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ORIGINAL RESEARCH

Influence of Atrial Fibrillation on Functional Tricuspid Regurgitation in Patients With HeartMate 3

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BACKGROUND: Functional tricuspid regurgitation (TR) can occur secondary to atrial fibrillation (AF). The impact of AF on functional TR and cardiovascular events is uncertain in patients with left ventricular assist devices. This study aimed to investigate the effect of AF on functional TR and cardiovascular events in patients with a HeartMate 3 left ventricular assist device.

METHODS AND RESULTS: We retrospectively reviewed 133 patients who underwent HeartMate 3 implantation at our center between November 2014 and November 2018. We excluded patients who had undergone previous or concomitant tricuspid valve procedures and those whose echocardiographic images were of insufficient quality. The primary end point was death and the presence of a cardiovascular event at 1 year. We defined cardiovascular event as a composite of death, stroke, and hospital readmission due to recurrent heart failure and significant residual TR as vena contracta width ≥3 mm. In total, 110 patients were included in this analysis. Patients were divided into 3 groups: no AF (n=51), paroxysmal AF (n=40), and persistent AF (PeAF) (n=19). Kaplan-Meier analysis showed that patients with PeAF had the worst survival (no AF 98%, paroxysmal AF 98%, PeAF 84%, log-rank P=0.038) and event-free rate (no AF 93%, paroxysmal AF 89%, PeAF 72%, log-rank P=0.048) at 1 year. Thirty-one (28%) patients had residual TR 1 month after left ventricular assist device implantation. Patients with residual TR had a significantly poor prognosis compared with those without residual TR (log-rank P=0.014).

CONCLUSIONS: PeAF was associated with increased mortality, cardiovascular events, and residual TR compared with no AF and paroxysmal AF.

Key Words: atrial fibrillation ■ echocardiography ■ heart failure ■ left ventricular assist device ■ tricuspid regurgitation

Treatment with a left ventricular assist device (LVAD) is used widely for patients with refractory heart failure (HF) as a bridge to transplantation and as a destination therapy.[1,2] Advances in LVAD technology have led to improvement in its efficacy and patient outcomes, and the MOMENTUM 3 (Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3) randomized clinical trial demonstrated superiority of the HeartMate 3 (HM3) device to the HeartMate II device in terms of survival without a disabling stroke or reoperation to remove or replace a malfunctioning pump.[2,3] However, right HF has remained an important cause of death after LVAD implantation. The severity of tricuspid regurgitation (TR) before LVAD implantation is one of the risk factors for right HF.[4,5] Moderate or more functional TR is common in patients with end-stage HF and is independently associated with worse survival. Functional TR occurs because of annulus enlargement and leaflet tethering secondary to right ventricular (RV) overload, pulmonary hypertension, and left ventricular (LV) dysfunction.[6,7] In addition, functional TR can occur because of right atrial (RA) enlargement and

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CLINICAL PERSPECTIVE

What Is New?

- Persistent atrial fibrillation (AF) was associated with increased mortality, cardiovascular events, and residual tricuspid regurgitation (TR) compared with no AF and paroxysmal AF in patients with HeartMate 3 (HM3).
- Patients with persistent AF had the largest right atrium and tricuspid valve annulus diameter and the highest prevalence of significant residual TR after HM3 implantation.
- Significant residual TR after HM3 implantation was associated with cardiovascular events.

What Are the Clinical Implications?

- More intensive therapy may be required for patients with HM3 and persistent AF. Close follow-up should be performed in patients with HM3 and residual TR.
- Larger, prospective multicenter studies are required to determine the optimal intervention in patients with AF as well as to investigate the benefit of concomitant tricuspid valve procedures for patients with persistent AF and TR.

Nonstandard Abbreviations and Acronyms

HM3	HeartMate 3
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
PAF	paroxysmal AF
PeAF	persistent AF
RA	right atrial/atrium
TR	tricuspid regurgitation
TTE	transthoracic echocardiogram
TV	tricuspid valve
VC	vena contracta

tricuspid annular dilatation caused by AF.[7,8] AF is common in patients with end-stage HF.[9,10] However, the impact of AF on the functional TR of patients with LVADs is uncertain. Therefore, this study aimed to investigate the effect of AF on TR and cardiovascular events in patients with HM3 implantation.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Patients and Data Collection

We retrospectively reviewed 261 consecutive patients who underwent durable LVAD implantation at Columbia University Medical Center between November 2014 and November 2018. Because the prognostic outcome and change of TR and tricuspid valve (TV) geometry after LVAD implantation can differ between device types,[2,3,11] we included only patients who received the HM3 (Abbott Inc., Chicago, IL). Patients were included when they had a preoperative (≤2 months before LVAD implantation) transthoracic echocardiogram (TTE) with interpretable imaging of the TV. We excluded patients with a history of TV procedures and those who underwent concomitant TV surgery. Concomitant TV surgery was performed at the surgeon's discretion based on the severity of TR, regardless of AF type. Clinical, laboratory, and hemodynamic data were collected from a review of our electronic medical records.

The Institutional Review Board of Columbia University Medical Center approved this retrospective study with a waiver of informed consent.

AF and Outcome

The AF diagnosis was based on clinical history, electrocardiographic data, and device interrogation. AF type was classified into 2 groups: paroxysmal AF (PAF) and persistent AF (PeAF). Patients with PAF were defined as those with a history of self-terminating AF or AF lasting ≤7 days at the time of LVAD implantation. Patients with PeAF were defined as those with AF lasting >7 days at the time of LVAD implantation.[9,10] None of the patients included underwent a maze procedure. Patients with AF were managed with medical treatment.

