ORIGINAL ARTICLE

Short- and long-term outcomes of continuous--flow left ventricular assist device therapy in 79 patients with end-stage heart failure

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KEY WORDS

adverse events, end-stage heart failure, left ventricular assist device, survival

ABSTRACT

INTRODUCTION An increasing number of patients with end-stage heart failure, along with a shortage of heart donors, necessitates the use of mechanical circulatory support.

OBJECTIVES This single-center retrospective study evaluated short- and long-term outcomes of continuous-flow left ventricular assist device (CF-LVAD) therapy in patients with end-stage heart failure.

PATIENTS AND METHODS We collected and assessed data of 79 patients (77 men, 2 women; mean age, 50.3 years; mean INTERMACS profile, 3.1) implanted with a CF-LVAD between 2009 and 2017 (HeartMate 3 in 19 patients [24%]; HeartMate 2 in 9 [11.4%]; and HeartWare in 51 [64.6%]).

RESULTS The mean time on CF-LVAD support was 604 days (range, 1–1758 days). There were 2 device exchanges due to pump thrombosis and 1 explantation due to heart regeneration; 9 patients (11.4%) underwent heart transplant. Stroke (nondisabling, 48%) occurred in 27.8% of patients (ischemic in 9 patients; hemorrhagic, in 14; both types, in 1) despite the standardized anticoagulation regimen. Major gastrointestinal bleeding and pump thrombosis were reported in 13 patients (16.5%), while 18 patients (22.8%) developed driveline infections (recurrent in 15 patients [19%]). Hemorrhagic stroke and bacteremia had a negative impact on survival. Hemorrhagic stroke was the main cause of death. Survival probability was 0.9 at 1 month and 0.81, 0.71, 0.61, and 0.53 at 1, 2, 3, and 4 years, respectively.

CONCLUSIONS Although CF-LVAD support is associated with substantial adverse events, they do not significantly affect mortality (except hemorrhagic stroke and bacteremia). Novel devices seem to overcome these limitations, but larger studies are needed to support these findings.

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INTRODUCTION It is estimated that heart failure (HF) currently affects 26 million people, and its prevalence is expected to increase by 46% in 2030.[1,2] Orthotopic heart transplant (OHT) is considered the gold standard treatment for end--stage HF. However, owing to the shortage of donors, new technologies such as ventricular assist devices, predominantly left ventricular assist devices (LVADs), have emerged as a potential therapeutic alternative. While indications for LVAD implantation constantly evolve, the main indication continues to be stable or unstable inotropic dependence due to severe left ventricular dysfunction in patients who have already been listed for or are considered to be listed for OHT.[3,4] In the last decade, LVADs have become the predominant technology used in the management of this population, showing satisfactory outcomes in terms of significantly improved survival and quality of life. The total number of implantations worldwide has already exceeded 17 000.[5-7]

WHAT'S NEW?

The number of patients with heart failure, including the end-stage form of this disease, is constantly increasing. Due to a worldwide shortage of heart donors, new technologies have come into play, such as mechanical circulatory support. In the last decade, continuous-flow left ventricular assist devices (CF-LVADs) have become the predominant technology used in this population of severely ill patients. This type of therapy enables survival to heart transplant or heart regeneration and improves the quality of life, but it is not free from limitations, mainly device-related adverse events. The analysis of the frequency and causes of adverse events during CF-LVAD support could facilitate the search for preventive strategies. Moreover, the knowledge on the timing of these events as well as their impact on survival could help choose the optimal time frame for heart transplant in this population of patients.

The objective of this study was to assess the outcomes of continuous-flow LVAD (CF-LVAD) therapy in patients with end-stage HF treated in a single institution, including issues relating to early implantations and the learning curve.

PATIENTS AND METHODS The study was designed as a retrospective single-center registry, with data collected prospectively (part of the EUROMACS registry [European Registry for Patients with Mechanical Circulatory Support]). The study was approved by the appropriate institutional review board.

