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Five-year outcomes of patients supported with HeartMate 3: a single-centre experience

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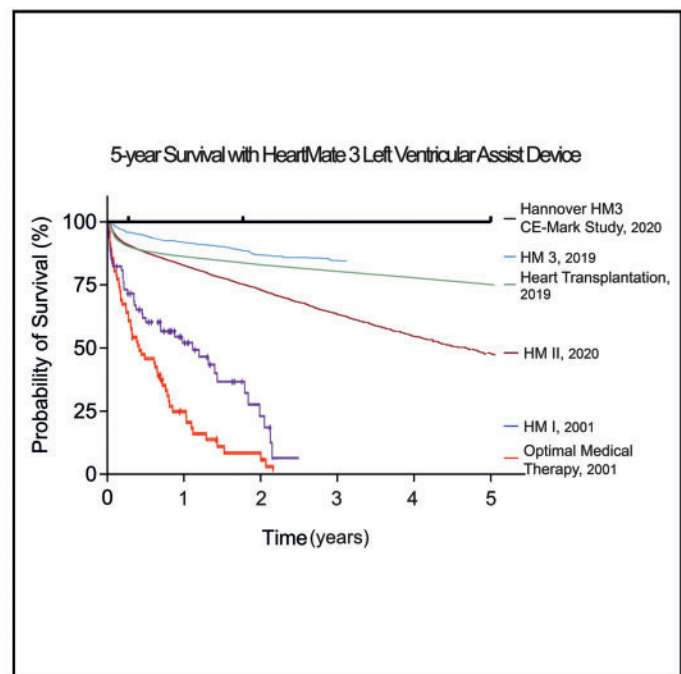
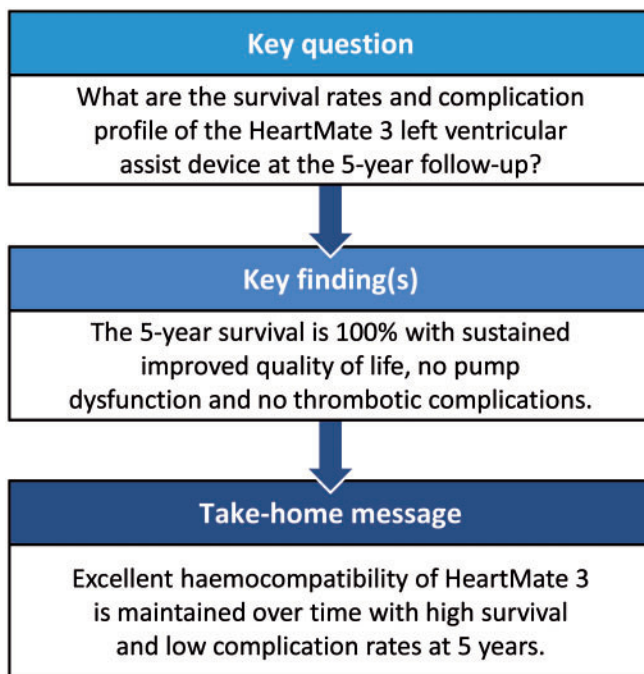
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Abstract

OBJECTIVES: The HeartMate 3 left ventricular assist device was first implanted in 2014 and received the Conformité Européenne mark in 2015. Since then, several trials demonstrated its high haemocompatibility associated with good survival and low adverse events rates. Herein, we report our institutional experience with patients supported with HeartMate 3 for 5 years.

METHODS: This prospective cohort study included patients receiving a HeartMate 3 implantation in 2014 as part of the HeartMate 3 Conformité Européenne Mark clinical trial. Patients had follow-up visits every 3 months while on left ventricular assist device support, and all patients completed the 5-year follow-up. The primary end point was survival at 5 years. Secondary end points included adverse events, health status and quality of life.

RESULTS: Eight patients (men: 75%) aged 59 years (min–max: 52–66 years) were enrolled. At 5 years, survival was 100%. Patients remained on support for a median time of 1825 days (min–max: 101–1825 days); 2 patients successfully received cardiac transplants. No right heart failure, haemolysis, pump thrombosis, pump malfunction or neurological events occurred in any patients. A driveline infection was observed in 6 patients (0.25 events/patient-year). Compared to baseline, a significant improvement in quality of life and in New York Heart Association functional class was noted after the implant and for the whole follow-up time. A slight decline in kidney function and in the 6-min walk test results occurred after 3 years.

CONCLUSIONS: This study reports the longest single-centre follow-up of the HeartMate 3, showing excellent haemocompatibility over time with high survival and low complication rates at 5 years.