The primary end point was death and the presence of a cardiovascular event at 1 year. We defined cardiovascular event as a composite of death, stroke, and hospital readmission due to recurrent HF after the index hospitalization for LVAD implantation. If a patient had more than one of these events, the event that occurred first was noted as the cardiovascular event. Recurrent HF was defined as right HF according to the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) definition, which is based on symptoms or findings of right HF and elevated central venous pressure. The specific criteria are (1) direct measurement of central venous pressure by right heart catheterization showing RA pressure >16 mm Hg, or a significantly dilated inferior vena cava with absence of inspiratory variation on echocardiography or clinical findings of elevated jugular venous distension at least halfway up the neck in the upright position; and (2) further manifestations of elevated central venous pressure

as characterized by clinical findings of peripheral edema, presence of ascites or palpable hepatomegaly on physical examination or diagnostic imaging, or laboratory evidence of impaired hepatic (total bilirubin level >2.0 mg/dL) or renal dysfunction (creatinine level >2.0 mg/dL).[12] The clinical examinations and diagnoses were performed in all patients by specialist HF cardiologists. In the present study, HF events related to device failure, such as device thrombosis, inflow or outflow obstruction, and driveline fracture or infection, were excluded.[5,13]

TTE Examination

All TTE examinations were performed by a trained, registered cardiac sonographer before and 1 month after LVAD implantation, and the echocardiographic parameters were interpreted by experienced attending physicians at our institution. Any disagreements were resolved on consensus reading. We routinely performed TTE-guided speed optimization at least 2 weeks after LVAD implantation, before hospital discharge. Device speed was optimized according to the recommendations at TTE.[14] Optimal pump speed was defined as the highest speed allowing neutral alignment of the interventricular septum and intermittent aortic valve opening without increased mitral regurgitation. If a patient underwent several TTEs during the study period, only data from the TTE closest to the LVAD implantation date and from that performed at 1 month after implantation were analyzed.

Functional TR was identified in the absence of an abnormal TV leaflet.[7] TR was evaluated quantitatively using the vena contracta (VC) width, by averaging the measurements of 2 orthogonal planes (parasternal off-axis view for the RV and apical 4-chamber view).[6,15] TR severity was graded into 3 groups by VC width: no–mild (<3 mm), moderate (3–6.9 mm), and severe (≥7 mm), according to the guidelines of the American Society of Echocardiography.[15] Residual TR was evaluated 1 month after LVAD implantation. Significant and residual TR after LVAD implantation was defined as at least moderate TR with a biplane VC width of ≥3 mm. We assessed the effective regurgitant orifice area using the proximal isovelocity surface area method in patients with significant functional TR. The TV annulus diameter at the time of the maximum TV diastolic opening and systolic TV tenting height were measured in the apical 4-chamber view.[16–18] The RA volume index was calculated using single-plane disk summation techniques in a dedicated apical 4-chamber view. The RV end-diastolic dimensions were measured using modified apical 4-chamber views encompassing the entire RV. The RV function was evaluated quantitatively using RV fractional area change and the peak systolic tissue velocity of the RV lateral wall measured at the tricuspid annulus.[19] The LV end-diastolic dimension, LV end-systolic dimension, LV ejection fraction, left atrial (LA) dimension, LA volume index, and LV mass index were measured in accordance with previously published guidelines.[20] Significant mitral regurgitation was defined as at least moderate mitral regurgitation with an average VC width (from 2 orthogonal views) of ≥3 mm.[15] All TTE measurements were performed on at least 3 different beats and averaged.

Statistical Analysis

Results are presented as mean values and SDs for continuous variables. Categorical variables are presented as numbers and proportions. Results were considered significant at a threshold of $P<0.05$. The normality of the data was assessed using the D'Agostino-Pearson test. Student *t* test (for normally distributed data) or the Mann-Whitney test (for non-normally distributed data) was used for the comparison of continuous variables. The chi-square test was used for comparing categorical variables between more than 2 groups. The 1-way analysis of variance with post hoc Tukey test or the Kruskal-Wallis test with post hoc Conover test was used for continuous variables, as appropriate. Paired *t* tests and Wilcoxon tests were used for the comparison of baseline and follow-up data, as appropriate. The Kaplan-Meier method was used to estimate mortality and cardiovascular event rates, and groups were compared using the log-rank test. Statistical analyses were performed with SAS (version 9.4; SAS Institute, Cary, NC) and MedCalc (version 15.8; MedCalc Software, Ostend, Belgium).

RESULTS

Patients' Characteristics

A total of 261 patients underwent durable LVAD implantation during the 4-year study period. The flow chart of the study population is shown in Figure 1. We selected 133 patients who underwent HM3 implantation during the period. Of these patients, 3 patients with a history of TV procedures and 12 patients who underwent concomitant TV surgery at the time of LVAD implantation were excluded. Among the 12 patients who underwent concomitant TV surgery, there were no significant difference in the prevalence of each AF type (no AF versus PAF versus PeAF, 6 [10%] versus 4 [8%] versus 2 [8%]; $P=0.92$). Of the remaining 118 patients, 4 with missing echocardiographic data and 4 whose images were of insufficient quality to assess the TV were excluded. Therefore, we studied 110 patients who underwent HM3 implantation and had no history of a TV procedure.

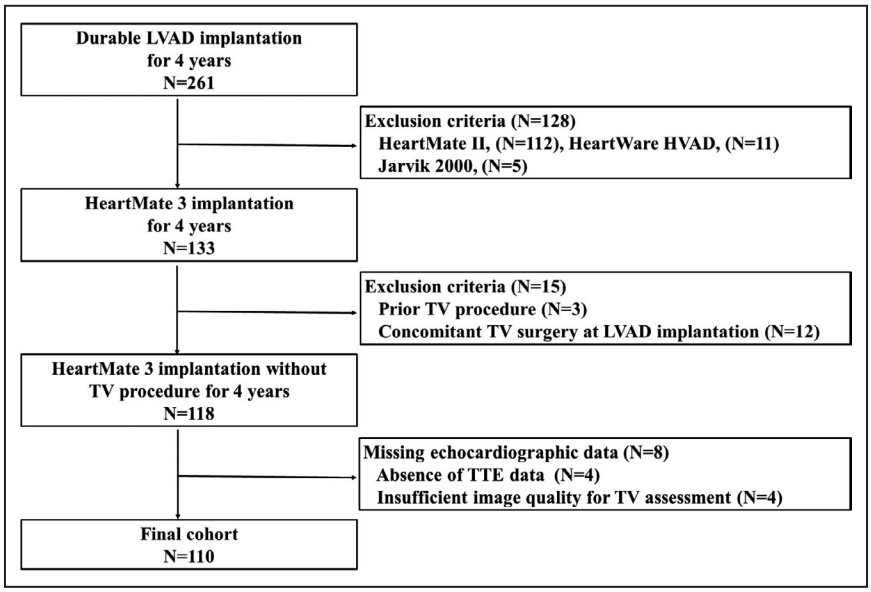

Figure 1. Flow diagram of patient selection.
LVAD indicates left ventricular assist device; TTE, transthoracic echocardiogram; and TV, tricuspid valve.

