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Impact of left ventricular assist device implantation on mitral regurgitation: An analysis from the MOMENTUM 3 trial

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KEYWORDS:

mitral regurgitation;
LVAD;
outcomes,
MOMENTUM 3,
HeartMate 3

BACKGROUND: Mitral regurgitation (MR) determines pathophysiology and outcome in advanced heart failure. The impact of left ventricular assist device (LVAD) placement on clinically significant MR and its contribution to long-term outcomes has been sparsely evaluated.

METHODS: We evaluated the effect of clinically significant MR on patients implanted in the MOMENTUM 3 trial with either the HeartMate II (HMII) or the HeartMate 3 (HM3) at 2 years. Clinical significance was defined as moderate or severe grade MR determined by site-based echocardiograms.

RESULTS: Of 927 patients with LVAD implants without a prior or concomitant mitral valve procedure, 403 (43.5%) had clinically significant MR at baseline. At 1-month of support, residual MR was present in 6.2% of patients with HM3 and 14.3% of patients with HMII (relative risk = 0.43; 95% CI, 0.22–0.84; $p = 0.01$) with a low rate of worsening at 2 years. Residual MR at 1-month post-implant did not impact 2-year mortality for either the HM3 (hazard ratio [HR], 1.41; 95% CI, 0.52–3.89; $p = 0.50$) or HMII (HR, 0.91; 95% CI, 0.37–2.26; $p = 0.84$) LVAD. The presence or absence of baseline MR did not influence mortality (HM3 HR, 0.86; 95% CI, 0.56–1.33; $p = 0.50$; HMII HR, 0.81; 95% CI, 0.54–1.22; $p = 0.32$), major adverse events or functional capacity. In multivariate analysis, severe baseline MR ($p = 0.001$), larger left ventricular dimension ($p = 0.002$), and implantation with the HMII instead of the HM3 LVAD ($p = 0.05$) were independently associated with an increased likelihood of persistent MR post-implant.

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See Related Editorial, page 538

CONCLUSIONS: Hemodynamic unloading after LVAD implantation improves clinically significant MR early, sustainably, and to a greater extent with the HM3 LVAD. Neither baseline nor residual MR influence outcomes after LVAD implantation.

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As heart failure (HF) progresses, geometric alterations in left ventricular (LV) structure (cavity dilatation, increasing diameter of the mitral annulus), reduced closing forces on valvular leaflets, and consequent worsening of ventricular function lead to a form of secondary mitral regurgitation (MR). This common finding in advanced HF refractory to medical therapy is associated with pulmonary hypertension, right ventricular failure, and a worse prognosis.¹ Thus, MR is encountered frequently in patients with advanced HF undergoing LV assist device (LVAD) implantation.²

Several questions have been raised regarding MR during consideration for LVAD implantation. First, it is uncertain to what degree hemodynamic unloading with an LVAD ameliorates MR. Second, baseline or residual (post-LVAD) uncorrected MR may confer adverse prognosis and remains poorly studied. As a result of these unanswered queries, clinicians debate the best management of MR at the time of LVAD surgery with particular emphasis on whether significant MR should be corrected concomitantly during the implant operation.^{3–6} In registry analyses, concomitant mitral valve (MV) procedures have been associated with reduced hospitalizations and better quality of life but not improved survival.³ Other multicenter studies have pointed to a survival benefit in those with uncorrected severe MR at baseline.⁴ However, single-center studies have demonstrated that post-LVAD implantation residual MR may adversely impact hemodynamics and right ventricular function, whereas others have suggested resolution of severe MR in most cases after LVAD implantation.^{5,6} Whether axial or centrifugal continuous-flow LVADs affect MR similarly or differentially is unknown.

This post hoc analysis of the MOMENTUM 3 pivotal trial (clinicaltrials.gov; grant no. NCT02224755), which randomized patients with advanced HF refractory to medical therapy to either the fully magnetically-levitated centrifugal-flow LVAD (HeartMate 3) or the axial-flow pump (HeartMate II), studied the prevalence, resolution, and outcomes of patients with and without uncorrected clinically significant MR at the time of LVAD implantation. We further sought to identify pre-implant markers for persistent clinically significant MR following LVAD implantation.

Methods

MOMENTUM 3 trial design

The MOMENTUM 3 trial was a multicenter, 1:1 randomized, pivotal study comparing the treatment efficacy of the HeartMate 3 (HM3) LVAD with the HeartMate II (HMII) LVAD in patients with advanced-stage HF (Abbott, Abbott Park, IL).⁷ Sixty-nine

U.S. sites enrolled a total of 1,028 patients, and 8 patients were withdrawn before the implant, leaving 1,020 patients who underwent implant with their assigned device. Details regarding the study design and the 2-year primary results from the full study cohort were published.^{7–9} The study protocol was approved by each institutional review board, and written informed consent was obtained from all patients or their authorized representatives. The trial was sponsored by Abbott.

Evaluation of MR

In the MOMENTUM 3 trial, data regarding MR was collected from echocardiograms performed at each site. Qualitative assessment of MR severity (e.g., none, mild, moderate, severe) was collected from site-based echocardiogram reports. Data from baseline (pre-implant) and the 1-, 3-, 6-, 12-, and 24-month post-implant visits were used for this analysis. Clinically significant MR was defined as either moderate or severe MR. For this analysis, patients with moderate or severe baseline MR were combined as the clinical outcomes post-LVAD implantation were noted to be similar between these patients (Figure S1). Residual MR refers to the presence of clinically significant MR after LVAD implantation.