Keywords: Left ventricular assist device • HeartMate 3 • Heart failure • Mechanical circulatory support

ABBREVIATIONS

CE	Conformité Européenne
HF	Heart failure
IQR	Interquartile range
LVAD	Left ventricular assist device
NYHA	New York Heart Association
VAD	Ventricular assist device

INTRODUCTION

Left ventricular assist devices (LVADs) play an increasing role among advanced treatments for end-stage heart failure (HF), based on improving results, better quality of life and longer survival times [1–4]. Part of this success can be attributed to the newest centrifugal pumps, which are characterized by reduced dimensions and higher biocompatibility. In particular, the HeartMate 3 Left Ventricular Assist System (Abbott, Burlington, MA, USA) represents a technological paradigm based on its design. With the hallmarks of a fully magnetically levitated motor (Full MagLev) with no mechanical contact points, larger gaps, sintered surfaces, artificial pulse and modular driveline, HeartMate 3 significantly improved patients' outcomes compared with previous generations of LVADs [2]. The first-in-man implant of the HeartMate 3 was performed in 2014 at Hannover Medical School (Hannover, Germany) [5] as part of the multicentre European trial that led to the Conformité Européenne (CE) mark approval in 2015 [1, 6]. This study demonstrated an overall survival of 74% at 2 years and substantial improvements in functional status and quality of life. Later, similar outcomes were confirmed by the MOMENTUM 3 (Multicentre Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3) trial [2, 7]. Notably, the CE mark trial [1], as well as the ELEVATE registry [8] and further clinical experiences [9–12], reported the excellent haemocompatibility of HeartMate 3 as evidenced by the extremely low rates of pump thrombosis.

Nevertheless, data on longer follow-up times are still scarce. Our goal was to present the 5-year outcomes after HeartMate 3 implantation in a cohort of patients from a single centre.

MATERIALS AND METHODS

Study design, population and outcomes

This report includes prospectively monitored consecutive patients receiving a HeartMate 3 implantation at a single, high-volume centre in 2014. All patients included in this report were part of the HeartMate 3 CE Mark Clinical Investigation Plan, including the first in-human HeartMate 3 implantation [5]. Details of the study protocol have been previously published [6, 13].

The study included adult patients with New York Heart Association (NYHA) functional class IIIB–IV symptoms, an ejection fraction $\leq 25\%$ and a cardiac index ≤ 2.2 l/min/m² without inotropic support or inotrope-dependent patients with optimal medical management or listed for a heart transplant. Only primary isolated LVAD implantations were included.

The primary end point was 5-year survival. Secondary end points were adverse events defined according to INTERMACS classifications, health status and quality of life (EQ-5D-5L questionnaire), functional status (NYHA class, 6-min walk test), rates of pump exchange, explant for recovery and transplant. Further data were collected to evaluate kidney function, liver function and haemolysis. Pump parameters were monitored. Follow-up for secondary end points was censored in case of an LVAD explant or transplant.

Surgical approach and clinical management

All patients underwent HeartMate 3 implantation through a conventional sternotomy, cardiopulmonary bypass support and outflow graft anastomosis to the ascending aorta. Intravenous heparin was started 6–8 h postoperatively with the goal of a partial thromboplastin time of 45–65 s. The heparin dose was increased over 2 days to reach a partial thromboplastin time of 55–65 s. Aspirin and a vitamin K antagonist were started once the patient was able to take oral medications and continued throughout support, with a target international normalized ratio of 2.0–3.0. All patients received a device for international normalized ratio self-check (CoaguCheck, Roche, Switzerland) after adequate training and a diary to note international normalized ratio values. Specialized ventricular assist device (VAD) coordinators had regular

phone contact with patients to guide them in their anticoagulation management. No changes in anticoagulation regimens were made during the follow-up period. The mean target blood pressure was 60–65 mmHg, measured by Doppler sonography. A 24/7 LVAD-dedicated hotline managed by VAD coordinators was available for patient counselling. Patients attended follow-up visits every 3 months while on LVAD support, and all patients completed the 5-year follow-up programme for survival.

Statistical methods

Categorical variables are reported as frequencies (*n*, %), and continuous variables are reported as median and minimum-maximum range (min–max). Adverse events are given as number and events per patient year. Variables were analysed with the Friedman test for repeated measures where appropriate. A Kaplan–Meier analysis estimated survival. Statistical analyses were performed with SPSS 26 (SPSS Inc., Chicago, IL, USA) and Prism 8 (GraphPad, San Diego, CA, USA).

Ethics statement

All patients included in this study were part of the HeartMate 3 CE Mark Clinical Investigation Plan (ClinicalTrials.gov: NCT02170363), which was approved by the ethics committee at our institution (number: CIV-14-01-011786). An extension of this study, the HeartMate 3 CE Mark follow-up study, was approved by the local ethics committee (number: 3220-2016). For both studies, ethical approval was requested and granted at each participating centre under the central coordination of Abbott Medical Devices (Abbott, Burlington, MA, USA). All participants provided informed consent.

RESULTS

Baseline characteristics and perioperative outcomes

Eight patients (6 men, 2 women) had HeartMate 3 implantation at Hannover Medical School between June and November 2014. The median age was 59 years (min–max: 52–66 years). Five patients were diagnosed with dilated cardiomyopathy, and 3 patients had ischaemic cardiomyopathy. The majority of patients were NYHA functional class IV (75%) and INTERMACS profile 3 (75%) with a median ejection fraction of 15% (min–max: 10–25) and a median cardiac index of 2.06 l/min/m² (min–max: 1.30–2.2). None of the enrolled patients required preoperative temporary mechanical circulatory support. All patients received implants as a bridge to a transplant. Further baseline characteristics are listed in Table 1. All implants were accomplished uneventfully (Table 2). No patient required postoperative temporary mechanical circulatory support, a right VAD implant or rethoracotomy for bleeding. The stay in the intensive care unit ranged from 2 to 9 days, and the overall median hospital stay was 26 days (min–max: 17–33 days).