Baseline demographic, clinical, and laboratory characteristics as well as perioperative data of 79 patients implanted with a CF-LVAD from December 2009 to December 2017 (follow-up until March 2018) were collected and assessed. Patients were followed until death, pump explantation, end of follow-up, or OHT. There were 77 men (97.5%) and 2 women (2.5%) at a mean (SD) age of 50.3 (11.3) years (range, 16.7–72.4 years) and with a mean (SD) body mass index of 25.5 (5.1) kg/m^2 (range, 13.8–45.2 kg/m^2). Two of the 79 patients were implanted outside our institution and were referred to our center within the first 3 months after implantation. The clinical characteristics of the study group are presented in TABLE 1.

Ischemic cardiomyopathy was the major cause of HF (36 [45.6%] of patients), followed by dilated cardiomyopathy (27 [34.2%] of patients). The duration of HF varied from a few weeks up to over 10 years. The distribution of patients according to the INTERMACS profile (The Interagency Registry of Mechanically Assisted Circulatory Support) at the time of CF-LVAD implantation and echocardiographic evaluation before LVAD implantation are shown in TABLES 2 and 3, respectively.

At the time of LVAD implantation, 57 patients (72.1%) were on inotropic support, while 34 patients (43%) were bridged with temporary circulatory support (TCS): 30 (38%) with an intra-aortic balloon pump; 2 (2.5%), with venoarterial extracorporeal membrane oxygenation (ECMO); 1 (1.3%), with an Impella device; and 1 (1.3%), with a CentriMag device.

All patients were considered as transplant candidates at the time of LVAD implantation. In 19 patients (24%), the HeartMate 3 (HM3) pump was implanted; in 9 patients (11.4%), HeartMate 2 (HM2); and in 51 patients (64.6%), HeartWare (HVAD). All patients implanted with HVAD and HM2 had full sternotomy performed at CF-LVAD implantation (66 [83.6%]). In 11 patients (13.9%) with HM3, a less invasive technique (ministernotomy and lateral minithoracotomy) was used. In 9 patients (11.4%), the HM3 implantation was accompanied with left atrial appendage closure (AtriClip PRO, AtriCure, Mason, Ohio, United States).

All patients were initially treated according to a standardized anticoagulation regimen, which consisted of unfractionated or low-molecular-weight heparin early in the postoperative period, followed by warfarin and an international normalized ratio (INR) target between 2 and 3. During follow-up, plasma INR levels were measured every 2 to 3 months at every ambulatory visit or at least once during hospitalization in our institution.

An antiplatelet drug such as aspirin or clopidogrel (the latter used only in cases of aspirin resistance or other indications for this drug) at a dose of 75 mg/d was introduced on postoperative day 1 and uptitrated according to aggregation tests in cases of diminished sensitivity to a currently used drug.

Continuous warfarin therapy during LVAD support was administered to 73 patients, while in 6 patients, it was discontinued or never introduced due to adverse events (AEs). Aspirin was given to 26 patients (mean [SD] dose, 113 [53] mg) and clopidogrel, to 44 (mean [SD] dose, 107 [61] mg). In 1 patient, both medications were administered (both at a dose of 75 mg and in combination with warfarin) due to thromboembolic events during LVAD support. In 8 patients, antiplatelet therapy was discontinued, while in 19 patients, the typical protocol including a target INR of 2 to 3 was changed due to severe recurrent bleedings or thromboembolic events.

All patients were either discharged home or referred to a cardiac rehabilitation center.