Analysis cohort

The patient cohort for this analysis is shown in Figure 1. Of the 1,020 patients who underwent LVAD implant in the MOMENTUM 3 trial, 4 patients did not have an echocardiographic assessment of the MV performed at baseline and were excluded from the analysis. An additional 89 patients had a prior or concurrent MV repair or replacement and were also excluded. A total of 927 patients were included in the final analysis cohort. The post-implant completion rates of MV echocardiographic assessment are shown in Table S1. Of patients on LVAD support, a small percentage were missing echocardiogram evaluations at each time point (< 9%), and rates were similar between those with and without significant baseline MR.

End-points

Within each treatment arm, clinical outcomes were compared between patients with and without significant baseline MR. The frequency of significant residual MR at 1-month was evaluated. The primary composite end-point of the MOMENTUM 3 trial was survival free of disabling stroke (defined by a Modified Rankin score > 3, in which scores range from 0 to 6, with higher scores indicating more severe disability, including death) or reoperation to remove or replace a malfunctioning device at 2 years. Other end-points include overall survival, adverse events, readmissions, New York Heart Association classification, and the 6-minute walk test. To evaluate the impact of residual MR on outcomes, we performed a landmark

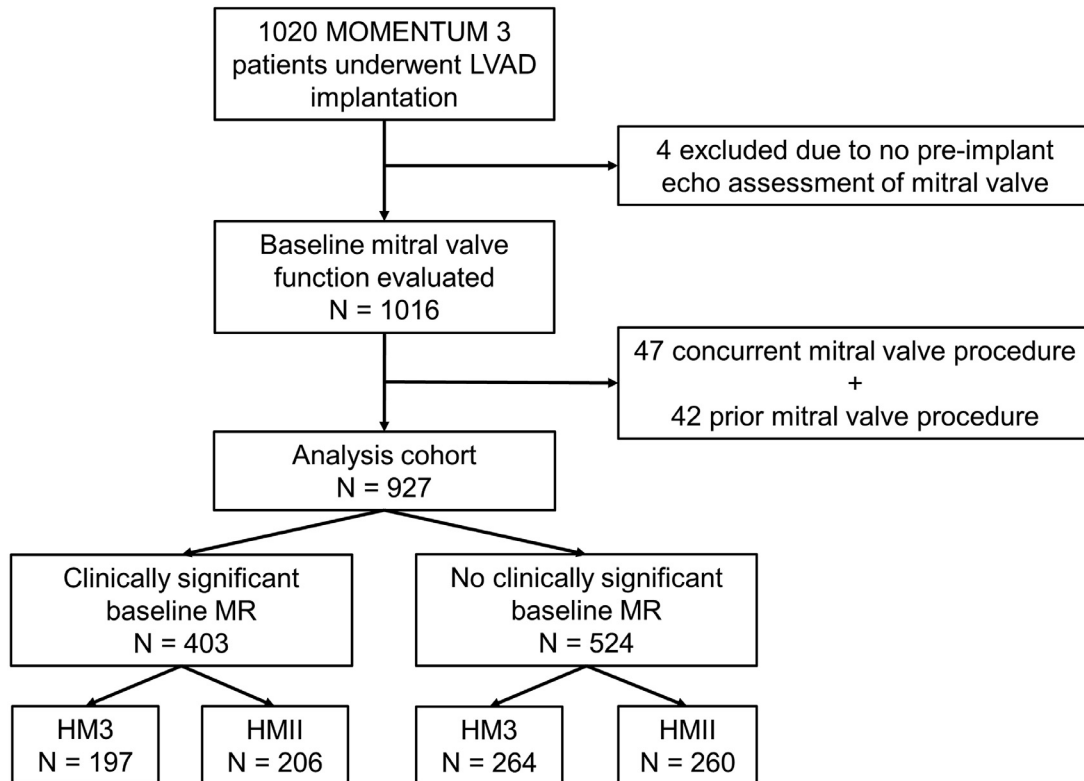


Figure 1 Patient cohort. LVAD, left ventricular assist device; HM3, HeartMate 3; HMII, HeartMate II; MR, mitral regurgitation.

analysis to compare survival in patients with and without clinically significant MR at 1-month post-implant.

Statistical analysis

Continuous variables are described as median and interquartile or mean \pm standard deviation. Categorical variables are described as counts and percentages. Univariate comparisons of categorical variables were performed with the Wilcoxon's rank sum test. Univariate comparisons of categorical variables were performed with the chi-square test or Fisher's exact test as appropriate. The Kaplan–Meier method and log-rank test were used for time-to-event analyses. Survival estimates are presented with 95% CIs. Hazard ratio (HR) was calculated using Cox proportional hazards modeling. Adverse event rates are shown as events-per-patient-year (EPPY), and event rates were compared between groups using Poisson regression. Rate differences are described as relative risk (RR) and 95% CI. Longitudinal changes in functional status were analyzed by linear mixed-effects modeling.

