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Implementation of an intensified outpatient follow-up protocol improves outcomes in patients with ventricular assist devices

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Abstract

Background Ventricular assist devices (VAD) are increasingly used as long-term treatment for advanced heart failure. However, survival after VAD implantation is still unsatisfactory, and no specific outpatient follow-up algorithms have been formally established. Here, we evaluate the effect of an intensified follow-up protocol (IFUP) on survival rates and VAD-associated complications.

Methods and results This is a retrospective study of 57 patients who received a VAD at our center between February 2013 and December 2017. Inclusion criteria were discharge home after VAD implantation and follow-up in our VAD outpatient clinic. Patients implanted after October 2015 ($n=30$) were monitored according to IFUP. This protocol embodied formalized, multi-disciplinary clinical visits every 4–8 weeks including a cardiologist, a cardiothoracic surgeon and a VAD-coordinator and was characterized by optimized anticoagulation and wound management as well as guideline-directed medical therapy. One-year survival in the IFUP patients was 97%, compared to 74% in the pre-IFUP era ($p=0.01$). Implementation of IFUP was associated with a 90% risk-reduction for 1-year mortality (relative risk 0.099; $p=0.048$). The rate of complications, e.g., device thrombosis and major bleeding, was significantly reduced, resulting in superior event-free survival in the IFUP group ($p=0.003$). Furthermore, by implementation of IFUP, a more stable anticoagulation adjustment was achieved as well as an improved adherence to guideline-directed medical therapy.

Conclusion Implementation of an IFUP for VAD patients is associated with a significant decrease in 1-year all-cause mortality. This emphasizes the need for more vigilance in the management of VAD patients by a dedicated multi-disciplinary team.

Introduction

Heart failure (HF) is one of the leading causes of death worldwide despite improvements in HF treatments in recent years and broad implementation of guideline-directed therapies [1–3]. With the progression of the disease to advanced stages, medical therapy may not provide sufficient stabilization of those patients [4–8]. In such cases, cardiac transplantation or the use of mechanical circulatory support (MCS) devices are indicated [1, 9–11]. The landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial was the first to demonstrate superior survival and quality of life in advanced HF patients on long-term MCS with a ventricular assist device (VAD) compared to patients with medical treatment [12]. Over the past decades, MCS devices have experienced tremendous developments and improvements [13–16]. Initially, the devices were introduced as a temporary solution bridging to heart transplantation [bridge to transplant (BTT)]. Due to the increasing number of patients with end-stage HF and lack of donor organs, VADs have emerged as long-term solution in patients waiting for heart

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transplantation (BTT) or, alternatively, permanent treatment in patients not eligible for heart transplantation [destination therapy (DT)] [1, 17]. This led to a rapid expansion in VAD use in recent years [17–19]. Latest data report a proportion of nearly 50% of VAD implants with a strategy of DT [20]. With this growing number of devices implanted as long-term therapy, physicians are increasingly faced with the care of these patients primarily in an outpatient setting over many years [21]. Despite improvements in technology, significant complications including bleeding, thromboembolism and driveline infections remain and affect the long-term outcome of those patients. Current survival after VAD implant is reported at 1 year at 80% and 2 years at 70% [17, 20]. Hence, latest recommendations emphasize the need for appropriately trained specialists including HF physicians, surgeons and nursing staff in an outpatient clinic for the post-discharge disease management [1]. Previous studies have shown that establishing a successful outpatient care is essential and can lead to improved survival [21–23]. However, there are currently no validated, specific follow-up algorithms for the management of patients with long-term MCS devices in an outpatient setting.

The present study reviews a single center experience in VAD management after implementation of a standardized comprehensive outpatient care model. This model was termed "intensified follow-up protocol", or IFUP. The objective of this study was to examine the effect of IFUP on overall outcome in patients on VAD support. The primary endpoint of the study is survival to transplant or ongoing MCS after 1 year. Additionally, rates of complications, management of anticoagulation and medical therapy are compared.

Methods

The study conforms with the principles outlined in the Declaration of Helsinki [24]. The study protocol was approved by the local ethics committee.

Patient population

Patients who received a left VAD or biventricular mechanical support device (BiVAD) from February 2013 to December 2017 and were afterwards discharged home and seen for follow-up at the Heidelberg University Hospital VAD outpatient clinic were included in this study. This included both patients who were implanted as BTT as well as DT. Patients who were already listed for heart transplantation or in the process of being listed were categorized as BTT. Patients with contraindications for heart transplant or who refused heart transplantation were categorized as DT. If at the time of VAD implantation, the status was still to be determined, patients were categorized as bridge to decision (BTD). For study inclusion, the minimum age at implantation was 18 years.