Patients' characteristics are presented in Table 1. The mean cohort age was 61±12 years and 18 patients (16%) were female. The etiology of HF was ischemic cardiomyopathy in 45 patients (41%). Among all patients of the cohort, 51 (46%), 40 (36%), and 19 (17%) patients had no AF, PAF, and PeAF at the time of LVAD implantation, respectively. There were no significant differences with respect to age, sex, INTERMACS profile level, etiology of HF, and treatment strategy between the groups. The PAF and PeAF groups had a decreased cardiac index compared with the no AF group (no AF versus PAF versus PeAF; 2.0±0.5 versus 1.8±0.5 versus 1.7±0.5 L/min per m^2; P=0.03).

Changes in Echocardiographic Parameters

We summarize baseline and follow-up echocardiographic parameters in Table 2 and Table S1. On the baseline TTE, patients in the PeAF group had the largest TV annulus diameter (P<0.001) and LA size (P=0.01) whereas there were no significant differences in TV tenting height, RV end-diastolic dimension, RV fractional area change, and TR severity among the groups. At the follow-up TTE, patients with PeAF had the largest TV annulus diameter (P<0.001), RA size (P=0.05), and LA size (P=0.001), and they had the highest prevalence of significant residual TR (P=0.03). Thirty-one patients (28%) had significant residual TR in the present study. Of these, 11 (22%) patients had no AF, 10 (25%) had PAF, and 10 (53%) had PeAF (P=0.03). Comparing baseline and follow-up TTEs, there were no significant changes in RV end-diastolic dimensions (48.9±7.2 versus 47.7±6.8 mm, P=0.07), RV fractional area change (27.9±6.9 versus 27.2±6.2%, P=0.36), RV systolic excursion velocity (8.2±2.5 versus 8.2±2.2 cm/s, P=0.90), and RA volume index (41.6±20.4 versus 42.9±18.7 mL/m^2, P=0.69). However, LV and LA sizes decreased and LV ejection fraction improved significantly in the entire cohort (Table S1). Increased TV annulus diameter and exacerbation of TR severity were exhibited in the PeAF group, but there were no significant changes in the no AF group (Figures 2 and 3).

Prognostic Outcomes for AF Groups and Significant Residual TR

In the present study, 5 patients died within 1 year: 1 patient (2%) in the no AF group, 1 (3%) in the PAF group, and 3 (16%) in the PeAF group. The causes of death were right HF (3 patients), stroke (1 patient), and withdrawal of care due to cancer (1 patient) (Table 3). Twelve patients had cardiovascular events, consisting of death (3 patients), stroke (2 patients), and hospital readmission due to recurrent HF (7 patients) within 1 year after HM3 implantation (Table 3). Kaplan-Meier curve analysis demonstrated 1-year survivals of 98%, 98%, and 84% in the no AF, PAF, and PeAF groups, respectively (log-rank test, P=0.038) (Figure 4). The curve analysis also showed 1-year event-free rates of 93%, 89%, and 72% in the no AF, PAF, and PeAF groups, respectively (log-rank P=0.048) (Figure 4). Among the groups, patients with PeAF had the highest prevalence of residual TR and the worst mortality and cardiovascular event rates within 1 year. Therefore, we assessed the cardiovascular events in patients with significant

Table 1. Patients' Characteristics

	All (n=110)	No AF (n=51)	Paroxysmal AF (n=40)	Persistent AF (n=19)	*P* Value	Post Hoc Test*
Age, y	61±12	59±14	61±12	64±9	0.32	
Female sex (%)	18 (16%)	11 (22%)	5 (13%)	2 (11%)	0.38	
White (%)	65 (59%)	28 (55%)	24 (60%)	13 (68%)	0.54	
Body surface area, m^2	2.0±0.2	2.0±0.2	2.0±0.3	2.1±0.2	0.04	b
Hypertension (%)	71 (65%)	33 (65%)	25 (63%)	13 (68%)	0.91	
Diabetes mellitus (%)	39 (35%)	22 (43%)	10 (25%)	7 (37%)	0.20	
Hypercholesterolemia (%)	71 (65%)	31 (61%)	27 (68%)	13 (68%)	0.74	
Chronic obstructive pulmonary disease (%)	15 (14%)	7 (14%)	6 (15%)	2 (11%)	0.90	
Implantable cardioverter defibrillator (%)	91 (83%)	40 (78%)	34 (85%)	17 (89%)	0.49	
Ischemic cardiomyopathy	45 (41%)	20 (39%)	16 (40%)	9 (47%)	0.82	
Intention to treat					0.53	
BTT (%)	24 (22%)	9 (18%)	8 (20%)	7 (37%)		
DT (%)	70 (64%)	34 (67%)	26 (65%)	10 (53%)		
DT to BTT (%)	16 (15%)	8 (16%)	6 (15%)	2 (11%)		
Interagency Registry for Mechanically Assisted Circulatory Support profile level					0.26	
1 (%)	13 (12%)	5 (10%)	5 (13%)	3 (16%)		
2 (%)	58 (53%)	26 (51%)	21 (53%)	11 (58%)		
3 (%)	34 (31%)	20 (39%)	10 (25%)	4 (21%)		
4 (%)	5 (5%)	0 (0%)	4 (10%)	1 (5%)		
Laboratory parameters						
Serum urea nitrogen, mg/dL	27.3±15.3	29.6±15.9	23.1±11.0	30.1±19.8	0.17	
Creatinine, mg/dL	1.5±0.5	1.4±0.4	1.5±0.6	1.7±0.5	0.19	
Albumin, g/dL	3.8±0.5	3.7±0.6	3.8±0.5	3.9±0.5	0.33	
Total bilirubin, mg/dL	0.9±0.8	0.9±0.6	1.1±1.0	0.9±0.5	0.52	
Hemoglobin, g/dL	11.6±2.2	11.5±2.2	11.7±2.4	11.7±2.2	0.91	
Hemodynamic parameters						
Mean pulmonary artery pressure, mm Hg	35.4±10.5	34.9±9.9	36.5±11.6	34.3±10.1	0.68	
PCWP, mm Hg	23.2±8.9	21.8±7.6	24.8±10.0	23.5±9.7	0.27	
CVP, mm Hg	9.8±5.9	8.9±5.8	10.5±6.1	10.9±5.9	0.33	
Cardiac index, L/min per m^2	1.9±0.5	2.0±0.5	1.8±0.5	1.7±0.5	0.03	a, b
Pulmonary vascular resistance, wood units	3.6±2.0	3.7±1.7	3.6±2.0	3.5±2.8	0.37	
CVP/PCWP, mm Hg	0.43±0.23	0.41±0.25	0.43±0.20	0.50±0.22	0.39	
Pulmonary artery pulsatility index	5.1±6.0	6.2±7.4	4.5±5.0	3.4±2.3	0.36	

The values are presented as means±SD or number (%). AF indicates atrial fibrillation; BTT, bridge to transplant; CVP, central venous pressure; DT, destination therapy; and PCWP, pulmonary capillary wedge pressure.