Multivariate logistic regression was performed to identify independent predictors of residual MR in patients with clinically significant baseline MR. The outcome of interest for the regression model was the presence of significant residual MR between 1 and 6 months post-implant. First, a set of univariate comparisons of baseline variables listed in Table 1 was performed to screen for potential covariates. Covariates identified in the univariate analyses with $p < 0.10$ were entered using stepwise selection into a multivariate logistic regression model (p entry criteria = 0.15 and p stay criteria = 0.10). The odds ratio (OR) for each covariate in the model is presented with 95% CI.

All reported p values are 2-tailed, and p values < 0.05 are considered statistically significant. Statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC).

Results

Baseline characteristics

Of the 927 patients, 403 (43.5%) had significant baseline MR (Figure 1). Baseline characteristics of patients grouped by pre-implant MR severity are shown in Table 1. Approximately 50% of the patients in each group were implanted with the HM3 LVAD. Patients with significant baseline MR were less likely to have an ischemic etiology of HF compared with patients without MR (39.5% vs 48.5%; $p = 0.006$). They also had higher pulmonary capillary wedge pressure (24 vs 22 mm Hg; $p < 0.001$), mean pulmonary artery pressure (36 vs 33 mm Hg; $p < 0.001$), and pulmonary vascular resistance (3.0 vs 2.7 wood units; $p = 0.02$). Significant baseline MR was also associated with a worse ejection fraction (15% vs 19%; $p = 0.01$) and larger LV end-diastolic dimension (70 vs 66 mm; $p < 0.001$).

Improvement in MR with LVAD support

At baseline, 42.7% of patients with HM3 and 44.2% of patients with HMII had clinically significant MR (Figure 2A). After 1 month of LVAD support, the overall rates of significant MR improved with both pumps to 4.5% for patients with HM3 and 7.4% for patients with HMII. Rates of residual MR remained low through the remainder of the 2-year follow-up. Of the patients with significant baseline MR, only 6.2% of patients with HM3 compared with 14.3% of patients with HMII had significant residual

Table 1 Baseline Characteristics of Patients With and Without Significant Baseline MR

Baseline characteristic	Significant baseline MR (n = 403)	No significant baseline MR (n = 524)	p-value ^a
HM3 pump	197 (48.9%)	264 (50.4%)	0.65
Age, years	63 (53–69)	62 (52–68)	0.11
Male	314 (77.9%)	440 (84.0%)	0.02
Caucasian	265 (65.8%)	375 (71.6%)	0.06
Destination therapy	237 (58.8%)	326 (62.2%)	0.29
Ischemic heart failure	159 (39.5%)	254 (48.5%)	0.006
INTERMACS profile 1-2	139 (34.6%)	158 (30.3%)	0.17
BMI, kg/m ²	27 (24–31)	29 (25–33)	<0.001
MAP, mm Hg	77 (71–84)	79 (73–86)	0.01
PCWP, mm Hg	24 (18–30)	22 (16–28)	<0.001
Mean PAP, mm Hg	36 (30–42)	33 (26–40)	<0.001
RAP, mm Hg	10 (6–15)	9 (5–14)	0.008
PAPI	2.6 (1.8–4.3)	2.8 (1.8–4.6)	0.20
PVR, wood units	3.0 (2.0–4.1)	2.7 (1.8–4.0)	0.02
Cardiac index, liter/min/m ²	1.82 (1.55–2.20)	1.94 (1.62–2.26)	0.02
LVEF (%)	15 (15–20)	19 (15–20)	0.01
LVEDD, mm	70 (64–77)	66 (61–73)	<0.001
LVESD, mm	65 (58–71)	60 (54–67)	<0.001

Abbreviations: BMI, body mass index; HM3, HeartMate 3; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MAP, mean arterial pressure; MR, mitral regurgitation; PAP, pulmonary artery pressure; PAPI, pulmonary artery pulsatility index [(systolic PAP – diastolic PAP)/RAP]; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

^aWilcoxon's rank sum test for continuous variables. Fisher's exact test or chi-square test for categorical variables as appropriate.

MR at the 1-month visit (RR, 0.43; 95% CI, 0.22–0.84; $p = 0.01$) (Figure 2B). Median pump speeds and flows did not differ based on the presence of significant baseline MR or residual MR for either pump (Table S2).

Impact of significant baseline MR on outcomes

Primary composite end-point

Kaplan–Meier estimates of the primary composite end-point are shown in Figure 3A. There were no differences in the time to death, disabling stroke, or reoperation in patients with vs without significant baseline MR for both HM3 (HR, 0.80; 95% CI, 0.54–1.20; $p = 0.29$) and HMII (HR, 0.79; 95% CI, 0.58–1.09; $p = 0.15$). In addition, the presence or absence of significant baseline MR did not alter the superiority of HM3 vs HMII with fewer patients with HM3 failing the primary end-point (significant MR group: HR, 0.59; 95% CI, 0.39–0.88; $p = 0.009$; no significant MR group: HR, 0.57; 95% CI, 0.41–0.78; $p < 0.001$).

Survival and competing outcomes

Kaplan–Meier estimates of overall survival are shown in Figure 3B. There were no mortality differences in patients with vs without significant baseline MR for the HM3 (18.1% vs 21.5%; HR, 0.86; 95% CI, 0.56–1.33; $p = 0.50$) and HMII arms (19.9% vs 26.3%; HR, 0.81; 95% CI, 0.54–1.22; $p = 0.32$). The competing outcomes through 2 years are shown in Figure S2. In addition to mortality, transplantation rates were also similar, regardless of baseline MR severity.