Patient data and follow-up parameters

For each clinic visit patient data, such as laboratory parameters, heart rate, blood pressure, medication and the occurrence of complications were documented from the patient files. Additionally, age, gender, underlying disease, Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile, pre-operative extracorporeal life support, device type, data regarding the pre-discharge course (length of intensive care unit and total hospital stay, post-operative right heart failure [25] or temporary right ventricular support, surgical complications requiring re-operation, temporary renal failure requiring dialysis, infections) and date of heart transplantation or occurrence of death were documented, if applicable. Optimal anticoagulation was defined as an international normalized ratio (INR) target value between 2.5 and 3.5. International normalized ratio values were documented for every patient during each clinic visit. Afterwards, the percentages of INR values within target range were calculated for each follow-up era. Similarly, the mean arterial blood pressure (MAP) was measured by duplex sonography through the brachial or radial artery during each clinic visit. Optimal blood pressure was defined as a MAP below 80 mmHg. For each patient era, the percentage of MAP values within target range was calculated. Follow-up duration was up to 1 year after device placement. Patient survival was censored at heart transplantation or at device explant.

Follow-up before IFUP

Before the IFUP was implemented, patients with MCS devices were not followed-up according to a pre-determined management protocol. Patients were randomly seen either in the outpatient clinic of the department of cardiac surgery or the department of cardiology. The next follow-up visit was each time scheduled arbitrarily according to the treating physician. Additionally, laboratory workup was not routinely ordered and was determined along with further testing at the discretion of the treating physician.

Intensified follow-up protocol

The intensified follow-up protocol (IFUP) was initiated in October 2015. Patients implanted after October 2015 were hence monitored according to the new protocol. IFUP embodied a formalized, multi-disciplinary algorithm for outpatient visits including the following key components (Fig. 1):

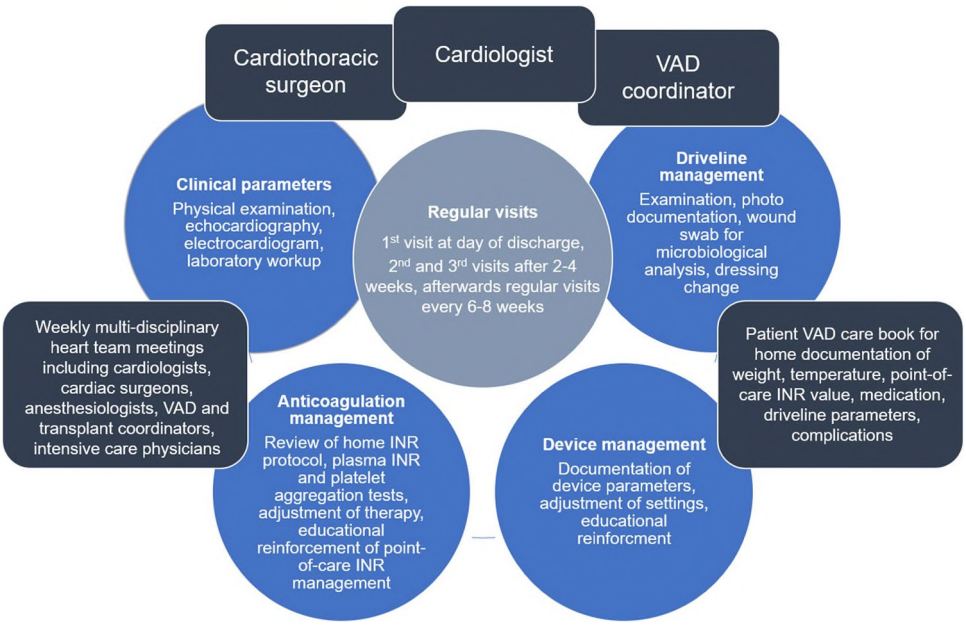

Fig. 1 Key components of the intensified follow-up protocol (IFUP). The IFUP is conducted by a multi-disciplinary team including a cardiologist, a cardiothoracic surgeon and a ventricular assist device (VAD) coordinator. The first visit at our VAD outpatient takes place on the day of discharge from the rehabilitation clinic. The second and third clinic visits take place within a maximum of 4 weeks apart. Clinic visits thereafter are planned every 6–8 weeks. Upon complete stability and absence of adverse incidents, frequency of clinic visits can be decreased to every 8 weeks. The light blue circles display the central pillars of the IFUP facilitating optimal post-discharge care. Dark blue boxes contain additional integral elements of IFUP beyond the regular clinic visits

