First experiences with HeartMate 3 follow-up and adverse events

Jasmin S. Hanke, MD, Günes Dogan, MD, Sebastian V. Rojas, MD, Amelie Zoch, BSc, Christina Feldmann, PhD, Ezin Deniz, MD, Murat Avsar, MD, Gregor Warnecke, MD, PhD, Axel Haverich, MD, PhD, and Jan D. Schmitto, MD, PhD

ABSTRACT

Background: The novel HeartMate 3 (HM3) left ventricular assist device (LVAD) received its CE mark in October 2015. It is a new compact LVAD featuring fully magnetically levitated pump, artificial pulse, large pump gaps, and a modular driveline. Here, we present outcomes and adverse events of a single-center cohort 6 months after HM3 implantation.

Methods: We retrospectively studied a patient cohort of 27 patients who were supported with the HM3 at a single institution. We excluded patients with biventricular assist devices and other types of assist devices as well as LVAD exchange and re-operative procedures.

Results: Twenty-seven patients were enrolled into the study. Within 1 year after HM3 implantation, 1 patient received a heart transplant and 3 patients died. Thirty-day survival was 88.9% and 6 months 85.2%. No pump thrombosis and no strokes were observed within 6 months. Right heart failure was diagnosed in 1 patient after HM3 implantation (3.7%). No technical complications of the pump were documented. No pump exchanges were necessary.

Conclusions: The novel LVAD HM3 has already shown good CE mark trial results. Within this first report after the CE mark trial, the 6-month survival after HM3 implantation was 85.2%. The HM3 showed excellent midterm results with 0% stroke and 0% pump thrombosis rates 6 months after implantation. (J Thorac Cardiovasc Surg 2017;154:173-8)

Survival after HM3 implantation.

Central Message

The HM3 showed excellent midterm results with 0% stroke and 0% pump thrombosis rates 6 months after implantation. The rates of other complications remained low.

Perspective

There is a need for new devices with improved technology to reduce adverse events to further increase the acceptance and durability of mechanical support. Here, we present the first experience study on outcomes and complications of a single-center cohort after HeartMate 3 implantation.

See Editorial Commentary page 179.

The left ventricular HeartMate II (HMII; St Jude Medical Corporation, St Paul, Minn) is the commercially most successful left ventricular assist device (LVAD), with more than 22,000 implantations worldwide. The overall importance of LVADs is increasing.¹ The recent technical development has led to numerous improvements as well as a miniaturization process of LVADs.² The novel

HeartMate 3 (HM3; Thoratec Corporation, Pleasanton, Calif) underwent its first-in-human implant in June 2014 at Hannover Medical School, Hannover, Germany,³ and received its CE mark based on its excellent midterm results in October 2015.⁴ It is a new compact LVAD that is associated with several new technical features (eg, fully magnetically levitated pump, artificial pulse, large pump gaps, modular driveline).³ These benefits have potential to lead to superior outcomes compared with

From the Department of Cardiac, Thoracic, Transplantation, and Vascular Surgery, Hannover Medical School, Hannover, Germany.

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Reprint requests: Jan D. Schmitto, MD, PhD, Director of the Mechanical Circulatory Support and Cardiac Transplant Program, Department of Cardiac, Thoracic, Transplantation, and Vascular Surgery, Hannover Medical School, Carl-Neuberg-Str, 1 30625 Hannover, Germany (E-mail: Schmitto.Jan@mh-hannover.de).

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Scanning this QR code will take you to a supplemental video for the article.

Abbreviations and Acronyms

ECC	= extracorporeal circulation
fHb	= free hemoglobin
HM3	= HeartMate 3
HMII	= HeartMate II
LDS	= lactate dehydrogenase
LVAD	= left ventricular assist device
PAP	= pulmonary artery pressure
POD	= postoperative day
VAD	= ventricular assist device

its predecessor HeartMate II (HM2; Thoratec Corporation, Pleasanton, Calif) and other comparable assist devices.

With increased clinical experience in mechanical support, there have been significant reductions in some adverse events,^{5,6} but further improvements are still needed to reduce complications, such as infection, bleeding, thrombus, and stroke,⁷⁻¹⁰ which remain major concerns in ventricular assist device (VAD) therapy. Consequently, there is a need for new devices with improved technology to reduce adverse events to further increase the acceptance and durability of LVAD support.

In the study, we present 1-year outcomes and complications of a single-center cohort after HM3 implantation.