Survival and adverse events

In total, 40 patient-years were analysed. The median duration of support was 1825 days (min–max: 101–1825 days), with 6

Table 1: Baseline characteristics

Variables	HeartMate 3 patients (n = 8)
Age (years)	59 (52–66)
Male gender	6 (75)
Body mass index (kg/m ²)	27.61 (20.28–32.44)
Body surface area (m ²)	2.01 (1.71–2.16)
Aetiology	
Dilated cardiomyopathy	5 (62.5)
Ischaemic cardiomyopathy	3 (37.5)
NYHA functional class	
III	2 (25)
IV	6 (75)
INTERMACS profile	
III	6 (75)
IV	2 (25)
History of stroke	1 (12.5)
Chronic obstructive pulmonary disease	3 (38)
Diabetes	2 (25)
Chronic kidney disease ^a	2 (25)
Implantable cardioverter-defibrillator implantation	7 (87.5)
Previous cardiac surgery	1 (12.5)
Preoperative echocardiography	
LVEF (%)	15 (15–20)
LVEDD (mm)	74 (68–78)
Mitral valve regurgitation	
0	3 (37.5)
I	4 (50)
II	1 (12.5)
Tricuspid valve regurgitation	
0	2 (25)
I	4 (50)
II	1 (12.5)
III	1 (12.5)
Preoperative right heart catheter	
Mean right atrial pressure (mmHg)	12 (6–13)
Mean right ventricular pressure (mmHg)	12 (7–17)
Mean pulmonary artery pressure (mmHg)	28 (15–57)
Pulmonary capillary wedge pressure (mmHg)	23 (7–39)
Cardiac index–Fick (l/min/m ²)	2.05 (1.3–2.2)

Data are expressed as *n* (%) or median (min–max).

^aChronic kidney disease is defined as estimated glomerular filtration rate <60 ml/min/1.73 m².

LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.

patients remaining on device until the end of the follow-up period. Two patients successfully underwent heart transplants. The first patient received a compatible heart 101 days after the device was implanted. The second patient experienced episodes of low-flow alarms and received a transplant 646 days after the LVAD was implanted. The other patients were still on support at the end of the follow-up period, based on their non-urgent status. No patient underwent an LVAD explant or exchange, and no deaths occurred (Fig. 1A).

Adverse events are listed in Table 3. No cases of right HF, pump thrombosis, pump dysfunction or stroke were observed. Infections remained the major complication, with 6 patients developing driveline infections, but no pump infections were recorded. All driveline infections were managed according to the standard-of-care protocols developed by the Driveline Expert STaGInG and carE DESTINE study group [14]. Only 1 bleeding event (epistaxis treated with local medications and nasal packing) was observed; no changes in the anticoagulation regimen were

required. One patient required surgical intervention to release external compression of the outflow graft 55 months after implantation. The patient was admitted with dyspnoea, peripheral oedema and limitation of daily activities. LVAD flow decreased to 3.0 l/min with a pump speed of 5300 rpm, a pulse index of 3.7 and a motor power of 3.7 W. A computed tomography scan showed stenosis of the outflow graft lumen in the tract corresponding to bend relief. Through minimally invasive surgery, the

bend relief was longitudinally opened to release the compression due to a thick layer of membranous tissue. Intraoperatively, the estimated LVAD flow increased from 1.9 to 4.0 l/min, and the patient was discharged home on postoperative day 7 in good clinical condition.

Organ function, pump parameters and quality of life

Laboratory values are illustrated in Fig. 2A–F. Liver function remained stable over time, and lower bilirubin levels were observed at discharge (median: 5.3, min–max: 4–8) compared to preoperative values (median: 17.5, min–max: 10–36; $P=0.028$). One patient had higher preoperative levels of alanine aminotransferase and aspartate aminotransferase compared to the other patients, and his liver function normalized after surgery. Kidney function improved after the LVAD was implanted ($P=0.021$) and remained stable over the following 2 years. Subsequent declines at 3 years ($P=0.001$), 4 years ($P<0.001$) and 5 years ($P<0.001$) compared to discharge were noted. Haemolysis parameters remained stable over time (Fig. 2E and F).

Pump power and the pulsatility index remained stable from discharge to the end of the follow-up period (Fig. 3A–D). Pump speed increased gradually from discharge (median: 5250 rpm, min–max: 5000–5400) to 1 year (median: 5400 rpm, min–max: 5300–5800) but without reaching statistical significance. Pump flow demonstrated a parallel increase from discharge [median: 4.1, interquartile range (IQR): 3.1–5.0] to the 6-month follow-up (median: 3.8, IQR: 3.3–4.3) to 3 years (median: 4.45, IQR: 3.9–4.9; $P=0.004$) and stabilized afterwards.