Adverse events and readmissions

Adverse event rates in EPPY are shown in Figure 4 for patients with HM3 and HMII. When comparing rates between patients with and without significant baseline MR, there were no significant differences for hemocompatibility-related adverse events, sepsis, right HF, or cardiac arrhythmias. Rates for all-cause readmissions were also similar for patients with and without significant baseline MR.

Functional status

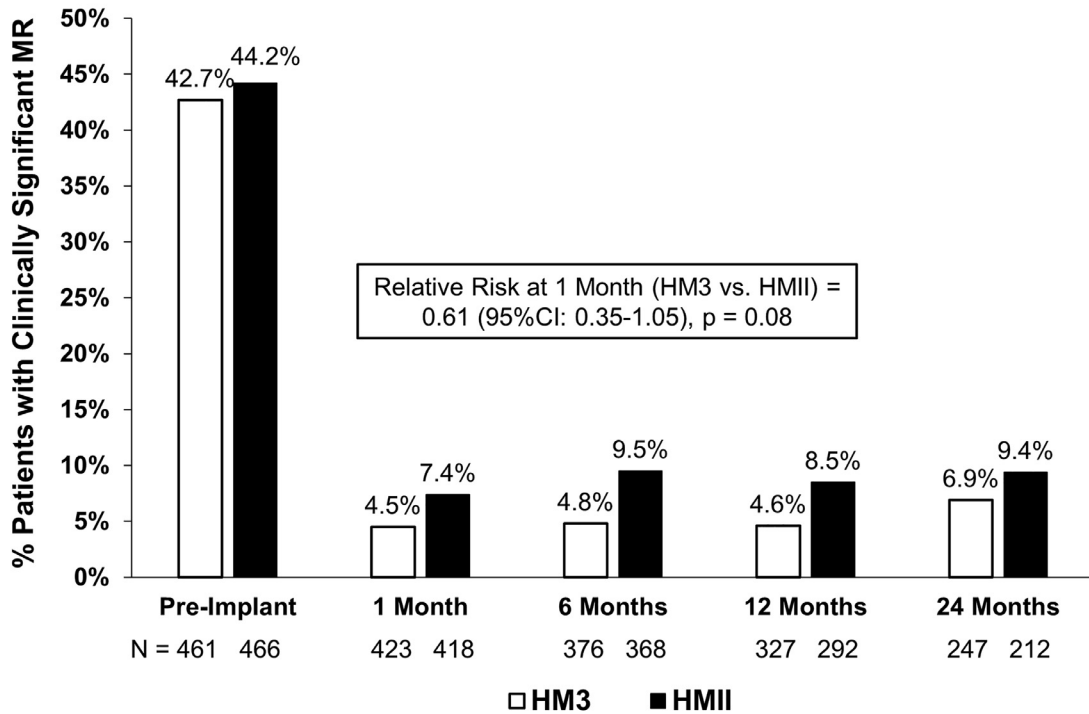
Longitudinal changes in New York Heart Association classification and the 6-minute walk test are shown in Figure S3. Significant improvements from baseline occurred with both pumps and were sustained throughout the 2 years. There were no differences in functional status between patients with and without significant baseline MR.

Impact of residual MR on outcomes

Landmark analysis of overall survival and competing outcomes

A landmark analysis of survival between patients with and without residual MR at 1-month post-implant is shown in Figure 5. This time point was chosen because maximal reduction in MR severity was noted at this early follow-up period. In patients with HM3, 2-year mortality was 22.3%