Adverse events Adverse events such as stroke, pump thrombosis (PT), driveline infections (DLI), and major gastrointestinal (GI) bleeding were defined according to the INTERMACS Adverse Events Definitions (December 6, 2015). Short-term TCS such as intra-aortic balloon pump, ECMO, and mid-term circulatory support devices were defined as TCS modifiers of the INTERMACS profile according to the INTERMACS Adverse Events Definitions (December 6, 2015) and the study by Cowger et al.[8,9]

Statistical analysis Baseline characteristics were presented as numbers and percentages for

TABLE 1 Baseline characteristics of the study patients (n = 79)

Characteristic	Patients, n (%)
Diabetes	28 (35.4)
Arterial hypertension	28 (35.4)
Chronic kidney disease stage 3 or higher	34 (43)
Chronic obstructive pulmonary disease	3 (3.8)
Atrial fibrillation or flutter	45 (57)
Carotid artery disease	35 (44.3)
Sustained ventricular arrhythmia or sudden cardiac arrest	37 (46.8)
Prior myocardial infarction	33 (41.8)
Prior ischemic stroke	11 (13.9)
Prior transient ischemic attack	5 (6.3)
History of cardiac surgical intervention	13 (16.4)
History of percutaneous coronary intervention	29 (36.7)
History of percutaneous mitral valve intervention	2 (2.5)

TABLE 2 Distribution of patients (n = 79) according to the INTERMACS profile at the time of continuous-flow left ventricular assist device implantation

INTERMACS patient profile	Patients, n (%)
Level 1: critical cardiogenic shock	10 (12.7)
Level 2: progressive decline	23 (29.1)
Level 3: stable but inotrope-dependent	24 (30.4)
Level 4: resting symptoms	8 (10.1)
Level 5: exertion intolerant	6 (7.6)
Level 6: exertion limited	2 (2.5)
Level 7: advanced NYHA class 3	6 (7.6)

Abbreviations: NYHA, New York Heart Association

TABLE 3 Echocardiographic measurements before continuous-flow left ventricular assist device implantation

Parameter	Value
LV end-diastolic diameter, mm	75 (10), 50–110
LV end-systolic diameter, mm	67 (11), 39–98
LV end-diastolic volume, ml	308 (112), 152–670
LV end-systolic volume, ml	256 (98), 100–576
LV ejection fraction, %	17 (4), 8–34
RV dimension (M mode), mm	35 (7), 22–53
TAPSE, mm	15 (3), 8–23
RV systolic pressure, mm Hg	47 (14), 17–80
Aortic regurgitation grade[a], median (IQR), range	0 (1), 0–3
Mitral regurgitation grade[a], median (IQR), range	3 (1), 0–4
Tricuspid regurgitation grade[a], median (IQR), range	2.5 (1), 0–4

Data are presented as mean (SD), minimum–maximum unless otherwise indicated.

a Valve regurgitation grade: 1, trace; 2, mild; 3, moderate; 4, severe

Abbreviations: IQR, interquartile range; LV, left ventricular; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion

categorical variables, and as mean (SD) and median for continuous variables. In a univariable analysis, categorical variables were compared using the 1-sided exact Fisher test. An additional Cox multivariable analysis was performed to confirm predictors of mortality among LVAD-related AEs. An actuarial survival analysis was performed using the Kaplan–Meier method. Log-rank tests were used to compare different groups. In the univariable analysis, all reported values were 1-tailed, whereas in the Cox multivariable analysis, they were 2-tailed. A *P* value less than 0.05 was considered significant. Data were analyzed with the Stata 15 software (StataCorp LLC, College Station, Texas, United States).

RESULTS All implantations were performed on cardiopulmonary bypass. The mean time of surgery was 6 hours and 14 minutes (median, 5 hours and 40 minutes) with a mean cardiopulmonary bypass at 83 minutes (median, 69 minutes; range, 12–494 minutes). In 70 patients (88.6%), nitric oxide inhalation was used postoperatively at a mean time of 15.9 hours (median, 16 hours; range, 1–131 hours). The mean time of postoperative ventilation was 26 hours and 44 minutes (median, 18 hours and 25 minutes). Thirteen patients (16.4%) required renal replacement therapy at a mean time of 8.3 days (median, 7 days; range, 2–17 days), while 3 patients required intraoperative or postimplantation ECMO, including 1 patient with severe right ventricular failure (RVF).