METHODS

Patients

We retrospectively studied a cohort of 27 patients who were supported with the continuous-flow LVAD HM3 at a single institution between June 2014 and April 2016. Eight of these patients of the study cohort were part of the HM3 CE mark trial in 2014. For the performance of this retrospective study, the database of Hannover Medical School, Hannover, Germany, was queried. All causes of death and adverse events were determined through examination of medical records. Only primary implantations were included in this study. Exclusion criteria were biventricular assist devices and other types of assist devices as well as LVAD exchange and re-operative procedures. All patients underwent HM3 implantation via full sternotomy via conventional technique with outflow graft anastomosis to the ascending aorta (Video 1). No concomitant procedures were performed. Heparin was started 6 hours after surgery. Intravenous heparin was administered as a bridge until anticoagulation with phenprocoumon was in the therapeutic range, with a target international normalized ratio of 2.0 to 3.0, plus aspirin at 100 mg per day. Blood pressure was measured by Doppler sonography in all patients. Target blood pressure was 60 mm Hg (mean).

Study Design

The data were retrospectively collected by electronic medical record review. Baseline characteristics were obtained for all patients before HM3 implantation. After HM3 implantation, survival, causes of death, and complications were recorded for all patients. Follow-up was 100% complete. Minimal follow-up time was 7 months; maximal follow-up time was 28 months. Because this was a retrospective study, the hospital ethical review board waived the need for patient consent to the study.

VIDEO 1. HeartMate 3 implantation at Hannover Medical School. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(17\)30178-2/addons](http://www.jtcvsonline.org/article/S0022-5223(17)30178-2/addons).

Statistical Methods

All statistical analyses were performed using SPSS version 22 software (IBM SPSS Statistics; IBM Corporation, Chicago, Ill). Categorical variables are reported in frequencies and continuous variables are reported as mean $\pm$ standard deviation or as median with range if applicable. Complications (adverse events) were recorded and analyzed according to the standard INTERMACS classifications.

RESULTS

Baseline Characteristics

This first single-center retrospective study consisted of 27 consecutive patients who received an HM3 device between June 2014 and April 2016 at Hannover Medical School, Hannover, Germany. Other implanted LVADs (eg, HeartMate II, Thoratec; HVAD, HeartWare [Framingham, Mass]; MVAD, HeartWare; HA5, Reliant Heart [Houston, Tex]) and biventricular assist devices as well as LVAD exchanges were excluded from analysis.

Detailed baseline characteristics of the patient cohort can be found in Table 1. In total, 23.4 patient years (284.5 months; 8544 days) were analyzed.

Average time on cardiopulmonary bypass was 86.6 ± 45.0 minutes. Average erythrocytes concentrate application until discharge was 5.1 ± 4.7 .

Preoperatively, 1 patient was supported by Impella (ABIOMED, Inc, Danvers, Mass) due to a fulminant myocardial infarction. No patients were preoperatively supported by extracorporeal membrane oxygenation or intra-aortic balloon pump. The most common preoperative risk factor was pulmonary hypertension (PAP mean greater than 25 mm Hg) (22.4%). Four (14.8%) patients were diagnosed with type 2 diabetes. Four (14.8%) patients had a myocardial infarction within the past 90 days before LVAD implantation.

Outcomes After HM3 Implantation

The Kaplan-Meier curves in Figure 1 illustrate the patient survival. Fifteen days after HM3 implantation, a survival of