A) All Patients



B) Patients with Significant Baseline MR

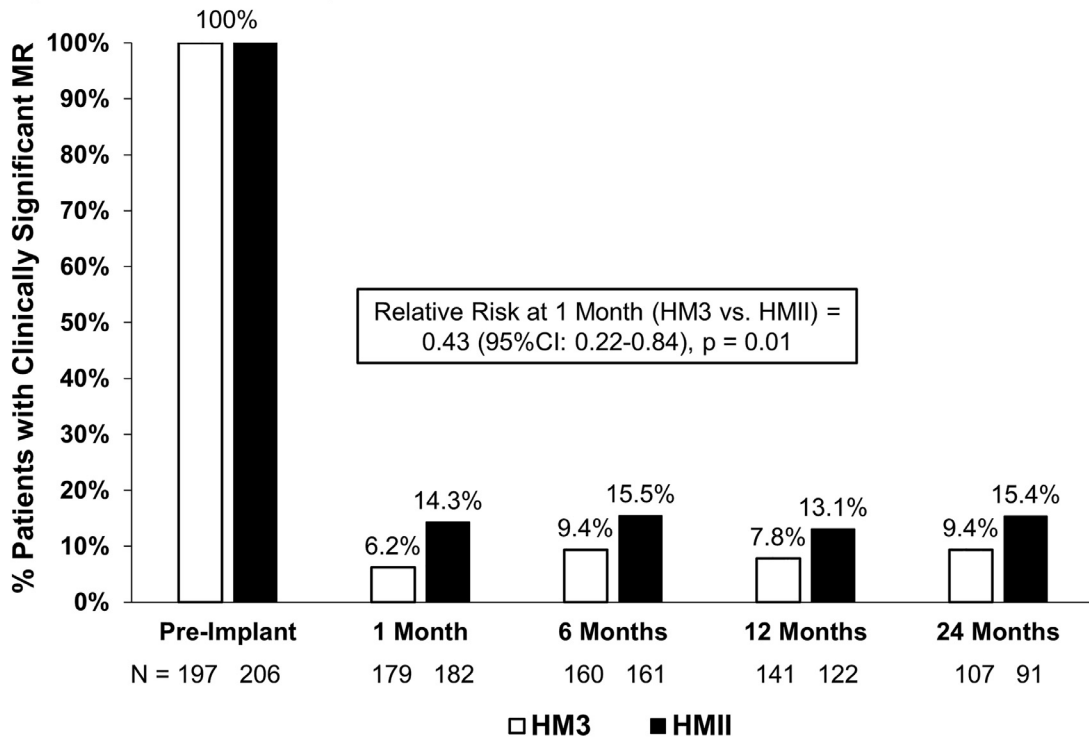
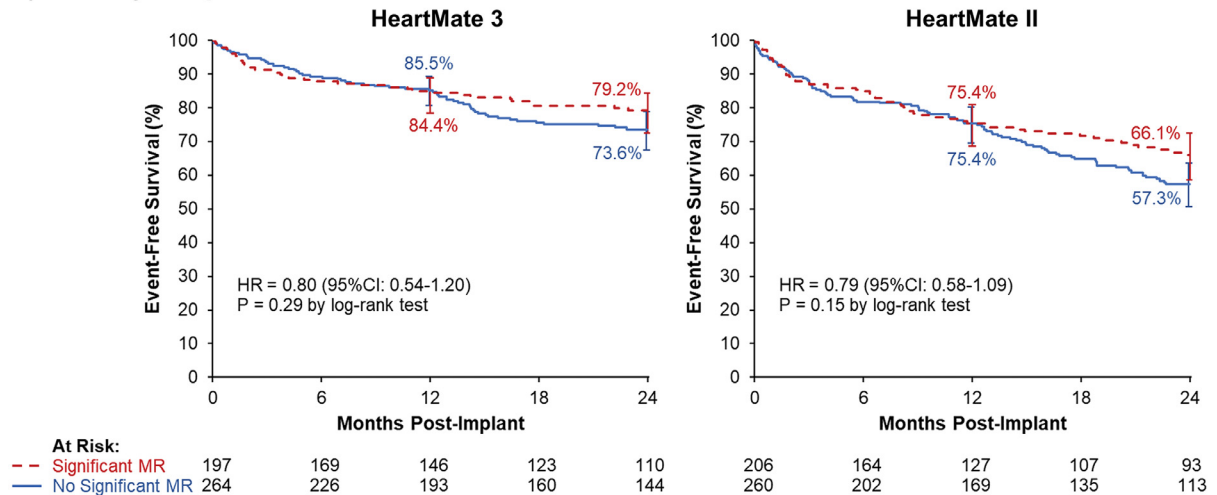


Figure 2 Significant MR over time in (A) all patients and (B) patients with significant baseline MR. CI, confidence interval; HM3, HeartMate 3; HMII, HeartMate II; MR, mitral regurgitation.

for those with residual MR compared with 17.5% for those with no residual MR (HR, 1.41; 95% CI, 0.52–3.89; $p=0.50$). In HMII patients, survival was 17.3% vs 21.6%, respectively, (HR, 0.91; 95% CI, 0.37–2.26; $p=0.84$).

Residual MR at 1-month post-implant did not significantly alter long-term survival with either pump type. Competing outcomes for patients with and without residual MR at 1-month post-implant are shown in Figure S4.

