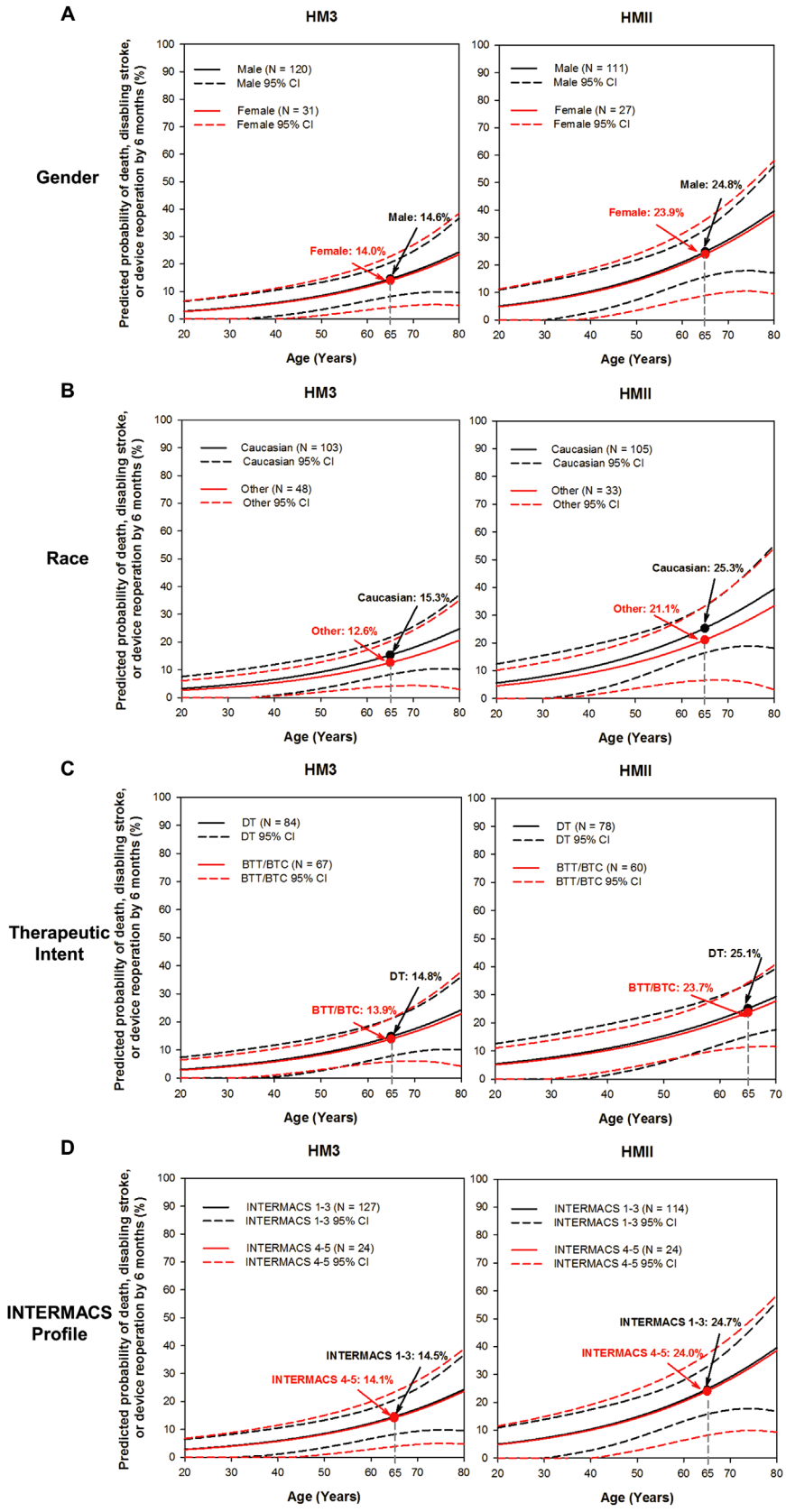

Figure 5 Estimated risk of primary end-point failure in HM3 and HMII patients over the age range of 20 to 80 years, stratified by: (A) gender; (B) race; (C) therapeutic intent; and (D) INTERMACS profile.

outcomes with patients with higher acuity of illness (INTERMACS Profiles 1 or 2) faring worse after durable LVAS implantation. MOMENTUM 3 includes a distribution of patients with an INTERMACS profile that is quite typical for those implanted with current generation LVASs, as the majority of patients were in the higher acuity group (85% in