Variable names	HeartMate 3 patients ($n=8$)
Combined procedures, n (%)	1 (12.5) PFO closure
Operating time (min), median (min–max)	168 (105–320)
Cardiopulmonary bypass time (min), median (min–max)	84 (47–130)
Intraoperative blood products (U), n (%)	
Packed red cells	1 (0–4)
Fresh frozen plasma	0 (0–2)
Platelets	0 (0–1)
Rethoracotomy for bleeding, n (%)	0 (0)
Mechanical ventilation time (h), median (min–max)	15.4 (7.6–21.5)
Postoperative ECMO, n (%)	0 (0)
Intensive care unit stay (days), median (min–max)	3 (2–9)
Postoperative hospital stay (days), median (min–max)	26 (17–33)

CMO: extracorporeal membrane oxygenation; PFO: patent foramen ovale.

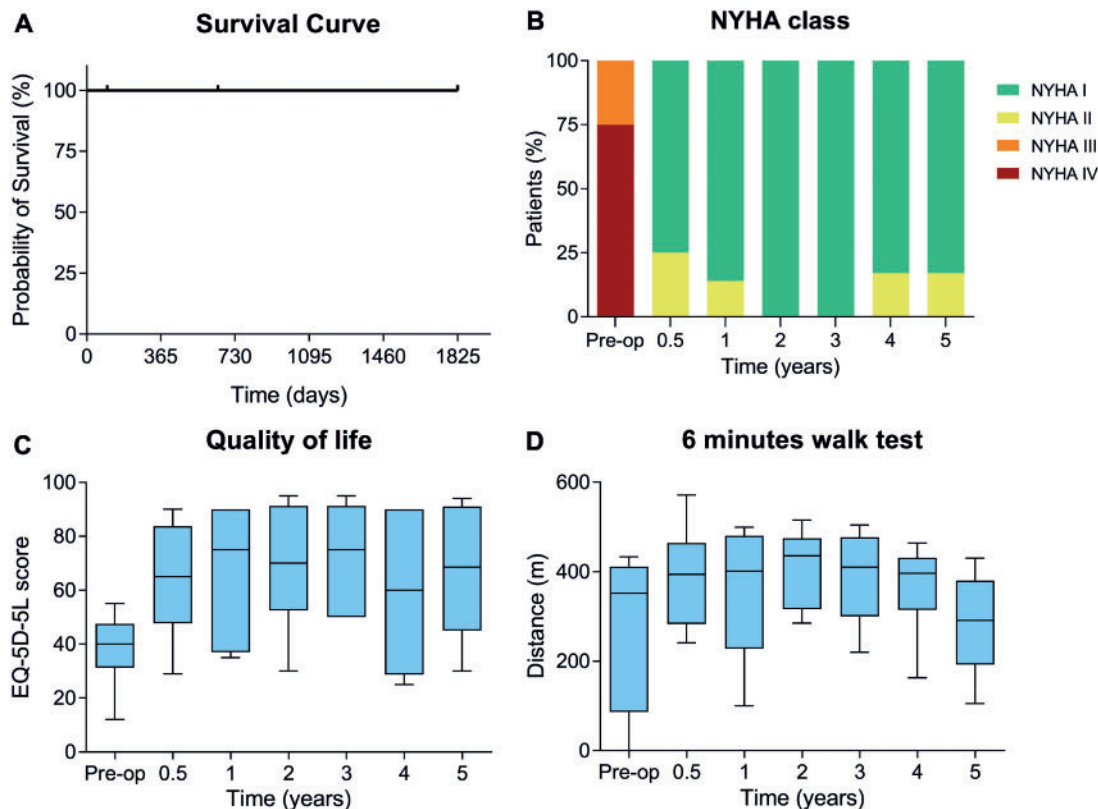


Figure 1: Survival curve (A) and assessment of patient status: quality of life evaluation (B) (EuroQoL visual analogue score), NYHA functional class (C) and results of 6-min walk test (D). NYHA: New York Heart Association; Pre-op: preoperative.

Table 3: Adverse events during the follow-up period

Variables	0.5 Years		1 Year		2 Years		3 Years		4 Years		5 Years		Events/ patient- year
	<i>n</i> = 7		<i>n</i> = 7		<i>n</i> = 6		<i>n</i> = 6		<i>n</i> = 6		<i>n</i> = 6		
	Patients	Events	Patients	Events	Patients	Events	Patients	Events	Patients	Events	Patients	Events	
Bleeding events													
Overall bleedings	0	0	1	1	0	0	0	0	0	0	0	0	0.031
Requiring surgery	0	0	0	0	0	0	0	0	0	0	0	0	0
Gastrointestinal bleeding	0	0	0	0	0	0	0	0	0	0	0	0	0
Infections													
Not LVAD related	0	0	1	1	1	1	0	0	0	0	0	0	0.062
Driveline infections	1	1	1	1	2	3	1	1	2	2	0	0	0.250
Pump infections	0	0	0	0	0	0	0	0	0	0	0	0	0
Right heart failure	0	0	0	0	0	0	0	0	0	0	0	0	0
New atrial fibrillation	0	0	0	0	0	0	1	1	0	0	0	0	0.031
New ventricular tachycardia	2	2	0	0	0	0	0	0	0	0	0	0	0.062
Stroke	0	0	0	0	0	0	0	0	0	0	0	0	0
Pump thrombosis	0	0	0	0	0	0	0	0	0	0	0	0	0
Modular cable exchange	0	0	0	0	1	1	0	0	2	2	2	2	0.155
Other ^a	0	0	0	0	0	0	0	0	0	0	1	1	0.031

^aExternal compression of outflow graft.