1. Scheduled clinic visits. The first clinic visit takes place on the day of discharge from the rehabilitation clinic. The second and third visits are planned 2–4 weeks apart. Afterwards, the frequency of visits is reduced and patients are seen every 6–8 weeks resulting in a minimum of 7–9 visits per year. Clinic visits were maintained for the length of VAD support regardless of the ongoing duration. Deviations from the visit schedule were accepted if there was a medical justification.
2. Multi-disciplinary team including a cardiologist, a cardiothoracic surgeon and a VAD-coordinator. Patients were evaluated by the three disciplines at each visit facilitating an interdisciplinary consultation.
3. Defined protocol for routine diagnostics and test. This included physical examination, electrocardiogram, transthoracic echocardiogram as well as a set panel of laboratory measurements. Further tests beyond the standard protocol were based on individual clinical concerns and incidents. Laboratory measurements included: sodium, potassium, calcium, chloride, creatinine, glomerular filtration rate [GFR, calculated with the Modification of Diet in Renal Disease (MDRD) formula], blood urea nitrogen (BUN), glucose, creatine kinase, high-sensitivity troponin T (hsTNT), lactate dehydrogenase, liver enzymes (ALT, AST), gamma glutamyl transferase, cholinesterase, bilirubin, amylase, lipase, phosphate, uric acid, C-reactive protein, albumin, low density lipoprotein-cholesterol, triglyceride, hemoglobin, white blood cell count, platelet count, INR (international normalized ratio), antithrombin III activity, D-dimer, fibrinogen, transferrin, ferritin, haptoglobin, thyroid-stimulating hormone, N-terminal pro brain natriuretic peptide (NTproBNP).
4. Intensified anticoagulation management. This included: review of each patient's home INR protocol, measurement of plasma INR and platelet aggregation tests. At each visit, necessary adjustments in anti-platelet dose or medication were performed as well as educational reinforcement on point-of-care INR management if values were not within range.
5. Optimized wound and driveline management. Examination of the appearance of the percutaneous driveline, photo documentation, wound swab for microbiological analyses, dressing changes. Repeated guidance was given to patient and relatives every visit.
6. Device management. The documentation routinely included information on device parameters and performed adjustments of device settings. Reinforcement of the patients´ competencies on device management and procedures.

Statistical analysis

Statistical analysis was performed with SPSS software [International Business Machines Corporation (IBM), Armonk, NY]. Comparisons between the two groups were performed with the student's *t* test for normally distributed metric data (as tested by the Kolmogorov–Smirnov test). The Mann–Whitney *U* test was used as a nonparametric test. Qualitative patient characteristics were compared using the Chi square test or Fisher's exact test for categorical variables. To estimate the effects of the initiation of IFUP on patients' all-cause mortality and event-free survival (defined as survival free from death, major bleeding, stroke and VAD thrombosis), Kaplan–Meier survival curves were created. The log-rank test was used to compare survival curves. A multivariable analysis was performed for survival after VAD implantation, using objective clinical factors that were thought to limiting prognosis of patients. Covariates included age, body mass index, diabetes mellitus, creatinine, underlying cardiac disease, device type and INTERMACS profile as well as selected post-operative parameters (length of intensive care unit and total hospital stay, post-operative right heart failure, infections). All analyses were exploratory and a two-tailed p value of ≤ 0.05 was taken as a cut-off for statistical significance. Quantitative data are presented as mean ± standard error of mean or as median and interquartile ranges (25–75), depending on the distribution of the data. For qualitative parameters absolute and relative frequencies are presented.

Results

Patient population

The present study includes 57 patients under MCS. Thirty patients were followed up according to the intensified protocol (IFUP) as compared to 27 patients in the pre-IFUP era. Clinical characteristics of implanted patients did not differ significantly in the pre-IFUP and post-IFUP eras regarding age, gender, underlying disease or comorbidities (Table 1). In both eras most patients suffered from a dilative cardiomyopathy ($n = 34/57$; 60%). The implant strategy was similar in both groups with the majority of patients implanted as BTT ($n = 43/57$, 75%) and only one patient implanted as BTD in the IFUP era. The most commonly implanted device was HVAD (HeartWare, Framingham, MA, USA; 35/57, 61%). The use of device types differed significantly with HeartMate III (Thoratec, Pleasanton, CA, USA) devices implanted only in the later period, due to its approval not earlier than 2016 [10, 26]. Vice versa, the Synergy IC system (CircuLite Inc., Saddle Brook, NJ, USA) was implanted in only two patients in the pre-IFUP period, before the device was removed from the market [27]. Overall, 13 patients received a biventricular mechanical support (Excor, Berlin Heart, Berlin, Germany) with a similar distribution in both groups (Table 1).