A) Primary Endpoint



B) Overall Survival

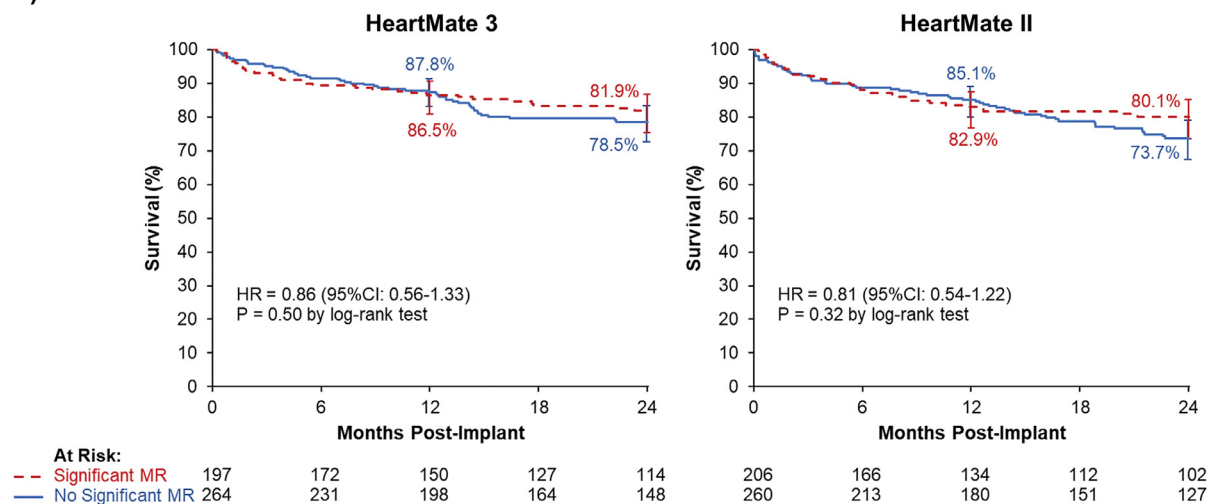


Figure 3 Impact of significant baseline MR on the (A) primary end-point and (B) overall survival in the HM3 and HMII arms. The primary composite end-point is survival free of disabling stroke (defined by a Modified Rankin score > 3, in which scores range from 0 to 6, with higher scores indicating more severe disability including death) or reoperation to remove or replace a malfunctioning device at 2 years. HRs are presented for significant baseline MR vs no significant baseline MR. CI, confidence interval; HM3, HeartMate 3; HMII, HeartMate II; HR, hazard ratio; MR, mitral regurgitation.

Readmissions

All-cause readmission rates in patients with vs without residual MR at 1-month post-implant are shown in Table S3. The readmission rates were 2.28 EPPY in patients with residual MR vs 2.37 EPPY in patients without residual MR and did not differ significantly (RR, 0.96; 95% CI, 0.82–1.14; $p = 0.66$).

Aortic insufficiency

Post-implant rates of aortic insufficiency (AI) are shown in Table S4. The occurrence of moderate or severe AI with either pump was low throughout the study follow-up (<7% at each visit). Although the total number of patients experiencing dysfunction in both valves was small, patients with HM3 with residual MR had a higher rate of AI than

those without residual MR (25.0% vs 2.4% at 24 months; $p = 0.002$).

Predictors of persistent significant MR post-implant

A portion of patients with significant baseline MR continued to experience significant MR after LVAD implantation. To identify predictors of persistent significant MR post-implant, we performed univariate comparisons of all the baseline variables listed in Table 1. The covariates identified by univariate analyses with $p < 0.10$ were entered into the multivariate logistic regression model using stepwise selection (Table 2). Severe baseline MR (OR, 2.30; 95% CI, 1.38–3.84; $p = 0.001$) and larger LV end-diastolic dimension (OR, 1.49; 95% CI, 1.15–1.92 per + 10 mm;

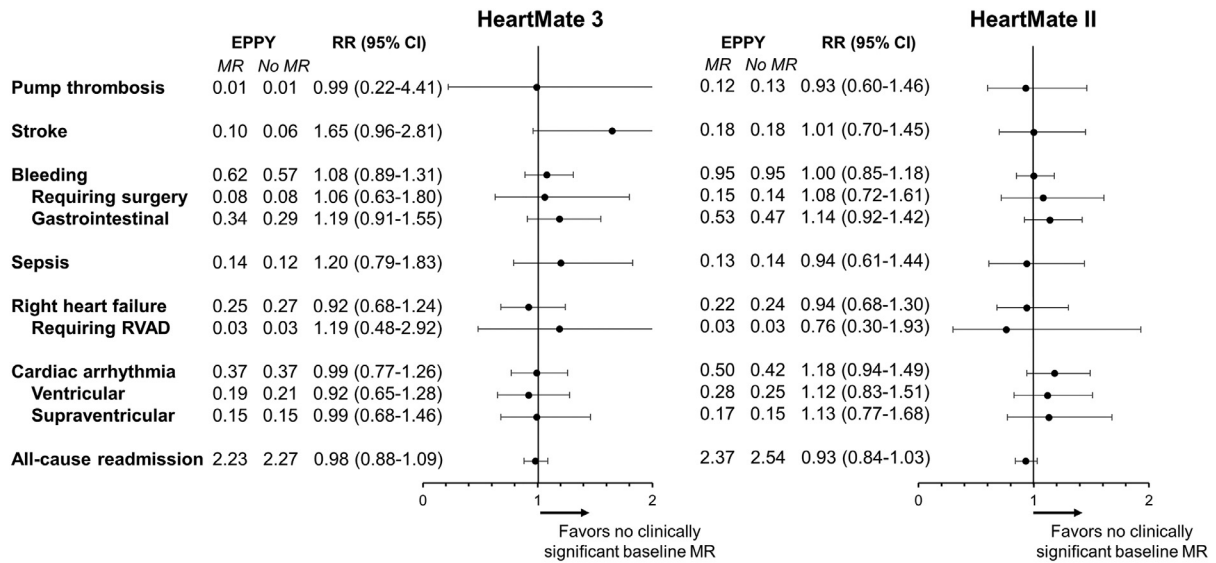


Figure 4 Impact of significant baseline MR on adverse event and readmission rates in the HM3 and HMII arms. RRs are presented for significant baseline MR vs no significant baseline MR. The RR of an adverse event favors no significant baseline MR when the lower boundary of the 95% CI is >1.0. When the 95% CI spans the line of unity, there is no significant difference between those with and without significant baseline MR. EPPY, events-per-patient-year; HM3, HeartMate 3; HMII, HeartMate II; MR, mitral regurgitation; RR, relative risk; RVAD, right ventricular assist device.