LVAD: left ventricular assist device.

At baseline, all patients were in NYHA functional class IIIB or IV. At 5 years, 83% of patients were classified as NYHA functional class I and 17% were NYHA functional class II (Fig. 1B). Quality of life showed significant improvements from baseline (median: 40, min-max: 12–55) to 6 months (median: 65, min-max: 29–90; $P=0.015$), sustained to 5 years (Fig. 1C). The results of the 6-min walk test (Fig. 1D) showed a gradual improvement from baseline (median: 351 m, min-max: 0–433) to 2 years (median: 435.5 m, min-max: 285–515; $P=0.033$) and a decline until the 5th year (median: 310 m, min-max: 105–477).

DISCUSSION

This single-centre follow-up analysis of the HeartMate 3 CE mark study reports data on the 5-year outcomes of 8 patients implanted with the HeartMate 3 Left Ventricular Assist System. The results confirm the observations previously described at 6 months, 1 year and 2 years [1]. In detail, the 5-year survival was 100% with a sustained improvement in quality of life and NYHA functional class over time. No gastrointestinal bleeding, pump thrombosis or dysfunction occurred, and no cases of either haemorrhagic or embolic stroke were observed. Driveline infections remained the major complication. Liver function and haemolytic parameters were stable over time. A moderate decrease in kidney function and in 6-min walk test results was noticed after 3 years.

Since centrifugal LVADs were introduced, improvements in patient outcomes have been observed [2–4]. Indeed, data on large populations demonstrated 85% survival at 1 year, 76% at 2 years and 46% at 5 years [3]. As of 2011, centrifugal LVADs were correlated with survival rates at 6, 12 and 24 months of 90%, 84% and 79%, respectively [15]. The post-market Registry to Evaluate the HeartWare Left Ventricular Assist System (ReVOLVE) on the HVAD System (Medtronic, Inc., Minneapolis, MN, USA) reported a 2-year mortality of 17% with 60% of patients remaining on the device [16]. More recently, the European HeartMate 3 CE mark

trial observed a 2-year survival of 74% [1], confirmed by the US-based MOMENTUM 3 trial with 79% survival at 2 years [2]. Interestingly, in an unadjusted comparison, the Society of Thoracic Surgeons INTERMACS 2019 Annual Report demonstrated that patients with centrifugal flow pumps with full magnetic levitation had a 1-year survival of 87%, which was similar to that of patients who received a transplant and significantly higher than that of patients with axial devices (82%) [4].

Nevertheless, data from longer follow-up periods for patients with the HeartMate 3 are not yet fully available [17] while more data are available from patients with axial pumps or HVAD [18, 19]. In the ADVANCE BTT (HeartWare Ventricular Assist Device Bridge to Transplant) trial implemented with its continued access protocol, after 4 years, 54% of patients were alive on the original device, received a heart transplant or had the device explanted for recovery [20]. Likewise, ReVOLVE patients showed a survival rate of 59% at 5 years [19] and 51% at 7 years [18]. Our cohort of patients showed a survival rate of 100% at 5 years, with 6 patients remaining on an LVAD, and 2 patients successfully receiving transplants. Despite the small sample size, this study demonstrates the feasibility of 100% survival of patients with LVADs who remain on support for 5 years.

The key to obtain such a result is the combination of a dedicated LVAD infrastructure and the active involvement of patients and families in the therapeutic process (Fig. 4). Indeed, it is essential to prepare patients prior to the operation by giving them psychological assessments and training focused on driveline dressing techniques, battery and controller exchange, blood pressure, volume and anticoagulation management. These interventions will result in better compliance and prevention of complications. Moreover, a constant connection between the multidisciplinary LVAD team and the patients is mandatory. Regular visits to the outpatient clinic, the constant presence of VAD coordinators and a 24/7 dedicated LVAD hotline should be offered [21]. In addition, proper support to general practitioners and peripheral hospitals should be provided by the referring centre to guarantee optimal care to patients living in remote areas.