Table 2 Differences in Baseline Characteristics: Age ≤65 vs Age >65 Years

Characteristic	Age ≤65 years ($n = 178$)	Age >65 years ($n = 111$)
Male sex	147 (83)	84 (76)
White race[a]	118 (66)	90 (81)
Ischemic cause of heart failure[b]	75 (42)	61 (55)
LVEF	17.0 ± 5.2	17.6 ± 4.5
PCWP (mm Hg)	23 ± 9	22 ± 9
Cardiac index (liters/min/m^2)	1.9 ± 0.6	2.0 ± 0.6
RAP (mm Hg)	11 ± 7	10 ± 5
Serum creatinine (mg/ml)[c]	1.3 ± 0.4	1.5 ± 0.4
INTERMACS profile		
1	3 (2)	0 (0)
2	56 (31)	37 (33)
3	92 (52)	53 (48)
4	25 (14)	19 (17)
5 to 7	2 (1)	2 (2)
Therapeutic intent[d]		
Bridge to transplant	63 (35)	13 (12)
Bridge to candidacy	39 (22)	12 (11)
Destination therapy	76 (43)	86 (77)

Data are expressed as number (%) or mean ± standard deviation. GI, gastrointestinal; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure.

[a]Race ($p = 0.02$).

[b]Ischemic etiology ($p = 0.04$).

[c]Serum creatinine ($p < 0.01$).

[d]Therapeutic intent ($p < 0.01$).

INTERMACS Profiles 1, 2 or 3). The recent INTERMACS annual report gathered from >20,000 pump implants showed a 55% and 37% increase in early mortality for INTERMACS Profiles 1 and 2, respectively.[17] We did not find that INTERMACS level was independently predictive of primary end-point outcome; however, as would be expected in a clinical trial with strict inclusion criteria, we did not enroll sufficient patients in the "crash-and-burn" cardiogenic shock (INTERMACS Profile 1) category.

As with any investigation, there are limitations to our analyses. First and foremost, this investigation represents an early experience with the HM3 device, as the trial represents the first use of this new LVAS in the United States. Second, the analysis was limited to a small cohort of enrollees with follow-up to only 6 months. A longer duration of follow-up and greater number of enrollees will be needed to assess the effects of the various subgroups on individual components of clinical outcome, particularly all-cause survival. This will require a further re-examination of this issue once the larger trial experience is available. Also, with only 49 patients experiencing a primary end-point failure event, simultaneous inclusion of all 5 subgroup variables and device type into the multivariable analysis may have led to overfitting of the model.

Table 3 Differences in Key Adverse Events: Age ≤65 vs Age >65 Years

	Age ≤65 ($n = 178$)		Age >65 ($n = 111$)		
Adverse event	Patients (%)	Events	Patients (%)	Events	p
Any bleeding	53 (30%)	90	51 (46%)	105	0.006
GI bleeding	22 (12%)	39	23 (21%)	44	0.07
Any stroke	14 (8%)	16	13 (12%)	13	0.30
Hemorrhagic stroke	6 (3%)	6	6 (5%)	6	0.55
Ischemic stroke	10 (6%)	10	7 (6%)	7	0.80
Disabling stroke	5 (3%)	5	9 (8%)	9	0.05
Other neurologic event	10 (6%)	10	7 (6%)	7	0.80
Suspected thrombosis	10 (6%)	12	4 (4%)	6	0.58
Right heart failure	43 (24%)	46	36 (32%)	39	0.14
Renal failure	9 (5%)	10	20 (18%)	20	<0.001
Major Infection	63 (35%)	90	48 (43%)	86	0.21
Drive-line infection	21 (12%)	23	6 (5%)	9	0.10

GI, gastrointestinal.

In conclusion, this pre-specified, secondary 6-month analysis of the MOMENTUM 3 trial has demonstrated that the observed superiority of the HM3 compared with the HMII LVAS is not the result of a singular influence of any particular pre-specified subgroup analyzed. We have further determined that younger age at LVAS implant coupled and use of the HM3 LVAS are distinctly favorable factors with regard to primary end-point success. Analysis of the long-term experience in the trial will be necessary to better define the impact of sub-group variables on all-cause survival.

Disclosure statement

D.J.G., M.R.M., Y.N., C.T.S., N.U., J.E., R.C. and J.C. are consultants for Abbott. C.A.M. and R.C. are on the speakers bureau for Abbott. R.C. is on the speakers bureau and heart failure advisory board for Medtronic. L.F. and J.B.O. are employees of Abbott. The MOMENTUM 3 trial is funded by Abbott (ClinicalTrials.gov NCT02224755).

Appendix A. Supporting information

Supplementary materials associated with this article can be found in the online version at www.jhltonline.org.

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