The mean stay at the intensive care unit after implantation was 14 days (median, 7 days; range, 1–128 days). The mean length of hospital stay was 61 days (median, 53 days; range, 4–228 days). The mean time from implantation to discharge or in-hospital death was 36 days (median, 29 days; range, 1–125 days).

The overall reoperation rate was 30.4% (24 patients), and the predominant cause was bleeding (23 [29.1%]). One patient underwent reposition of an inflow cannula after 2 days because of inappropriate pump placement.

Early postoperative outcomes There were no intraprocedural deaths. One patient experienced nondisabling stroke. The 30-day mortality rate was 10%, and the 30-day stroke rate, 7.6% (3 patients, hemorrhagic stroke [HS]; 3 patients, ischemic stroke [IS]; including 1 patient who had HS and subsequently IS).

Long-term outcomes on left ventricular assist device support The mean time on LVAD support was 604 days (median, 426 days; range, 1–1758 days). The mean time to death was 399 days (median, 245 days; range, 1–1471 days). A total of 130.6 patient-years were analyzed (96.1, 22.4, and 12.1 for HVAD, HM2, and HM3, respectively). There were 2 device exchanges (one due to PT and the other due to pump-associated infection) and 1 pump explantation due to heart regeneration. Nine patients (11.4%) underwent OHT after a mean time of 656 days (median, 608 days; range, 323–1058 days).

The probability of 1-, 3-, and 6-month survival according to the Kaplan–Meier analysis was 0.9, 0.89, and 0.87, respectively, while the probability of 1-year survival was 0.81; 2-year, 0.71; 3-year,

TABLE 4 Distribution of adverse events for different types of pumps

Adverse event	HVAD device (n = 51), PY = 96.1	HM2 device (n = 9), PY = 22.4	HM3 device (n = 19), PY = 12.1	Total (n = 79), PY = 130.6
Hemorrhagic stroke	0.125 (23.5)	0.089 (22.2)	0	0.107 (17.7)
Ischemic stroke	0.073 (13.7)	0.045 (11.1)	0.083 (5.3)	0.069 (11.4)
Pump thrombosis	0.094 (17.6)	0.179 (44.4)	0	0.099 (16.5)
TIA	0.073 (13.7)	0	0	0.054 (8.9)
Major gastrointestinal bleeding	0.104 (19.6)	0.134 (0.33)	0	0.099 (16.5)
Major nasal bleeding	0.094 (17.6)	0	0.248 (15.8)	0.092 (15.2)
Driveline infection	0.125 (23.5)	0.223 (55.5)	0.083 (5.3)	0.138 (22.8)
Bacteremia	0.156 (29.4)	0.089 (22.2)	0.413 (26.3)	0.168 (27.8)
Bacteremia + driveline infection	0.042 (7.8)	0.045 (11.1)	0	0.038 (6.3)
Death	0.198 (37.2)	0.134 (33.3)	0.248 (15.8)	0.191 (31.6)

Data are presented as the number (percentage) of events per patient-year.

Abbreviations: HM2, HeartMate 2; HM3, HeartMate 3; HVAD, HeartWare; PY, patient-year; TIA, transient ischemic attack

0.61; and 4-year, 0.53 (FIGURE 1). Six patients remained on support longer than 4 years.

Strokes and transient ischemic attack Stroke was noted in 22 patients (27.8%): IS in 9 patients (11.4%) and HS in 14 patients (17.7%); 1 patient had both. Disabling stroke occurred in 12 patients (15.2%) and transient ischemic attack (TIA), in 7 patients (8.9%) after a mean time of 455 days (median, 302 days; range, 72–1151 days). The mean time to IS was 401 days (median, 207 days; range, 0–1609 days) and to HS, 490 days (median, 373 days; range, 1–1465 days).