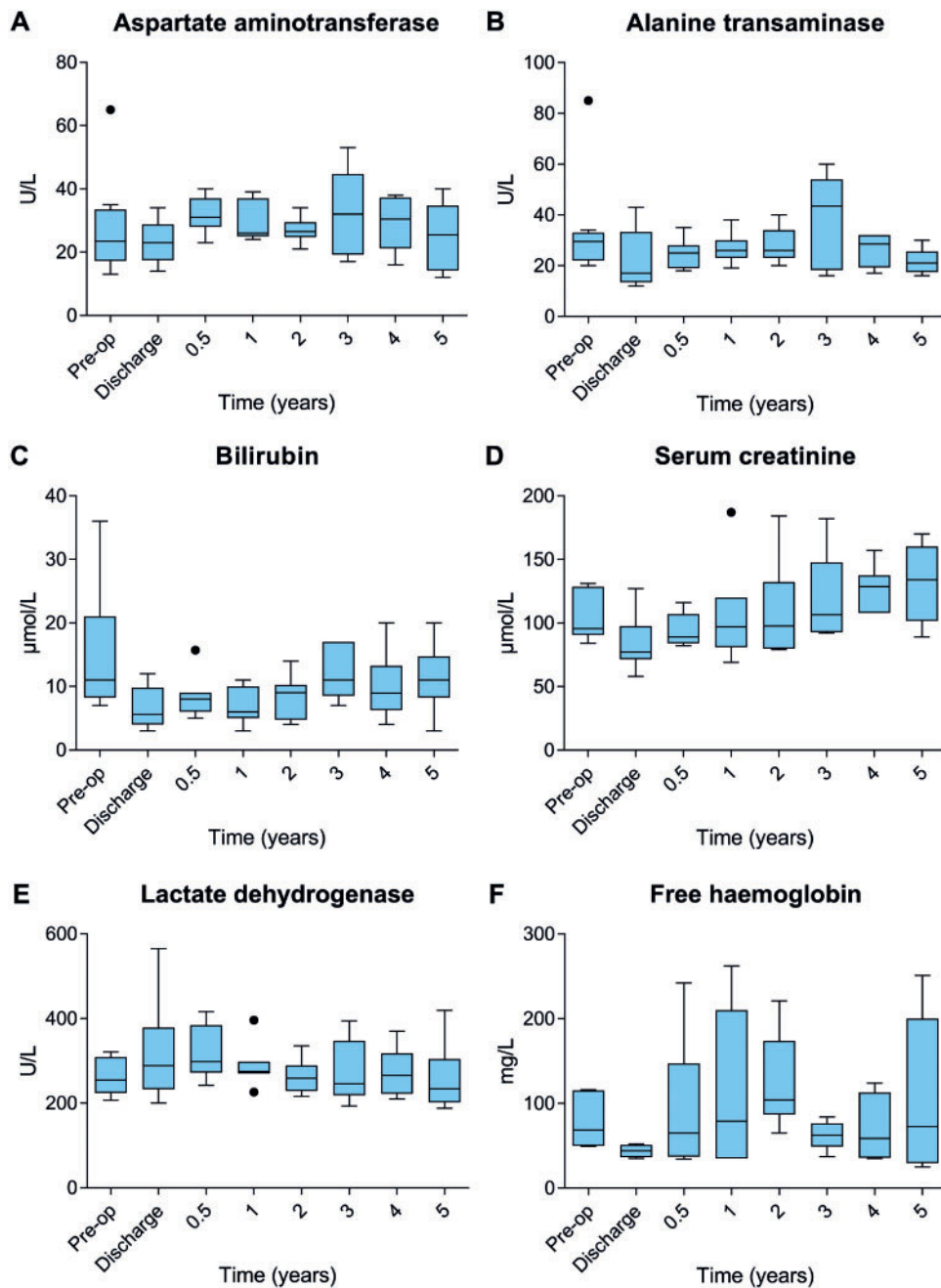


Figure 2: Laboratory parameters: aspartate aminotransferase (A), alanine transaminase (B), bilirubin (C), serum creatinine (D), lactate dehydrogenase (E) and free haemoglobin (F). Pre-op: preoperative.

Whereas survival is the primary end point of most trials, there is a debate regarding the quality of life of patients who have LVADs. In this study, we observed improvements in patients' quality of life after surgery. These improvements were evident in previous reports [1, 6], but this study demonstrates that they are sustained over time. It is known that cardiopulmonary exercise capacity and functional performance improve after an LVAD implantation [22] and remain stable within the first 2 years [23]. However, limited data are available for longer follow-up periods. In our cohort, 3 patients showed impairment in their exercise capacity: at 5 years postoperatively, they were able to walk less than 300 m. Two out of these 3 patients were also diagnosed with chronic obstructive lung disease, which might have

impacted their performance over time based on the fact that it is a known determinant of poor exercise capacity together with age and body mass index [24].

A relevant factor for good quality of life was identified in the few haemocompatibility-related adverse events. Indeed, neither pump thrombosis nor strokes were observed in this study. HeartMate 3 has been described as a highly haemocompatible pump based on its design with no mechanical contact points, large gaps, sintered surfaces and an artificial pulse generated by speed modulation that occurs every 2 s [7, 11]. In the MOMENTUM 3 trial, pump replacement occurred in 2.3% and 11.3% of patients receiving HeartMate 3 and HeartMate II, respectively [2]. Even better results were described in the CE mark