Disease severity at implant is documented as INTERMACS profile. In both groups, approximately 50% of the patients were classified as INTERMACS level 1–3, requiring continuous inotropic support prior to device implantation (pre-IFUP vs. IFUP: $n = 13$ vs. $n = 15$; $p = 0.9$) and the proportion of patients on extracorporeal life support before VAD implantation was similar (Table 1). Levels of serum hemoglobin and creatinine as well as the cardiac biomarkers NTproBNP and hsTNT were similar between both groups. However, bilirubin levels were significantly higher in the pre-IFUP era. In the pre-discharge period after VAD implantation, parameters as such as length of intensive care unit and total hospital stay, right ventricular failure/need for temporary right ventricular support, surgical complications or temporary renal failure did not significantly differ between pre-IFUP and IFUP period. Only slightly fewer infections occurred in the IFUP era (Table 1). Outcomes were death in 8 (14%), heart transplantation in 4 (7%) and ongoing VAD support in 45 (79%) patients within 1 year after device implantation.

One-year survival

All-cause mortality within 1 year post VAD implantation in the entire study cohort was 14% ($n = 8/57$). Seven patients from the pre-IFUP era deceased within 1 year after VAD implantation as opposed to only one patient in the later era. Main causes of death included infection and sepsis ($n = 2$), VAD thrombosis ($n = 1$), ischemic stroke ($n = 1$) and intracranial haemorrhage ($n = 1$) as well as multi-organ failure ($n = 1$) and intractable pulseless electrical activity ($n = 1$). In one patient from the pre-IFUP era, the cause of death remained unclear. Actuarial survival for the entire cohort, comparing those who received VADs before vs. after the implementation of IFUP in October 2015, is presented as Kaplan–Meier curves in Fig. 2. Survival was significantly improved after initiation of the intensified follow-up protocol ($p = 0.01$) with a 1-year survival rate of 97% vs. only 74% in the pre-IFUP era.

To address the effect of potential confounding factors possibly influencing patient mortality, a multivariable analysis was performed (Table 2). Results show that only the implementation of IFUP was significantly associated with a reduction in risk of death within 1 year after device implant. The implementation of IFUP proved to be an independent predictor of 1-year survival with an approximately 90% reduction in risk for death (hazard ratio 0.099; $p = 0.048$). Notably,

Table 1 Baseline characteristics before ventricular assist device (VAD) implantation

	pre-IFUP ($n = 27$)	IFUP ($n = 30$)	p value
Age (year)	56 (18–74)	54 (21–70)	0.3
Male gender	21 (78%)	27 (90%)	0.4
BMI (kg/m^2)	26.6 ± 0.8	26.8 ± 0.9	0.9
INTERMACS profile			**0.002**
1	7 (26%)	3 (10%)	
2	2 (7%)	7 (23%)	
3	4 (15%)	5 (17%)	
4	10 (37%)	1 (3%)	
5	4 (15%)	7 (23%)	
6	0	7 (23%)	
1–3	13 (48%)	15 (50%)	0.9
Pre-operative ECLS	7 (26%)	7 (23%)	0.8
Underlying disease			0.5
DCMP	18 (67%)	16 (53%)	
ICMP	9 (33%)	14 (47%)	
Implant strategy			
Destination therapy	7 (26%)	6 (20%)	0.8
Bridge to transplant	20 (74%)	23 (77%)	0.8
Bridge to decision	0	1 (3%)	0.3
Device implanted			
HVAD (Heart Ware)	18 (67%)	17 (57%)	0.6
HeartMate III (Thoratec)	0	7 (23%)	**0.02**
Synergy IC (CircuLite)	2 (7%)	0	0.2
Excor (Berlin Heart)	7 (26%)	6 (20%)	0.8
Comorbidities			
CKD	20 (74%)	16 (53%)	0.1
ESRD	3 (11%)	5 (17%)	0.5
Arterial hypertension	19 (70%)	20 (67%)	0.8
Diabetes mellitus	10 (37%)	10 (33%)	0.8
Previous stroke	7 (26%)	8 (27%)	0.9
Lab parameters			
Hemoglobin (mg/dl)	11.8 (10.1–13.8)	11.6 (10.0–14.1)	0.9
Platelets (per nl)	189 (125–329)	172 (141–226)	0.09
Creatinine (mg/dl)	1.36 (1.03–1.7)	1.23 (1.03–191)	0.4
GFR (ml/min/1.73 m^2)	52.9 (39.7–85.8)	68.35 (37.8–78)	0.8
Total bilirubin (mg/dl)	1.3 (0.8–3.1)	0.9 (0.5–1.9)	**0.03**
ALT (U/l)	34.0 (23.0–148.0)	28.5 (14.0–63.0)	0.08
NTproBNP (ng/l)	11318 (3612–15606)	14497 (2641–24604)	0.9
hsTNT (pg/ml)	40.5 (28.5–96.5)	38.5 (22.0–101.0)	0.3
Post-operative course			
Length of hospital stay (day)	55 ± 34	43 ± 19	0.1
Lenght of ICU stay (day)	32 ± 29	23 ± 14	0.1
Right heart failure	12 (44%)	16 (53%)	0.5
Temporary RVAD	2 (7%)	7 (23%)	0.1
Temporary renal failure	8 (30%)	6 (20%)	0.4
Infection	13 (48%)	6 (20%)	**0.02**
Surgical complications	10 (37%)	14 (47%)	0.5