$p = 0.002$) were independently associated with an increased likelihood of persistent MR post-implant. In addition, treatment with HM3 vs HMII decreased the likelihood of experiencing persistent MR (OR, 0.60; 95% CI, 0.36–1.01; $p = 0.05$).

Discussion

The principal finding of our study demonstrates that nearly 50% of all LVAD implants are associated with significant MR at baseline, and hemodynamic unloading with an LVAD reduces the severity of uncorrected MR to a clinically insignificant degree within 1 month, a finding that is sustained over the 2-year follow-up period. We also note that the magnetically-levitated centrifugal-flow HM3 pump

is associated with a greater reduction in the severity of MR than the axial-flow HMII LVAD. Importantly, neither the presence of clinically significant baseline MR nor residual MR at 1-month is associated with adverse long-term outcomes after LVAD implantation.

The presence of significant MR in advanced HF as a therapeutic target is disputed.¹⁰ Surgical MV repair or replacement for secondary MR has not been shown to improve survival in HF. However, 2 separate studies using transcatheter MV repair have reported distinctive results. In 1 study, the use of the MitraClip (Abbott) in patients with severe MR after maximizing disease-modifying medical therapy has been shown to lower mortality and HF hospitalizations compared with medical therapy alone.¹¹ In contrast, another study that enrolled patients with severe MR

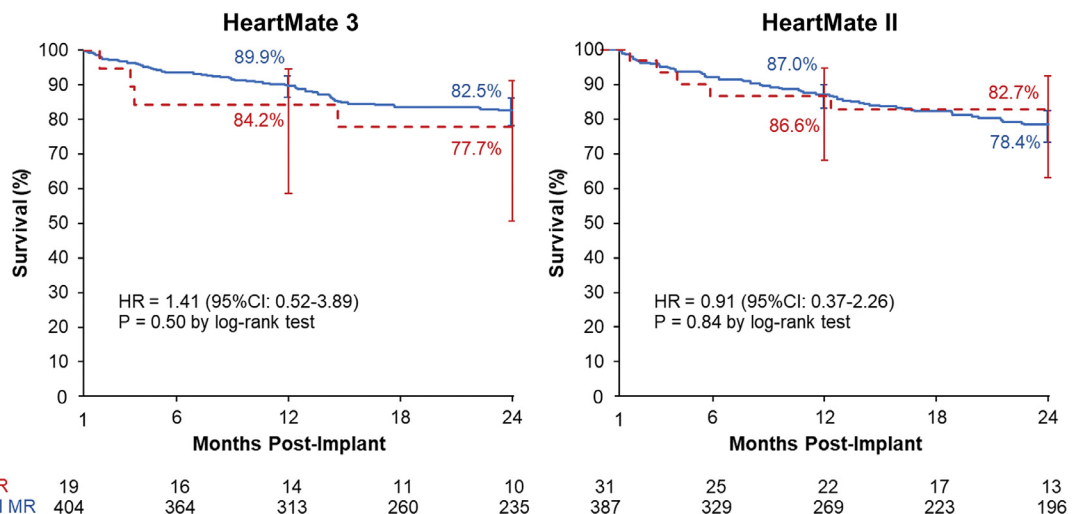


Figure 5 Impact of residual MR at 1-month post-implant on overall survival in the HM3 and HMII arms. HRs are presented for residual MR vs no residual MR. HR, hazard ratio; HM3, HeartMate 3; HMII, HeartMate II; MR, mitral regurgitation.

Table 2 Predictors of Persistent Significant MR Post-Implant

Univariate analyses	Persistent MR post-implant (n = 87)	No persistent MR post-implant (n = 299)	p-value ^a
HM3	34 (39.1%)	156 (52.2%)	0.03
Age, years	62 (50–67)	63 (53–70)	0.04
Ischemic heart failure	26 (29.9%)	124 (41.4%)	0.05
Severe MR at baseline	49 (56.3%)	104 (34.8%)	<0.001
LVEDD, mm	74 (67–81)	69 (64–76)	<0.001
Multivariate logistic regression	OR (95% CI)		p-value ^b
Severe vs moderate baseline MR	2.30 (1.38–3.84)		0.001
LVEDD, +10 mm	1.49 (1.15–1.92)		0.002
HeartMate 3 vs HeartMate II	0.60 (0.36–1.01)		0.05

HM3, HeartMate 3; LVEDD, left ventricular end-diastolic dimension; MR, mitral regurgitation; OR, odds ratio.
^aWilcoxon's rank sum test for continuous variables. Fisher's exact test or chi-square test for categorical variables, as appropriate.
^bStepwise selection with *p*-value entry criteria = 0.15 and *p*-value stay criteria = 0.10.

and more advanced LV dilatation failed to demonstrate the benefits of the MitraClip out to 2 years.¹² These findings have led to a vigorous debate over how these 2 trials resulted in such markedly disparate outcomes. The notion that MR proportionate to the degree of ventricular dilatation may be best served by a therapy that targets the ventricle rather than the valve has been proposed.^{13,14} The 2-year mortality in such patients irrespective of treatment of the MV is 34% and mimics the survival seen in an advanced HF population.¹² Our data suggest that LVAD implantation is associated with a rapid and marked improvement in the severity of MR with a 2-year mortality rate (~20%) that is significantly lower even when compared with interventional studies of percutaneous MR repair. Whether patients deemed unsuitable for percutaneous MV repair should be evaluated for potential LVAD consideration or at least followed closely at advanced HF programs is now an open question.