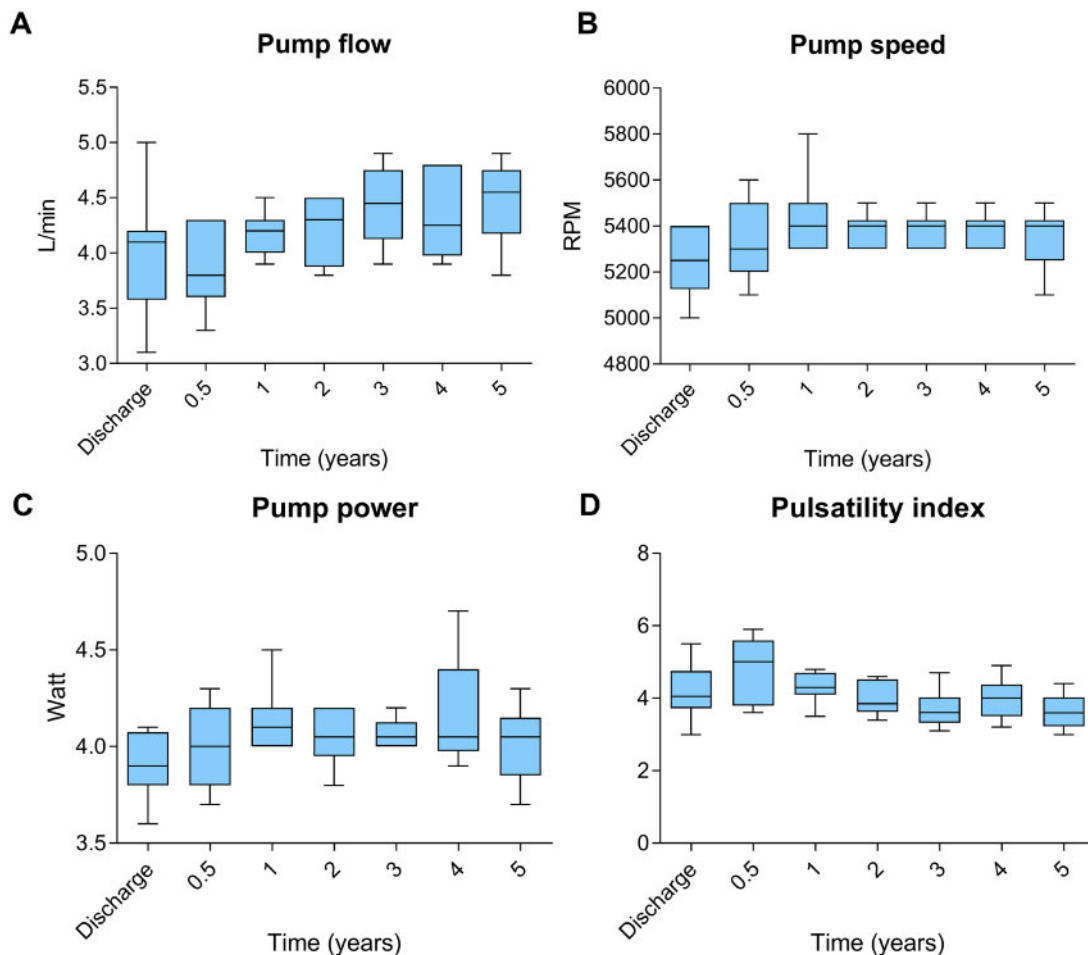


Figure 3: Left ventricular assist device parameters and settings: pump flow (A), pump speed (B), pump power (C) and pulsatility index (D). RPM: revolutions per min.

trial [1], the ELEVATE registry [8] and other clinical experiences [9] where no pump thrombosis was observed. Additionally, HeartMate 3 has been associated with a lower risk of strokes [2]. A more detailed analysis of the MOMENTUM 3 study showed that strokes occurred at a median time of 131 days after implant [25], with a 3.3 times lower incidence for HeartMate 3 compared to HeartMate II [25]. Therefore, one can speculate that the higher haemocompatibility of HeartMate 3 is much more evident with time than it is in the short-term follow-up.

Nevertheless, haemocompatibility-related adverse events also include bleeding events. Indeed, gastrointestinal bleeding is one of the principal reasons for rehospitalization of patients with LVADs. In the MOMENTUM 3 study [2], HeartMate 3 was associated with lower rates of bleeding compared to HeartMate II, and similar rates were described in the CE mark trial where the overall bleeding rate declined 20% after 6 months [1, 6]. In our cohort, bleeding events accounted for 0.031 events/patient-year, further lowering the haemocompatibility-related adverse events score [11]. These results can be explained by the existence of pump features such as a frictionless rotor able to reduce shear stress, blood damage and acquired von Willebrand factor deficiency [26]. All our patients received standard anticoagulation treatment per protocol. However, a low-intensity, anticoagulation regimen could potentially lead to a further reduction in bleeding events [10, 12], but more studies are needed to confirm this hypothesis.

As expected, the most frequent complications in this study were driveline infections. In the MOMENTUM 3 trial, driveline infections occurred frequently with no differences between devices [2]. Whereas the incidence of overall infections was slightly lower in the CE mark trial [1], the rate of driveline infections was comparable between the 2 studies. Despite the rapid technological evolution, infections still represent a huge burden for patients, and no significant improvements have been made over time [14]. This finding supports the idea that a fully implantable LVAD with a transcutaneous energy transmission system is needed to lower the risk of infection. Moreover, the development of transcutaneous energy transmission systems will abolish the need for periodic driveline repairs or for exchanging the modular cable that was required in 50% of our patients because their very active lifestyles led to cable deterioration.