*Post hoc test: significant differences are observed between (a) the no AF and the paroxysmal AF group and (b) the no AF and the persistent AF group.

residual TR. Patients with residual TR at 1 month had a worse outcome compared with those without residual TR (log-rank *P*=0.014), with an event-free rate of 76% at the 1-year follow-up (Figure 5 and Table S2).

DISCUSSION

We studied the effect of AF on TR, TV geometry, RV function, and cardiovascular events in patients with HM3 implantation. The major findings of this study were as follows: (1) PeAF was associated with increased mortality and cardiovascular events compared with no AF and PAF. (2) LVAD therapy with HM3 implantation significantly decreased LV and LA size and improved LV ejection fraction; however, there were no significant changes in RV and RA size, RV fractional area change, and RV systolic excursion velocity. (3) Patients with PeAF had the largest RA and TV annulus diameter and the highest prevalence of significant residual TR after 1 month of HM3 implantation. (4) Thirty-one patients had significant residual TR, and they had a worse outcome compared with those without residual TR.

HF is one of the most important causes of mortality in patients with AF and its incidence increases with

Table 2. Baseline and Follow-Up Echocardiographic Parameters

Echocardiographic Parameters	All (n=110)	No AF (n=51)	Paroxysmal AF (n=40)	Persistent AF (n=19)	*P* Value	Post Hoc Test*
Baseline						
TV annulus diameter, mm	38.4±4.8	36.6±4.1	38.7±5.2	42.5±3.2	<0.001	b, c
TV tenting height, mm	9.7±1.9	9.6±2.1	9.6±1.6	10.3±2.0	0.39	
TR grade (vena contracta width)					0.13	
None to mild, <3 mm (%)	71 (65%)	33 (65%)	25 (63%)	13 (68%)		
Moderate, 3–6.9 mm (%)	31 (28%)	11 (22%)	14 (35%)	6 (32%)		
Severe, >7 mm (%)	8 (7%)	7 (14%)	1 (3%)	0 (0%)		
Significant TR (%)	39 (35%)	18 (35%)	15 (38%)	6 (32%)	0.91	
Significant TR (EROA), cm^2	0.22±0.13	0.26±0.15	0.20±0.12	0.18±0.08	0.27	
RVEDD, mm	48.9±7.2	48.4±7.1	48.6±7.6	51.1±6.4	0.37	
RVFAC, %	27.9±6.9	27.7±7.0	28.6±7.3	27.1±5.8	0.73	
RV systolic excursion velocity, cm/s	8.2±2.5	8.3±2.6	8.5±2.5	7.4±2.5	0.27	
RA volume index, mL/m^2	41.6±20.4	37.9±17.4	42.2±21.6	50.5±23.5	0.10	
LVEF, %	14.9±5.0	14.6±9.8	15.3±5.1	14.8±5.0	0.54	
LVDd, mm	67.6±9.5	66.9±9.8	67.3±9.2	69.9±9.4	0.29	
LVDs, mm	62.4±9.7	61.9±10.0	61.9±9.6	64.6±9.3	0.54	
Left ventricular mass index, g/m^2	134.3±39.6	136.8±38.5	128.8±42.9	139.3±35.7	0.26	
LA dimension, mm	48.1±7.9	46.1±7.5	49.0±7.5	51.9±8.3	0.01	b
LA volume index, mL/m^2	49.7±18.9	45.6±15.2	49.2±18.4	61.7±24.2	0.01	b, c
Significant MR (%)	69 (63%)	37 (73%)	25 (63%)	7 (37%)	0.02	b
Follow-up						
TV annulus diameter, mm	39.1±4.9	36.5±4.0	40.1±4.6	44.2±2.7	<0.001	a, b, c
TV tenting height, mm	8.8±2.0	8.4±2.1	8.9±1.3	9.4±2.6	0.14	
TR grade (vena contracta width)					0.01	b, c
None to mild, <3 mm (%)	79 (72%)	40 (78%)	30 (75%)	9 (47%)		
Moderate, 3–6.9 mm (%)	19 (17%)	6 (12%)	9 (23%)	4 (21%)		
Severe, >7 mm (%)	12 (11%)	5 (10%)	1 (3%)	6 (32%)		
Significant TR (%)	31 (28%)	11 (22%)	10 (25%)	10 (53%)	0.03	b, c
Significant TR (EROA), cm^2	0.28±0.13	0.29±0.14	0.24±0.10	0.30±0.16	0.57	
RVEDD, mm	47.7±6.8	46.8±6.6	48.4±6.0	48.4±8.6	0.49	
RVFAC, %	27.2±6.2	27.6±6.0	26.9±6.4	26.7±6.5	0.81	
RV systolic excursion velocity, cm/s	8.2±2.2	8.2±2.2	8.3±2.2	8.4±1.9	0.82	
RA volume index, mL/m^2	42.9±18.7	38.7±15.6	44.2±17.7	51.7±25.0	0.05	b
LVEF, %	19.8±8.0	19.9±7.9	19.0±7.1	21.4±10.2	0.70	
LVDd, mm	53.8±10.4	54.0±9.0	51.9±10.5	57.2±12.8	0.20	
LVDs, mm	48.1±11.5	47.8±10.6	46.4±11.2	52.3±13.9	0.20	
LA dimension, mm	42.5±6.4	40.8±6.2	42.6±5.7	47.2±6.6	0.001	b, c
Significant MR (%)	4 (4%)	0 (0%)	2 (5%)	2 (11%)	0.09	
Pump speed, rpm	5459±291	5431±275	5464±329	5524±245	0.39	
Follow-up transthoracic echocardiogram timing, d	28.8±6.2	29.2±5.7	27.8±6.5	30.1±7.0	0.38	

The values are presented as means±SD or number (%). AF indicates atrial fibrillation; EROA, effective regurgitant orifice area; LA, left atrial; LVEF, left ventricular ejection fraction; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; MR, mitral regurgitation; RA, right atrial; RV, right ventricular; RVEDD, right ventricular end diastolic dimension; RVFAC, right ventricular fractional area change; TR, tricuspid regurgitation; and TV, tricuspid valve.