TABLE 1. Baseline characteristics of the study group

	HeartMate 3 patients
Total	27
Male, n (%)	25 (92.6)
Female	2 (7.4)
Average age male (y)	56.2 ± 10.8
Average age female (y)	63 ± 4.2
Average body mass index (kg/m ²)	27.95
Diagnoses, n (%)	
Dilated cardiomyopathy	18 (66.7)
Ischemic cardiomyopathy	9 (33.3)
NYHA profile, n (%)	
IV	26 (96.3)
III	1 (3.7)
INTERMACS profile, n (%)	
I	1 (3.7)
II	2 (7.4)
III	23 (85.2)
IV	1 (3.7)
Stay	
Average in-hospital stay after LVAD implantation (d)	21.9 ± 9.4
Average ICU stay (d)	3.6 ± 2.7
Average cardiopulmonary bypass time (min)	86.6 ± 45.0
Average erythrocyte concentrate until discharge	5.1 ± 4.7
Preoperative right heart catheter	
Average right atrial pressure (mm Hg)	
Systolic	13.3 ± 2.8
Diastolic	12.2 ± 3.9
Mean	11.3 ± 2.5
Average pulmonary artery pressure (mm Hg)	
Systolic	52.3 ± 23.2
Diastolic	23.9 ± 10.4
Mean	34.8 ± 15.3
Average pre-implant cardiac index (L/min/m ²)	1.9 ± 0.4
Echocardiography	
Average preoperative LV ejection fraction (Echo)	24.3 ± 11.1
Average pre-discharge LV ejection fraction (Catheter)	19.1 ± 7.3
Average pre-operative LV end diastolic diameter	75.9 ± 11.1
Average pre-discharge LV end diastolic diameter	64.5 ± 13.2
Preoperative mitral valve insufficiency, n (%)	
0	9 (33.3)
I	12 (44.4)
II	4 (14.8)
II-III	1 (3.7)
Preoperative tricuspid valve insufficiency, n (%)	
0	6 (22.2)
I	9 (33.3)
II	8 (29.6)
III	4 (14.8)

(Continued)

TABLE 1. Continued

	HeartMate 3 patients
Status, n (%)	
Cardiac transplantation	1 (3.7)
LVAD explantation due to recovery	0 (0)
Death after LVAD implantation	3 (11.1)

NYHA, New York Heart Association; LVAD, left ventricular assist device; ICU, intensive care unit; LV, left ventricular.

96.3% (26/27) was observed in the study cohort. After 30 days, the survival rate was 88.9%, 88.9% after 3 months, and 85.2% 6 months after HM3 implantation.

Of 27 patients, after a period of 6 months, 1 patient had successfully undergone heart transplantation on postoperative day (POD) 51. Three patients died during the study period. The remaining 23 patients are still ongoing on the device. Six-month survival after HM3 implantation is 85.2%.

The longest ongoing patient out of the HM3 study has been on device for more than 2 years as of November 15, 2016.

Pre- and postoperative laboratory values are listed in Table 2. Renal as well as liver laboratory parameters improved significantly after VAD implantation (Table 2).

Causes of Death

Six months after HM3 implantation, of 27 patients, 3 patients had died. The first patient died on POD 17 because of pneumonic sepsis. The second and the third patients died on POD 7 and POD 22 due to multiorgan failure. Right heart failure was diagnosed in the second patient.

Complications

Thirty days after HM3 implantation. Adverse events are listed in Table 3. The most common complication during the first 30 days was non-LVAD-associated infection, with 8 events in 7 (25.9%) patients of the study group.

FIGURE 1. Kaplan-Meier survival curves for the study group.

TABLE 2. Pre- and postoperative laboratory parameter of the study group

	Preoperative	Postoperative/ pre-discharge	P
SAST, U/L	82.3 ± 128.3	32.9 ± 26.3	.037
SALT, U/L	110.8 ± 229.6	38.0 ± 52.4	.035
GLDH, U/L	23.0 ± 86.7	3.5 ± 5.0	.002
SCHE, U/L	7.3 ± 2.4	5.1 ± 1.7	.015
Total bilirubin, μ mol/L	36.8 ± 80.7	32.4 ± 66.6	.111
Creatinine, μ mol/L	122.6 ± 44.6	95.9 ± 36.7	.008
Urea, mmol/L	8.9 ± 4.3	7.2 ± 5.6	.017
eGFR, mL/min	56.1 ± 19.8	63.8 ± 16.1	.123
Sodium, mmol/L	139.1 ± 3.0	137.0 ± 3.6	.168
C-reactive protein, mg/dL	33.1 ± 51.4	75.4 ± 85.7	.004

SAST, Serum aspartate aminotransferase; SALT, serum alanine aminotransferase; GLDH, glutamate dehydrogenase; SCHE, serum cholinesterase.

LVAD-related infections were observed in 2 (8.3%) patients.

Eight minor bleeding events were documented in 6 patients (22.2%) during the first month after HM3 implantation. Of those, 1 patient suffered gastrointestinal bleeding (3.7%) and 5 patients suffered minor bleeding, such as epistaxis. None of these bleeding events required surgical intervention. One patient underwent re-sternotomy 3 weeks after HM3 implantation due to a late cardiac tamponade.

No cases of pump thrombosis or stroke were observed. Right heart failure was observed in 1 patient (3.7%). There were no technical failures of the pump.