Patients who later visited our VAD outpatient clinic were separated according to the exerted follow-up regimen: intensified follow-up protocol (IFUP), when VAD was implanted from October 2015 to December 2017; and pre-IFUP, when implanted prior (from February 2013 to September 2017). Data are given as median (25–75 percentile), absolute number (%) or mean ± standard error of the mean. Bold text represents p values < 0.05

BMI body mass index (kg/m^2), *INTERMACS* Interagency Registry for Mechanically Assisted Circulatory Support profile: 1—critical cardiogenic shock, 2—progressive decline, 3—stable but inotrope dependent, 4—resting symptoms, 5—exertion intolerant, 6—exertion limited, 7—advanced NYHA (New York Heart

Table 1 (continued)

Association) class III, *ECLS* extracorporeal life support, *DCMP* dilated cardiomyopathy, *ICMP* ischemic cardiomyopathy, *CKD* chronic kidney disease, *ESDR* end stage renal disease, *GFR* glomerular filtration rate, *ALT* alanine aminotransferase, *NTproBNP* N-terminal pro brain natriuretic peptide, *hsTNT* high-sensitivity troponin T, *ICU* intensive care unit, *RVAD* right ventricular assist device

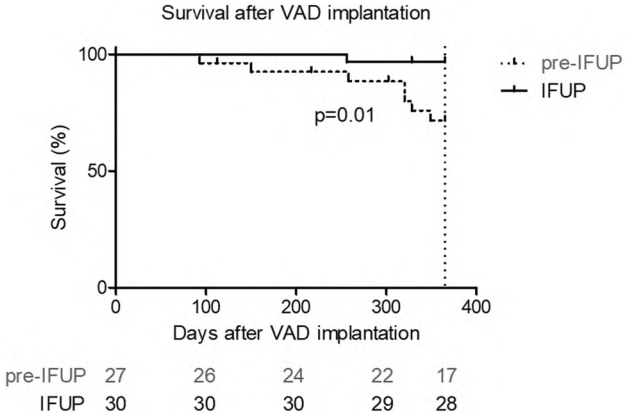

Fig. 2 Impact of an intensified follow-up protocol (IFUP) on survival after ventricular assist device (VAD) implantation. Patients implanted with a VAD from February 2013 to September 2017 (pre-IFUP) and from October 2015 to December 2017 (IFUP) at our centre were included in the study. Inclusion criteria were: post-operative discharge home and follow-up in our VAD outpatient clinic (pre-IFUP: $n=27$; IFUP: $n=30$). Kaplan–Meier survival curve for patients after VAD implantation in the two periods is given. Patients receiving heart transplantation ($n=4$) or device explantation ($n=1$) within the first year were censored (vertical bars). p value is given for log rank test

Table 2 Multivariable analysis of risk factors for all-cause mortality

	Hazard ratio	p value
Implementation of IFUP	0.099	**0.048**
INTERMACS profile 1–3	0.875	0.910
Age	0.945	0.192
Use of BiVAD	0.476	0.610
Creatinine	0.890	0.873
ICMP	1.834	0.558
BMI	1.093	0.462
Diabetes mellitus	2.924	0.394
Lenght of ICU stay	1.007	0.835
Post-operative hospital stay	1.008	0.786
Port-operative infection	0.854	0.848
Post-operative right heart failure	0.487	0.430

Bold text represents p values <0.05

IFUP intensified follow-up protocol, *INTERMACS* Interagency Registry for Mechanically Assisted Circulatory Support, *BiVAD* biventricular assist device, *ICMP* ischemic cardiomyopathy, *BMI* body mass index, *ICU* intensive care unit

the use of BiVAD, higher INTERMACS profiles or post-operative right heart failure showed no significant increase in the risk of death.

Complications during follow-up

The overall rate of complications within 1 year after VAD implantation did not differ significantly between the pre-IFUP and IFUP patients (Table 3). However, a significant reduction in the occurrence of VAD thrombosis and major bleeding events was demonstrated in those who received MCS after the IFUP was initiated. In the pre-IFUP era, the most common complication was VAD thrombosis followed by stroke and driveline infections. In the IFUP era the most frequent complications were driveline infections comprising more than 50% of the complication rate ($n=10/18$; 56%). Ischemic strokes were the second most common complications in both groups accounting to almost 30% of all complications in the entire study cohort ($n=11/39$; 28%). Of note, within the seven HeartMate III patients in the IFUP era, no one experienced major events such as major bleeding, ischemic stroke or VAD thrombosis, whereas, in contrast, in 10 of the 23 patients with other devices (HVAD or BiVAD), major complications occurred ($p=0.064$). Taken together, reduced number of complications plus improved survival added to an improved event-free survival, defined as survival free from death, major bleeding, stroke and VAD thrombosis, in the IFUP group ($p=0.003$; Fig. 3).