*Post hoc test: significant differences are observed between (a) the no AF and the paroxysmal AF group, (b) the no AF and the persistent AF group, and (c) the paroxysmal AF and the persistent AF group.

age.[9] The impact of AF on the clinical outcomes of patients with LVAD is unclear; however, AF is common in patients with advanced HF.[9,10,21] To our knowledge, there is no previous study that assessed the impact of AF on clinical outcomes in patients with HM3. In the present study, patients with PeAF had the worst

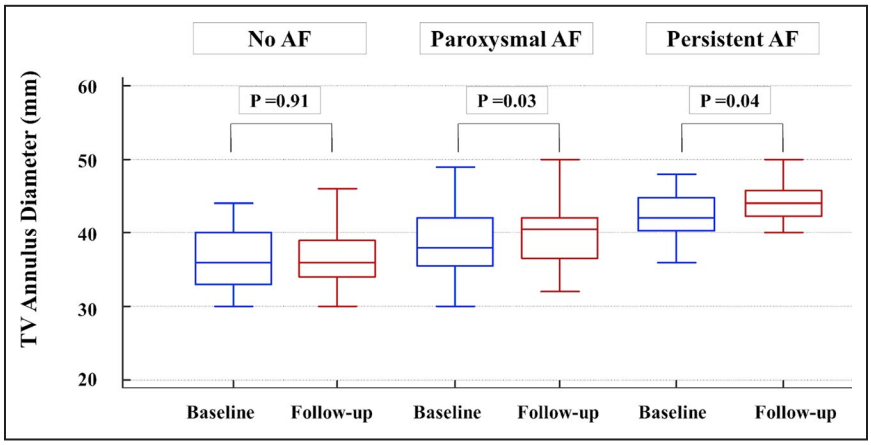

Figure 2. Change in TV annulus diameter.
AF indicates atrial fibrillation; and TV, tricuspid valve.

mortality and cardiovascular event rates compared with those with no AF and PAF. This result is consistent with that of a previous study, in which PeAF was associated with increased mortality and HF hospitalization in patients with HeartMate II.[10] PeAF may be a marker for sicker patients who would have worse outcomes after HM3 implantation. However, in the present study, there were no significant differences in age, sex, INTERMACS profile, the etiology of HF, treatment strategy, serum creatinine level, and RV function assessed by right heart catheterization and TTE between the groups. The MOMENTUM 3 randomized clinical trial demonstrated the superiority of the HM3 device to the HeartMate II device in disabling stroke.[2,3] Stroke events occurred less frequently compared with readmissions due to recurrent HF in the present study. Therefore, a key element is to improve the management of HF patients requiring LVAD implantation. Patients with AF had a decreased cardiac index among the groups. It is established that AF causes a loss of "atrial kick" and a reduction in LV diastolic filling, resulting in a decline in the cardiac index.[22] The AF and RV dysfunction predispose patients to one another and increase the risk of morbidity and mortality.[23] In addition, patients with PeAF had a higher prevalence of significant residual TR at 1 month after HM3 implantation. The TR initiates a vicious cycle of further RV dysfunction and dilatation, and consequently, worsening of TR.[17,24] Abe et al demonstrated that the coexistence of PeAF and significant TR was associated with a poor prognosis.[25] Regarding the potential mechanisms underlying these observations, the coexistence of AF and residual TR after HM3 implantation may lead to more adverse cardiovascular events, such as right HF and death.

Functional TR occurs mainly from tricuspid annular dilation and RV enlargement, which are mainly

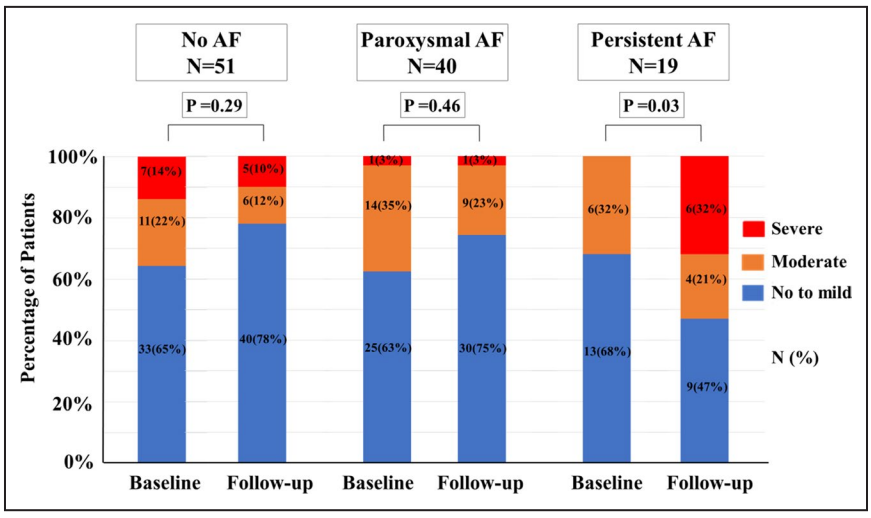

Figure 3. Change in TR grade.
AF indicates atrial fibrillation; and TR, tricuspid regurgitation.

Table 3. Causes of Death and Cardiovascular Events Within 1 Year

	All (n=110)	No AF (n=51)	Paroxysmal AF (n=40)	Persistent AF (n=19)	*P* Value
Causes of death					
Right HF	3 (3%)	1 (2%)	1 (3%)	1 (5%)	0.75
Stroke	1 (1%)	0 (0%)	0 (0%)	1 (5%)	0.09
Withdrawal of care	1 (1%)	0 (0%)	0 (0%)	1 (5%)	0.09
Cardiovascular events					
Readmission due to right HF	7 (6%)	2 (4%)	3 (8%)	2 (11%)	0.56
Stroke	2 (2%)	0 (0%)	1 (3%)	1 (5%)	0.09

The values are presented as means±SD or number (%). AF indicates atrial fibrillation; and HF, heart failure.