Six months after HM3 implantation. Of 27 patients, 24 reached the 6-month mark of this study. Six months after HM3 implantation, a total of 12 bleeding events in 8 patients were observed. Of those, 1 required surgery (3.7%) due to late cardiac tamponade (0.0035112 events per patient month). One case of gastrointestinal bleeding was observed (3.7%) (0.0035112 events per patient month).

No pump thrombosis and no strokes were witnessed in the study group during 6 months of HM3 support.

Six LVAD-related infections were documented in 4 patients (14.8%) (0.0210675 events per patient month). Three patients died in the first 3 weeks; the adjusted rate is 16.6%. All of the documented infections were driveline related. Eight non-LVAD-related infections were documented in 7 patients (33.3%) during the first year after HM3 implantation (0.0280899 events per patient month).

Right heart failure was diagnosed in 1 patient during the early postoperative course after HM3 implantation (3.7%) (0.0070224 events per patient month). No technical complications of the pump were documented. There were no pump exchanges.

Lactate Dehydrogenase and Free Hemoglobin

The average lactate dehydrogenase (LDH, U/L) as well as free hemoglobin (fHb, mg/L) laboratory values are displayed in Figure 2. The fHb curve shows a steep decline followed by a slight increase in the sixth postoperative month. After the sixth month, the curve is decreasing to normal values. LDH levels showed a decrease during the whole study period, with an average LDH value of 266.5 U/L after 6 months of HM3 support and an average fHb of 158.8 mg/L.

DISCUSSION

Heart transplantation remains the gold standard for eligible patients in the therapy of terminal heart failure even though it might not be available to everyone. Yet, the improvements of the new-generation pumps are promising and are likely to successfully close the gap between the lack of organ donors and patients on the transplant list.

In this study, 6-months outcomes after HM3 implantation are presented. One-year survival in this group of patients was 85.2%. The HM3 CE mark trial had shown a

TABLE 3. Adverse events in the study group

	1 Month n = 27		3 Months n = 24		6 Months n = 23		>6 Months n = 23		All (1 y) n = 27		Events per patient month
	Patients	Events	Patients	Events	Patients	Events	Patients	Events	Patients	Events	
Bleeding											
Bleeding event	6 (22.2)	8	3 (12.5)	3	0 (0)	0	1 (4.3)	1	8 (33.3)	12	0.0421347
Requiring surgery	1 (4.2)	0	0 (0)	1	0 (0)	0	0 (0)	0	1 (3.7)	1	0.0035112
GI bleeding	1 (3.7)	1	0 (0)	0	0 (0)	0	0 (0)	0	1 (3.7)	1	0.0035112
Pump thrombosis	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0
Technical complication	0 (0.0)	0	0 (0)	0	0 (0)	0	0 (0)	1	0 (0)	0	0
Infection											
LVAD-related	2 (8.3)	2	1 (4.2)	2	0 (0)	0	2 (8.7)	2	4 (14.8)	6	0.0210675
Non-LVAD-related	7 (25.9)	8	0 (0)	0	0 (0)	0	0 (0)	0	7 (25.9)	8	0.0280899
Right heart failure	1 (3.7)	1	1 (4.8)	1	0 (0)	0	0 (0)	0	1 (3.7)	1	0.0035112
Stroke	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0

GI, Gastrointestinal; LVAD, left ventricular assist device.

FIGURE 2. Lactate dehydrogenase (LDH [U/L]) and free hemoglobin (fHb [mg/L]) levels after HM3 implantation.

6-month survival of 92.0% and the MOMENTUM trial showed a 6-month survival of 86.2% in the study group.^{4,11} Reported key adverse events included reoperation for bleeding (14%), driveline infection (10%), gastrointestinal bleeding (8%), and debilitating stroke (8%) in the nonrandomized Conformité Européenne study.⁴ The US-based MOMENTUM trial reported rates of 9.9% for bleeding requiring surgery, 15.9% for gastrointestinal bleeding, 11.9% driveline infection, 0% pump thrombosis, and a stroke rate of 7.9%.¹¹ In our single-center cohort, 1 year after HM3 implantation there was 1 reoperation for bleeding (4.2%), 17% LVAD-related infections, 4% gastrointestinal bleedings, no strokes (0%), and no device failures (0%) in the first 6 months after implantation.