Treatment parameters during follow-up

Additionally, a significant improvement in the anticoagulation regimen was shown in patients in the IFUP era. In this cohort, 72% of the cumulative numbers of INR measurements during the clinic visits (148 of 206 measurements) within 1 year after device implantation were within the defined target range of 2.5–3.5 for optimal anticoagulation. In contrast, this was the case in only 56% of all measured INR values (79 of 142 measurements) in the pre-IFUP cohort ($p=0.002$). For optimal blood pressure control, a mean arterial pressure (MAP) below 80 mmHg was defined. Here, no significant difference could be achieved after initiating IFUP: in both groups, approximately 60% of blood pressure measurement revealed a MAP below 80 mmHg (Table 3).

After implementation of IFUP, a significant increase in the use of optimal HF medication was achieved (Table 3). Over 90% of the patients in the IFUP era received beta blockers as opposed to only 44% in the pre-IFUP era. Similarly, almost twice as many patients in the IFUP cohort received a mineralocorticoid receptor (MR) antagonist

Table 3 Treatment and complications during follow-up after ventricular assist device (VAD) implantation

	pre-IFUP ($n = 27$)	IFUP ($n = 30$)	p value
MAP < 80 mmHg	56%	62%	0.3
INR 2.5–3.5	56%	72%	**0.002**
Heart failure medication			
Beta blocker	44%	93%	**0.0001**
ACE inhibitor or ARB	70%	93%	**0.02**
MR antagonist	33%	70%	**0.006**
Loop diuretic	89%	90%	0.9
Optimal medical therapy (OMT)	11%	63%	**0.0001**
Complications	21 (78%)	18 (60%)	0.2
Driveline infection	6 (22%)	10 (33%)	0.4
VAD thrombosis	13 (48%)	4 (13)	**0.004**
Major bleeding	5 (19%)	0	**0.01**
Stroke	6 (22%)	5 (17%)	0.6

Patients who visited our VAD outpatient clinic were separated according to exerted follow-up regimen: intensified follow-up protocol (IFUP), when VAD was implanted from October 2015 to December 2017; and pre-IFUP, when implanted prior (from February 2013 to September 2017). Data are given as % of measures/documented values or as absolute number (%) or proportion. Bold text represents p values < 0.05

MAP mean arterial pressure, *INR* international normalized ratio, *ACE* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *MR* mineralocorticoid receptor, *OMT* optimal medical treatment meaning the combination of beta blocker + ACE inhibitor/ARB + MR antagonist

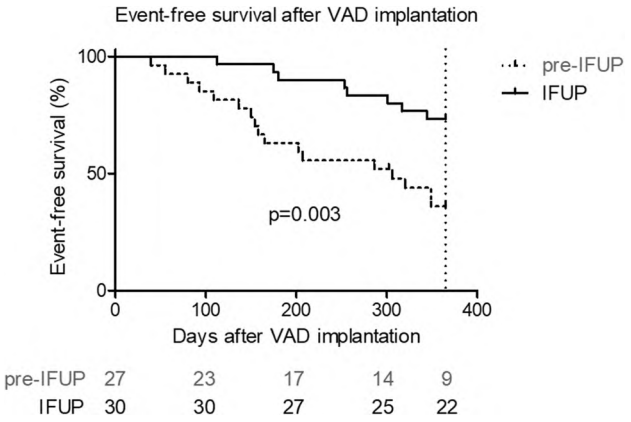

Fig. 3 Impact of an intensified follow-up protocol (IFUP) on event-free survival after ventricular assist device (VAD) implantation. Patients implanted with a VAD from February 2013 to September 2017 (pre-IFUP) and from October 2015 to December 2017 (IFUP) at our centre were included in the study. Inclusion criteria were: post-operative discharge home and follow-up in our VAD outpatient clinic (pre-IFUP: $n = 27$; IFUP: $n = 30$). Kaplan–Meier curve for event-free survival, defined as survival free from death, major bleeding, stroke and VAD thrombosis. Patients receiving heart transplantation ($n = 4$) or device explantation ($n = 1$) within the first year were censored (vertical bars). p value is given for log rank test

compared to the pre-IFUP patients ($p = 0.006$). The use of an angiotensin receptor blocker (ARB) or an angiotensin converting enzyme (ACE) inhibitor was also significantly increased in the post-IFUP era. Overall, guideline-directed optimal medical treatment (OMT) for HF comprising a beta blocker, MR antagonist and either ARB or ACE inhibitor was only present in 11% of all patients prior to IFUP and was significantly improved to over 60% after initiation of IFUP.