caused by AF, secondary to left HF diseases.[7,8] However, no previous study has focused on AF and TR in patients with LVAD implantation. Therefore, we assessed the influence of AF on functional TR. Patients with PeAF had the largest TV annulus diameter among the groups. Previous studies demonstrated that patients with PeAF had a larger TV annulus size and RA size compared with those with left-sided heart disease.[16,26] Kukucka et al have shown that tricuspid annular dilation, even without severe regurgitation, adversely affects survival after LVAD implantation.[27] Consistent with these studies, patients with PeAF had the largest TV annulus diameter and the worst prognostic outcome in the present study. The HM3 implantation and device speed augmentation lead to decreased LV size and there is no evidence of worsening of RV function. However, higher LVAD speeds in HM3 may affect the RV negatively as evidenced by increased RV volumes and less favorable RV geometry.[11,28] In the entire cohort of this study, HM3 therapy significantly decreased LV and LA size and improved LV ejection fraction; however, there were no significant changes in RV and RA size and function. Patients with PeAF had increased TV annulus diameter and exacerbation of TR severity after HM3 implantation; however, there were no significant changes in the no AF group despite the absence of significant differences in device speed. Therefore, AF may continue to affect TV annulus diameter even after HM3 implantation, resulting in a high prevalence of residual TR. In patients with PeAF, HM3 implantation may likely cause leftward displacement of the interventricular septum, which could lead to deterioration of preexisting TV annulus enlargement.

Our results suggested that more intensive therapy may be required for patients with PeAF. Patients with AF may benefit from rhythm control therapy to reduce the burden of AF. Hemodynamic improvement after catheter ablation for AF in a patient with LVAD has been

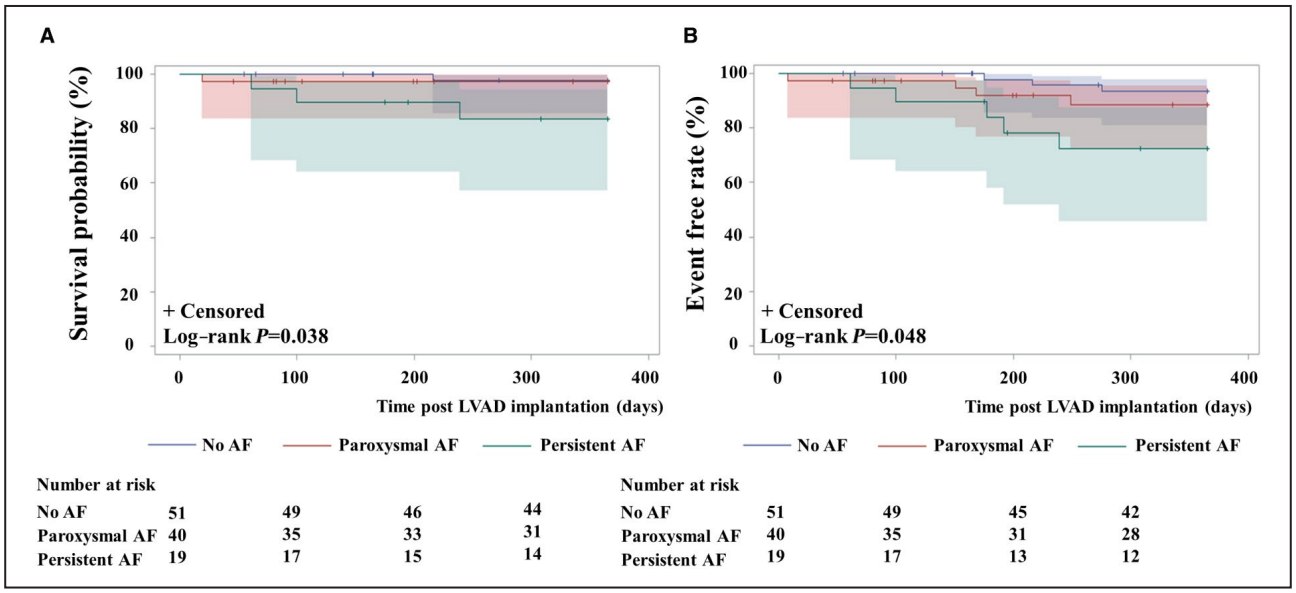

Figure 4. Kaplan-Meier analysis for mortality (A) and a cardiovascular event (B) according to the AF status.
AF indicates atrial fibrillation; and LVAD, left ventricular assist device.

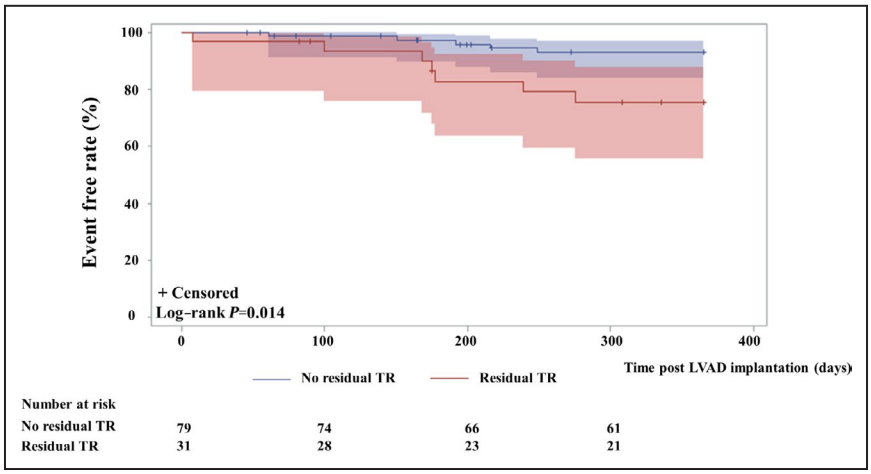

Figure 5. Kaplan-Meier analysis for a cardiovascular event by residual TR.
LVAD indicates left ventricular assist device; and TR, tricuspid regurgitation.

reported.[29] Andreas et al demonstrated that transcatheter edge-to-edge treatment of TR in a patient with LVAD was an effective strategy to gain time and bridge the patient to heart transplantation.[30] Concomitant TV surgery and the maze procedure at the time of LVAD implantation, and even catheter intervention in select patients, might be indicated in patients with AF and significant TR. However, there are conflicting data regarding the benefit of concomitant TV surgery for patients with significant TR.[5,31] Further clinical studies to determine the optimal intervention in patients with AF are required.