LVAD pump thrombosis has been extensively discussed in the past years. For HMII, Starling et al¹² reported that pump exchange or death due to pump thrombosis increased during 2011 and 2012, but the level of the increase remained small.^{10,13,14} A risk factor analysis suggested that a number of patient-related factors contribute to the risk of thrombosis.¹² Although other centers reported increased thrombosis rates, we reported a steady rate of 2.2%.¹³ Smedira et al¹⁴ analyzed a total of 995 thrombosed pumps and also reported an increase in pump thrombosis in 2010, which reached a maximum in 2012, and then plateaued at a level that was reportedly 3 times higher than pre-2010. In our study cohort, we did not observe cases of pump thrombosis. In accordance with our results, the CE mark study as well as the MOMENTUM trial also reported no pump thrombosis, respectively.^{4,11} Debilitating strokes were reported in 8% of the patients in the CE mark study and in 7.9% of the patients in the MOMENTUM trial.^{4,11} In our patient population, even 1 year after HM3 implantation, no strokes were observed.

Compared with the HMII, one of the distinctive features of the HM3 is its fully magnetically levitated (Mag-Lev) rotor, which eliminates the need for mechanical bearings or hydrodynamic blood bearings. There are large secondary

flow path gaps of 0.5 mm along the side of the rotor, and 1.0 mm above and below the rotor, which are 10 to 20 times that of other devices being used.³ In addition, the pump is capable of automatic speed modifications (reduction and increase of rotor speed every 2 seconds), creating a wash-out cycle as well as an “artificial pulse.” These features might lead to the reduction of complications, such as pump thrombosis and strokes. Yet, larger studies need to reconfirm the favorable outcomes of patients with the HM3. Nevertheless, the results of the studies are promising.

One of the major disadvantages of the HeartMate II compared with other available assist devices (eg, HeartWare HVAD) is the large pump housing and therefore the limited possibilities of less-invasive implantations. With the reduced size of its pump housing, minimally invasive implantation strategies become available using the HM3. Minimally invasive cardio-surgical procedures are anticipated to carry some positive effects (eg, reduction of trauma, blood loss, and infections; decrease in intensive care unit and in-hospital stays; and improved overall outcomes).^{2,15-22} The new developments and implantation techniques of LVADs could contribute to the improvement of therapy outcomes by reducing important operative complication rates, such as right ventricular failure by avoiding pericardial opening.¹⁶ Because the miniaturization process of LVADs is ongoing, minimally invasive procedures might gain importance; however, major comparative trials between conventional and less-invasive procedures have not yet been published.

Compared with its predecessor HeartMate II, the HM3 seems to be associated with superior short- and midterm outcomes and a reduction of adverse events.⁴ Additionally, based on lower power consumption, it has longer battery capacity, which improves quality of life of patients with a VAD. In case of severe device infection or pump thrombosis, LVAD exchange procedures are an opportunity to upgrade patients to a new-generation pump that offers, for example, advanced reduction of adverse events or longer battery hours.²³⁻²⁶ Our group previously reported the first case of LVAD upgrade from HeartMate II to HeartMate 3.

Studies to investigate the potential of less-invasive implantation techniques as well as studies on outcomes of upgrades from HMII to HM3 are needed to prove the benefits of these strategies. Enrollment for the HM3 less-invasive implantation trial, as well as a study on LVAD upgrades, started in 2015 and is currently ongoing.

Limitations

This study has several limitations. The data are retrospectively collected and analyzed and therefore is subject to the limitations associated with retrospective studies. All implantations were performed at a single center and therefore reproducibility may be limited and affected by institutional experience. The results of surgical studies are prone to

learning curves and single center's specific characteristics. Moreover, the study period began 2 years ago; therapeutic strategies and increased clinical experience might have improved today's results.

Additionally, the number of patients on the new device was small, which reduces the statistical power. As such, larger studies need to be performed on the outcomes of patients with the HM3. Furthermore, this study is limited to a single LVAD and does not compare the outcomes of other comparable assist devices. Larger, prospective, randomized controlled studies might be useful to compare the long-term outcomes of different types of assist devices.

CONCLUSIONS

The novel LVAD HM3 has already shown good CE mark trial results. Within this first report on 6-month outcomes of a cohort, the survival after HM3 implantation was 85.2%. The HM3 showed excellent midterm results with 0% stroke and 0% pump thrombosis rates 6 months after implantation.

Conflict of Interest Statement

Drs Haverich and Schmitto are consultants for Thoratec Cooperation. All other authors have nothing to disclose with regard to commercial support.

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