Discussion

Here, we present our single centre experience with an intensified outpatient follow-up protocol (IFUP) for patients with advanced HF treated with VAD. We provide evidence that a patient-tailored, multi-disciplinary approach not only improves guideline-directed medical therapy, anticoagulation management and event-free survival, but may also improve overall survival in patients treated with MCS.

Since the introduction of MCS devices as long-term treatment for end-stage HF, major improvements regarding quality of life and outcomes have been achieved [12–14, 18, 28]. The recent analysis of the International Society for Heart and Lung Transplantation Registry for Mechanical Circulatory Support (IMACS) database including over 14,000 patients with global representation reported 1- and 2-year survivals of 80% and 70%, respectively, in patients receiving continuous-flow left VAD or BiVAD [20]. In our present study, overall survival after 1 year of patients implanted from 2013 to 2017 was at 86%. However, as discharge home after VAD implantation was inclusion criterion, peri-operative mortality was excluded in our study and therefore survival rates are difficult to compare.

Management protocols for VAD post-implant care

With the ongoing risk of death in VAD-supported patients beyond hospital discharge and increasing long-term use of the devices, there is unquestionable need for a formalized management protocol post hospital discharge. For example, the device manufacturers Thoratec and Heartware published instructions for the device use and patient management [29, 30]. However, there is only little evidence-driven data available supporting certain guidelines or management protocols. This present study implemented a formalized and intensified care-management protocol for patients after discharge from the primary hospital stay. Implementation of IFUP led to a significant improvement in overall survival after 1 year compared to patients who were followed up without a certain care-management protocol. To our knowledge, there is only one study with comparable results conducted by the Kirklin group and published in 2011, demonstrating a 70% reduction of risk of death within 2 years in patients supported with a VAD after initiation of an intensified surveillance protocol [22]. This protocol entailed a multi-disciplinary approach and a strict schedule of clinic visits and a protocol of routine diagnostics, comparable to our IFUP. However, effects on, e.g., anticoagulation management, complications during follow-up and guideline-adherence were not reported. A more recent publication has only shown a trend towards an improvement of survival at 1 year after initiation of a multidisciplinary heart team compared to patients implanted prior to the heart team era [23]. The main ideas of the latter study were to measure the effects of the heart team (anaesthesiologists, intensive care physicians, perfusionists and VAD coordinators) and of structured weekly meetings to determine the treatment for patients with end-stage HF and did not comprise the outpatient management post discharge. Thus, the present study is the first study that not only demonstrates that an intensified post-discharge follow-up protocol improves survival, but also delineates possible explanations for this effect.

Factors accounting for an improved survival with intensified follow-up

One aspect evaluated in our study was the adherence to HF medication during VAD support. Notably, there is no current literature regarding HF therapy in these patients, leaving a huge gap in evidence. In 2013, the International society for Heart and Lung Transplantation (ISHLT) published guidelines for MCS recommending the use of MR antagonists for potential beneficial antifibrotic effects, ACE inhibitors or ARBs for risk reduction in patients with vascular disease and diabetes and beta blockers for hypertension or for rate control [31]. In our patient cohort, after implementation of the IFUP, the rate of patients treated with OMT for HF was significantly higher compared to the pre-IFUP group. This specifically included the more frequent use of beta blockers and MR receptor antagonists. Whether OMT contributes to the improved outcomes in our patients can only be speculated. For VAD patients in general, the need of HF therapy is still subject of studies. Of note, higher rate of OMT in the IFUP group did not improve blood pressure control. A high blood pressure has previously been identified as a risk factor for stroke or intracranial haemorrhage and recommendations of blood pressure management under MCS included a target MAP below 90 mmHg [31, 32]. At our centre, we even consider a MAP below 80 mmHg as target blood pressure. In both follow-up eras, only 60% of all measured MAPs during follow-up visits were below this cut-off without significant difference between both groups, suggesting that blood pressure control needs to be further attended to in the future.

In addition, an increased risk of adverse anticoagulation-related events, e.g., intracranial haemorrhage or pump thrombosis, is well documented when INR values are not within target range [32, 33]. Multiple studies have demonstrated superior anticoagulation management when INR is individually measured [34, 35]. Therefore, in addition to INR measurements during clinic visits, consistently each patient in the IFUP era was trained for home INR measurement (point-of-care) before hospital discharge after VAD implantation. Consequently, we found a significant increase of INR values within therapeutic range in the IFUP group, possibly related to an intensified patient education. A lower number of VAD thrombosis and major bleeding compared to the pre-IFUP era highlights the need for a special focus on anticoagulation management when seeing VAD patients in an outpatient setting.