LIMITATIONS

First, this was a retrospective, single-center, observational study and therefore subject to selection bias and confounding because the data are limited to the information documented in the patients' charts. Furthermore, the sample size was small, especially in the highest risk group; 19 patients with PeAF. Thus, our findings should be considered only exploratory and hypothesis-generating. Second, TR grade was defined using one quantitative method, VC width. Therefore, we evaluated the effective regurgitant orifice area using the proximal isovelocity surface area method in patients with significant TR. Third, the measurements of RV size and TV geometry are technically difficult to determine accurately with 2-dimensional echocardiography because of its anatomic complexity. Three-dimensional echocardiography currently offers an accurate assessment of the size and shape of the RV and TV deformation. However, high feasibility and reproducibility of TV annulus diameter measurement using 2-dimensional echocardiography in apical 4-chamber view have been reported despite being systematically smaller when compared with that obtained via 3-dimensional echocardiography.[18] Lastly, the concomitant TV procedure may have had an impact on the prognostic outcome. The decision to perform a TV procedure was made on the basis of TR severity. However, even among all HM3 patients (n=133), those with PeAF had the worst mortality and cardiovascular event rates (log-rank P=0.009 and P=0.008, Figure S1). Future prospective studies with larger cohorts will be needed to overcome the limitations of this study.

CONCLUSIONS

PeAF was associated with increased mortality, cardiovascular events, and residual TR compared with no AF and PAF. Significant residual TR after HM3 implantation was associated with cardiovascular events.

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Supplementary Material

Tables S1–S2
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Alterations of echocardiographic parameters according to AF status.

	All (n=110)			No AF (n=51)		
	Baseline	Follow-up	p value	Baseline	Follow-up	p value
TV annulus diameter (mm)	38.4 ± 4.8	39.1 ± 4.9	0.03	36.6 ± 4.1	36.5 ± 4.0	0.91
TV tenting height (mm)	9.7 ± 1.9	8.8 ± 2.0	< 0.001	9.6 ± 2.1	8.4 ± 2.1	0.001
TR grade (vena contracta width)			0.13			0.29
None to mild, <3 mm (%)	71 (65%)	79 (72%)		33 (65%)	40 (78%)	
Moderate, 3–6.9 mm (%)	31 (28%)	19 (17%)		11 (22%)	6 (12%)	
Severe, >7 mm (%)	8 (7%)	12 (11%)		7 (14%)	5 (10%)	
TR (CJA/RAA), (%)	13.2 ± 12.8	10.9 ± 11.6	0.10	14.3 ± 13.8	10.1 ± 11.2	0.02
Significant TR (%)	39 (35%)	31 (28%)	0.25	18 (35%)	11 (22%)	0.13
RVEDD (mm)	48.9 ± 7.2	47.7 ± 6.8	0.07	48.4 ± 7.1	46.8 ± 6.6	0.17
RVFAC (%)	27.9 ± 6.9	27.2 ± 6.2	0.36	27.7 ± 7.0	27.6 ± 6.0	0.72
RV systolic excursion velocity (cm/sec)	8.2 ± 2.5	8.2 ± 2.2	0.90	8.3 ± 2.6	8.2 ± 2.2	0.12
RA volume index (mL/m^2)	41.6 ± 20.4	42.9 ± 18.7	0.69	37.9 ± 17.4	38.7 ± 15.6	0.90
LVEF (%)	14.9 ± 5.0	19.8 ± 8.0	< 0.001	14.6 ± 9.8	19.9 ± 7.9	< 0.001
LVDd (mm)	67.6 ± 9.5	53.8 ± 10.4	< 0.001	66.9 ± 9.8	54.0 ± 9.0	< 0.001
LVDs (mm)	62.4 ± 9.7	48.1 ± 11.5	< 0.001	61.9 ± 10.0	47.8 ± 10.6	< 0.001
LA dimension (mm)	48.1 ± 7.9	42.5 ± 6.4	< 0.001	46.1 ± 7.5	40.8 ± 6.2	< 0.001
Significant MR (%)	69 (63%)	4 (4%)	< 0.001	37 (73%)	0 (0%)	< 0.001

	Paroxysmal AF (n=40)			Persistent AF (n=19)		
	Baseline	Follow-up	p value	Baseline	Follow-up	p value
TV annulus diameter (mm)	38.7 ± 5.2	40.1 ± 4.6	0.03	42.5 ± 3.2	44.2 ± 2.7	0.04
TV tenting height (mm)	9.6 ± 1.6	8.9 ± 1.3	0.01	10.3 ± 2.0	9.4 ± 2.6	0.19
TR grade (vena contracta width)			0.46			0.03
None to mild, <3 mm (%)	25 (63%)	30 (75%)		13 (68%)	9 (47%)	
Moderate, 3–6.9 mm (%)	14 (35%)	9 (23%)		6 (32%)	4 (21%)	
Severe, >7 mm (%)	1 (3%)	1 (3%)		0 (0%)	6 (32%)	
TR (CJA/RAA), (%)	12.5 ± 11.2	9.4 ± 10.9	0.06	11.5 ± 13.6	16.3 ± 13.1	0.10
Significant TR (%)	15 (38%)	10 (25%)	0.23	6 (32%)	10 (53%)	0.19
RVEDD (mm)	48.6 ± 7.6	48.4 ± 6.0	0.71	51.1 ± 6.4	48.4 ± 8.6	0.17
RVFAC (%)	28.6 ± 7.3	26.9 ± 6.4	0.26	27.1 ± 5.8	26.7 ± 6.5	0.84
RV systolic excursion velocity (cm/sec)	8.5 ± 2.5	8.3 ± 2.2	0.42	7.4 ± 2.5	8.4 ± 1.9	0.75
RA volume index (mL/m^2)	42.2 ± 21.6	44.2 ± 17.7	0.52	50.5 ± 23.5	51.7 ± 25.0	0.86
LVEF (%)	15.3 ± 5.1	19.0 ± 7.1	< 0.001	14.8 ± 5.0	21.4 ± 10.2	< 0.001
LVDd (mm)	67.3 ± 9.2	51.9 ± 10.5	< 0.001	69.9 ± 9.4	57.2 ± 12.8	< 0.001
LVDs (mm)	61.9 ± 9.6	46.4 ± 11.2	< 0.001	64.6 ± 9.3	52.3 ± 13.9	< 0.001
LA dimension (mm)	49.0 ± 7.5	42.6 ± 5.7	< 0.001	51.9 ± 8.3	47.2 ± 6.6	0.02
Significant MR (%)	25 (63%)	2 (5%)	< 0.001	7 (37%)	2 (11%)	0.06

AF, atrial fibrillation; EROA, effective regurgitant orifice area; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; MR, mitral regurgitation; RA, right atrial; RV, right ventricular; RVEDD, right ventricular end diastolic dimension; RVFAC, right ventricular fractional area change; TR, tricuspid regurgitation; and TV, tricuspid valve.