Combining valve surgery with LVAD implantation must be balanced with the trend toward early mortality in patients undergoing concomitant procedures.¹⁵ The results of our analysis may inform the decision to not mandatorily treat MV dysfunction during LVAD implantation for 2 reasons. First, the effectiveness of LVAD implantation alone in ameliorating clinically significant MR is robust and rapid. Second and more importantly, residual MR after LVAD implantation does not confer a late adverse outcome, either on survival, all-cause hospitalizations, or transplantation rates. Although this interpretation is reasonable, caution is advised as the exclusion of 4.6% (47 of 1,020) of trial patients with concomitant MV surgery may have confounded results. However, we believe that this proportion of patients was likely too small to have materially altered the observations in the larger trial dataset.

The HM3 LVAD demonstrated a lower rate of residual MR at 1 month when compared with the HMII pump. Although direct comparisons to the effectiveness of unloading of these 2 pumps are unavailable, studies with other hydrodynamic-based centrifugal-flow pumps have suggested that the axial-flow LVAD achieves greater unloading.¹⁶ Our

observations suggest that the unique characteristics of the magnetically-levitated HM3 pump, which include intrinsic pulsatility, may facilitate a reduction in MR by improved systolic leaflet coaptation. The mechanism behind this may be related to MR characterized by restriction of the posterior leaflet, in which excessive intracavity LV systolic pressure reduction exaggerates MR.¹⁷ An observational retrospective analysis of patients predominantly treated with the HMII axial-flow pump had demonstrated a trend toward residual MR when there was a greater posterior displacement of the mitral coaptation point.⁵ In our analysis, we were unable to establish the reasons for reduced residual MR with the HM3 LVAD because data collection did not include MV morphology, and simultaneous assessment of LV contractility, LVAD speed, systemic circulatory impedance, and LV end-diastolic volume.

One hypothesis-generating finding in our analysis relates to the association of residual MR with AI. We noted that the likelihood of AI rose appreciably when residual MR was present. Whether this was related to intentional LVAD speed reduction to ensure aortic leaflet mobility or MR resulting from increased ventricular loading because of AI cannot be determined by our analysis and will require another mechanistic study. These observations illustrate the difficulty and complexity in understanding the pathophysiology of MV dysfunction in advanced HF.

In addition to previously discussed limitations, we note that a small portion of patients had missing post-implant echocardiograms at each study visit; however, these rates were similar across groups and unlikely to have materially influenced the observed outcomes. The evaluation of MR and its severity was also qualitatively determined by each site. Ideally, a core lab could have provided more consistent quantitative data; however, quantification of secondary MR is challenging even within clinical trials because of dynamic loading conditions.¹⁸ In a trial of percutaneous MV repair, 34% of patients reduced their degree of MR from severe to moderate within 1 month without intervention.¹¹ In our analysis, we chose to include moderate and

severe MR together because of their known dynamic nature. This approach is further supported by our sub-analysis, separating moderate and severe MR (Figure S1), which showed no significant differences in primary or secondary outcomes post-LVAD between these categories. We also acknowledge that this is a post hoc analysis, and the sample size of patients with residual MR after LVAD implantation is small (as a result of the effectiveness of LVAD associated unloading). The small sample size of residual MR limits power and hence the ability of this analysis to appreciate any impact of this entity on measures of morbidity, particularly on sub-categories of hospitalization (e.g., heart failure-related events alone), time to transplantation, functional capacity and quality of life. Future analyses with larger cohorts can elucidate the potential impact of residual MR on adverse events and identify patients that should undergo surgical correction of MR for specific clinical indications.

Conclusions

Hemodynamic unloading after LVAD implantation improves clinically significant MR early, sustainably, and to a greater extent with the HM3 LVAD. Neither uncorrected baseline nor residual MR influence outcomes after LVAD implantation. These findings may call into question the need to surgically address clinically significant MR at the time of LVAD implantation.

Disclosure statement

M.K.K. is an advisory board member for Abiomed and Bayer; A.I. has received consultant fees and honoraria from Abbott, Abiomed, and Medtronic; S.C.C. has received consultant fees from Abbott and Medtronic; N.U. has received grant support, consultant fees from Abbott and Medtronic; J.C.C. has received grant support from Abbott; C.T.S. has received consultant fees from Abbott and Medtronic; D.H. has received consultant and Speaker's bureau fees from Abbott; D.J.G. is an educator and surgical proctor for Abbott; Y.N. has received consultant fees from Abbott; S. B. has received consultant fees from Abbott; I.D.G. has received grant support from CryoLife; J.C. is an employee of Abbott; P.S. is an employee of Abbott; M.R.M. is a consultant for Abbott (fees paid to Brigham and Women's Hospital), Portola, Bayer, Triple Gene, and Baim Institute for Clinical Research, and is an advisory board member for Medtronic, Janssen, NuPulseCV, Leviticus, FineHeart, and Mesoblast. The remaining authors have no conflicts of interest to disclose.

Supplementary data

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

Supplementary materials

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