Regarding adverse events, the latest INTERMACS report from 2017 reported bleeding and infections as the most common complications [18]. In line with these findings, in our cohort, driveline infections were among the most frequent complications. Notably, the rate of driveline infections was slightly higher after implementing the IFUP. However, the interpretation of this finding is limited. One could speculate that higher rates of driveline infections after implementation of IFUP may possibly reflect a more vigilant patient surveillance, rather than a failure of the management protocol, hence facilitating a timely management of the infection [36]. In this regard, early diagnosis and timely management of VAD complications through intensified follow-up management might ultimately lead to a reduction of treatment costs. This might allow putting the expected higher expenses of IFUP into perspective.

Other factors that impact outcomes in a modern age

Naturally, in the past years, many advances have been made to improve outcomes under MCS, e.g., progress in patient

selection, surgical techniques and medical management [37–39]. Furthermore, a growing expertise certainly plays an important role when VAD patients are seen at a single centre by a stable heart team. In addition to this, many technical advances have been made in recent years: since the introduction of long-term MCS devices, a number of new VAD generations have been developed additionally leading to significant improvement of survival [13, 14]. The most recent publication reported a further increase in survival with introduction of the latest continuous-flow pump (HeartMate III) when compared to the previous HeartMate II reaching an actuarial survival of 83% at 2 years [14]. These results are comparable to results for the HVAD device with a recently reported survival rate of 84% and 78% at 1 and 2 years, respectively [40]. A direct comparison between both modern devices is still pending. In our study, the most commonly used device in both follow-up periods was the continuous flow device HVAD (HeartWare) with similar proportions in both groups, pre-IFUP and IFUP. However, the novel HeartMate III device was only used in the IFUP era, potentially biasing our results [41]. Nevertheless, we could not identify the device type to be an independent predictor of mortality in the multivariable analysis, although it needs to be taken into account that the number of patients may be too low to provide a solid statistical statement regarding the role of the device type.

Another possible confounding factor is a difference in INTERMACS profiles between the two eras, pre-IFUP and IFUP. Although the number of instable patients (INTERMACS level 1–3) did not significantly differ between both groups, we observed a slight, but significant difference regarding the ambulatory patients (INTERMACS level 4–6): in the IFUP group, more patients with INTERMCAS profiles 5 and 6 were chosen for VAD implantation as opposed to primarily a more advanced INTERMACS score of 4 in the pre-IFUP era. This shift towards less advanced stages of disease may be explained by an improved, more cautious and earlier patient selection in the modern era [42] and must be considered when interpreting the data. However, INTERMACS profiles could not be validated to affect all-cause mortality in our multivariable analysis.

Limitations

This study was conducted as a single centre, retrospective study. The patient population was relatively small and only patients were included who survived to hospital discharge. With the rapidly proliferating use of MCS devices, upcoming larger multi-centre studies might resolve this issue and verify our results in the future. Another challenge was the quantification of other possible factors affecting survival (e.g., improved technology, surgical techniques, patient selection and growing expertise) which might have contributed to the presented improvement with IFUP. This could not be integrated in our small study. Another limitation is that our study only reports the first year of follow-up, whereas long-term VAD treatment is increasingly gaining importance, given the increasing waiting time on BTT and the growing number of DT patients. We only can speculate whether IFUP continues to be beneficial for the patients after the first year and it remains undetermined whether, e.g., intervals between clinic visits can be stretched after the first year in stable, event-free patients. However, our clinical experience is that beneficial effects of IFUP persist beyond the first year after VAD implantation, even if patients are seen only every 8–12 weeks.

Conclusions

Despite these limitations, our study shows the considerable benefits of an intensified clinical outpatient disease-management protocol that resulted in a statistically quantifiable improvement of event-free and overall survival 1 year after VAD implantation. In addition, an optimized adherence to HF medication and optimal anticoagulation could be achieved as well as a reduction in complication rate, particularly device thrombosis and major bleeding. In conclusion, our findings emphasize the current understanding that a formalized, intensified follow-up strategy after hospital discharge is crucial for optimal outcome in ambulatory patients treated with MCS devices.

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Compliance with ethical standards

Conflict of interest BS and AR received travel grants (for international conferences) and consultancy fees from Berlin Heart. PWR received speaker honoraria from Abbott (Thoratec). MMK received research grants from Abbott (Thoratec) and travel grants (for international conferences) from Medtronic (HeartWare). The other authors report no conflict of interest regarding the content herein.

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