A possible complication described in 0.72–1.6% of patients with a HeartMate 3 is the occurrence of outflow graft twist causing reduction in or disruption of the pump flow [27]. In our study, we did not observe any case of outflow graft twist, but 1 patient experienced external outflow graft compression. Outflow graft obstruction occurs only rarely, but in the case of persistent low flow without other clinical explanations, a contrast computed tomography scan should be performed to diagnose or exclude such a complication, even years after implantation.

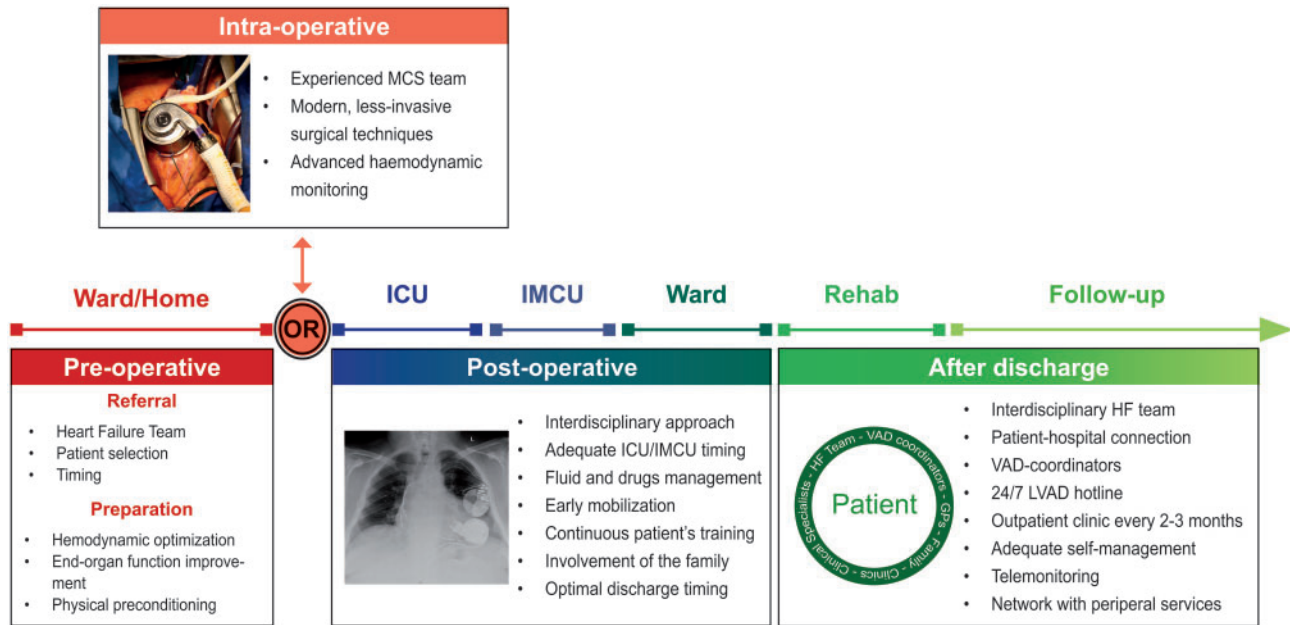


Figure 4: Key factors to improve long-term follow-up in patients with left ventricular assist devices. HF: heart failure; ICU: intensive care unit; IMCU: intermediate care unit; LVAD: left VAD; MCS: mechanical circulatory support; rehab: rehabilitation; VAD: ventricular assist device.

Limitations

The number of patients included is small, and further generalization of these results should be considered carefully. Moreover, all implants were performed at a single high-volume LVAD centre. Thus, results might have been affected by institutional experience that limited their reproducibility. All included patients received LVAD implantation in 2014. Consequently, results are not comparable to those of the most recent studies, which benefit from new therapeutic strategies and increased clinical experience. All patients were part of the HeartMate 3 CE mark trial, which was limited by the non-randomized and non-controlled design. The CE mark trial was designed to exclude patients previously supported with temporary mechanical circulatory support and to include 'all-comers' and did not distinguish patients by the intent for a bridge to a transplant or for destination therapy. Thus, this study included 2 patients who received transplants during the follow-up period.

CONCLUSIONS

This study is the first to report a 5-year survival of 100% in an initial group of 8 patients supported with LVAD, confirming the feasibility of this goal. Patients with end-stage HF can benefit from sustained improvement in their quality of life and a favourable adverse event profile for 5 years after the HeartMate 3 is implanted. LVAD is recognized as a guideline-supported treatment for advanced HF [28–30]. However, from a patient perspective, urgent technological advances are required to offer a physiological pulsatile flow preventing long-term complications such as gastrointestinal bleeding or kidney failure as well as a fully implantable device to reduce or even eliminate infections. Complete results from the follow-up of the HeartMate 3 CE mark study and further data will help us to better understand the role of HeartMate 3 in the long-term survival of patients with end-stage HF.

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Author contributions

Jan D. Schmitto: Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing—review & editing. **Silvia Mariani:** Data curation; Formal analysis; Methodology; Writing—original draft, review & editing. **Tong Li:** Data curation; Formal analysis; Methodology; Writing—review & editing. **Guenes Dogan:** Conceptualization; Data curation; Investigation; Supervision; Validation; Writing—review & editing. **Jasmin S. Hanke:** Conceptualization; Data curation;

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