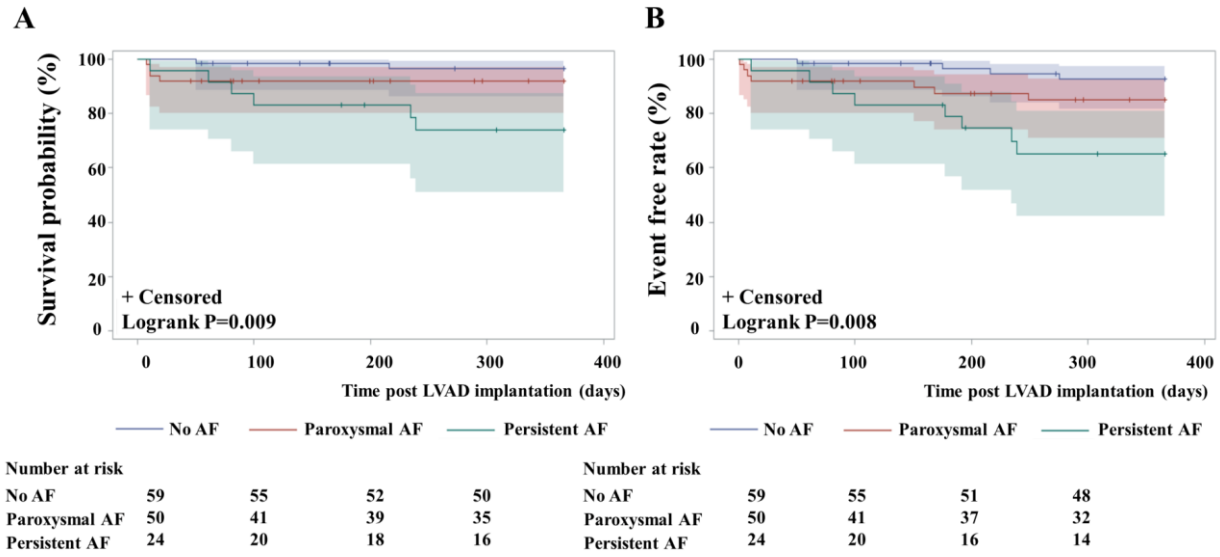
Table S2. Patients' characteristics with residual TR.

	Residual TR (n=31)	No residual TR (n=79)	p value
Age (years)	62 ± 13	60 ± 12	0.31
Female sex (%)	4 (13 %)	14 (18 %)	0.54
Caucasian (%)	15 (48%)	50 (63%)	0.15
BSA (m^2)	2.0 ± 0.2	2.0 ± 0.3	0.87
Hypertension (%)	19 (61 %)	52 (66 %)	0.54
Diabetes mellitus (%)	10 (32 %)	29 (37 %)	0.66
Hypercholesterolemia (%)	23 (74 %)	48 (61 %)	0.19
COPD (%)	0 (0%)	15 (19 %)	0.01
ICD (%)	25 (81%)	66 (84 %)	0.72
Ischemic cardiomyopathy	14 (45 %)	31 (39%)	0.57
Intention to treat			0.81
BTT (%)	8 (26 %)	16 (20 %)	
DT (%)	19 (61%)	51 (65 %)	
DT to BTT (%)	4 (13%)	12 (15%)	
INTERMACS profile level			0.68
1 (%)	4 (13 %)	9 (11 %)	
2 (%)	14 (45 %)	44 (56 %)	
3 (%)	12 (39 %)	22 (28 %)	
4 (%)	1 (3 %)	4 (5 %)	
Laboratory parameters			
BUN (mg/dL)	28.7 ± 19.5	26.8 ± 13.4	0.95
Creatinine (mg/dL)	1.5 ± 0.4	1.5 ± 0.6	0.38
Albumin (g/dL)	3.8 ± 0.6	3.7 ± 0.5	0.69
Total bilirubin (mg/dL)	1.1 ± 0.7	0.9 ± 0.8	0.22
Hemoglobin (g/dL)	11.7 ± 2.2	11.6 ± 2.3	0.83
AF			0.03
Paroxysmal AF	10 (32%)	30 (38%)	
Persistent AF	10 (32%)	9 (11%)	
Hemodynamic parameters			
Mean PA pressure (mmHg)	36.0 ± 11.5	35.1 ± 10.2	0.67
PCWP (mmHg)	24.1 ± 9.5	22.8 ± 8.7	0.50
CVP (mmHg)	11.3 ± 6.6	9.2 ± 5.5	0.10

Cardiac index (L/min/m2)	1.9 ± 0.6	1.8 ± 0.5	0.50
PVR (wood units)	3.4 ± 2.1	3.7 ± 2.0	0.40
CVP/PCWP (mmHg)	0.46 ± 0.21	0.42 ± 0.24	0.24
PA pulsatility index	4.4 ± 4.2	5.4 ± 6.6	0.85
Echocardiographic parameters			
LVEF (%)	16.1 ± 5.4	14.4 ± 4.7	0.14
LVDd (mm)	67.3 ± 9.0	67.7 ± 9.8	0.87
LVDs (mm)	61.5 ± 9.4	62.7 ± 9.8	0.55
LV mass index (g/m^2)	131.2 ± 30.6	135.6 ± 42.7	0.90
LA dimension (mm)	50.0 ± 8.0	47.4 ± 7.8	0.12
LA volume index (mL/m^2)	52.7 ± 24.4	48.5 ± 16.3	0.74
RVEDD (mm)	50.7 ± 6.6	48.2 ± 7.3	0.11
Pump speed at follow-up (rpm)	5,492 ± 232	5,446 ± 311	0.34

Residual TR was defined as at least moderate TR with a vena contracta width ≥3 mm.
AF, atrial fibrillation; BSA, body surface area; BTT, bridge to transplant; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CVP, central venous pressure; DT, destination therapy; ICD, implantable cardioverter defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; PA, pulmonary artery; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; and PVR, pulmonary vascular resistance.

Figure S1. Among all HM3 patients (n=133), Kaplan-Meier analysis for mortality (A) and a cardiovascular event (B) according to AF status.



AF, atrial fibrillation; LVAD, left ventricular assist device