Pump thrombosis Suspected or confirmed PT was found in 13 patients (16.5%). All patients received medical treatment and 1 patient was treated with successful pump exchange.[10] Pump thrombosis occurred after a mean time of 608 days (median, 563 days; range, 15–1351 days).

Left ventricular assist device–associated infections In the postoperative period, 3 patients (3.8%) developed wound infection at a mean time of 46 days (median, 41 days; range, 19–79 days) and 1 patient developed bacterial peritonitis after 45 days from LVAD implantation. Pneumonia (confirmed by chest radiography or microbiological tests) was reported in 17 patients (21.5%); 20 patients (25.3%) developed other kind of infection; and in 14 patients (17.7%), fever of unknown origin was observed (all microbiological tests were negative). One patient (1.3%) had fungemia and 8 patients (10.1%) had bacteremia after a mean time of 19.4 days (median, 17 days; range, 0–42 days) from implantation.

Driveline infections were present in 18 patients (22.8%), of whom 15 (19%) developed a chronic condition. The first symptoms of DLI were observed after a mean time of 351 days (median, 351 days; range, 21–960 days). The introduction of oral or intravenous antibiotics because of DLI was necessary 1 to 7 times (mean, 3.1) per patient after a mean time of 14 months (median, 12 months; range, 4–48 months). A surgical intervention was necessary in 8 patients (44.4%) after a mean time of 19 months (median, 19 months; range, 12–25 months) at a mean rate of 2.6 times (median, 2 times; range, 1–5 times).

There were no pump pocket infections. Bacteremia after CF-LVAD implantation occurred in 22 patients (27.8%), after a mean time of 301 days (median, 119 days; range, 0–1212 days). In 5 patients with DLI, bloodstream infection with the same pathogen occurred after a mean of 738 days (median, 742 days; range, 409–1212 days).

Major bleeding In our study, major GI bleeding occurred in 13 patients (16.5%), including 4 patients with recurrent bleeding. There were 21 major nasal bleedings (NB), which occurred in 12 patients (15.2%). Major bleedings appeared relatively early after implantation, with a mean time to first event of 127 days for NB (median, 24 days; range, 3–645 days) and 270 days for GI bleeding (median, 132 days; range, 19–1163 days).

Right ventricular failure In our study, 40.2% of patients required prolonged inotropic support over 7 days and 15.6%—over 14 days from implantation, which might indicate RVF. Severe RVF requiring temporary right ventricular support (ECMO used) was found in 1 patient.

Mortality data The overall mortality rate during LVAD support was 31.6% (25 patients). The main cause of death was HS (9 patients [11.4%]). Four patients died of multiorgan failure; 3, of severe pneumonia; 2, of PT; and 2, of IS. Another causes included pulmonary embolism (1 patient), intracerebral posttraumatic bleeding (1 patient), ileus (1 patient), and perioperative bleeding (1 patient). Data on the cause of death were unavailable in 1 patient.

Events per patient-year Events per patient-year were calculated overall and for individual devices. Although it was not the main focus of our study, a preliminary analysis of events per patient-year revealed better outcomes for HM3 patients compared with those for HVAD and HM2 patients, with an obvious limitation of a shorter support time. In the HM3 group, no HS, PT, or GI bleeding were observed (TABLE 4).

International normalized ratio analysis Due to a relatively high rate of stroke in our study, we analyzed all in-hospital INRs and those measured during ambulatory visits. There were 3152 INR measurements performed for 79 patients. The mean (SD) INR value was 2.15 (0.8) and the median INR value was 2.1 (range, 0.9–10.1). The percentage of INR of 2 to 3 was 0.49% for all measurements; INR below 2, 0.41%; and INR above 3, 0.1%. The percentages of INR of 2 to 3,

FIGURE 1
Kaplan–Meier survival curve for continuous-flow left ventricular assist device (CF-LVAD) therapy

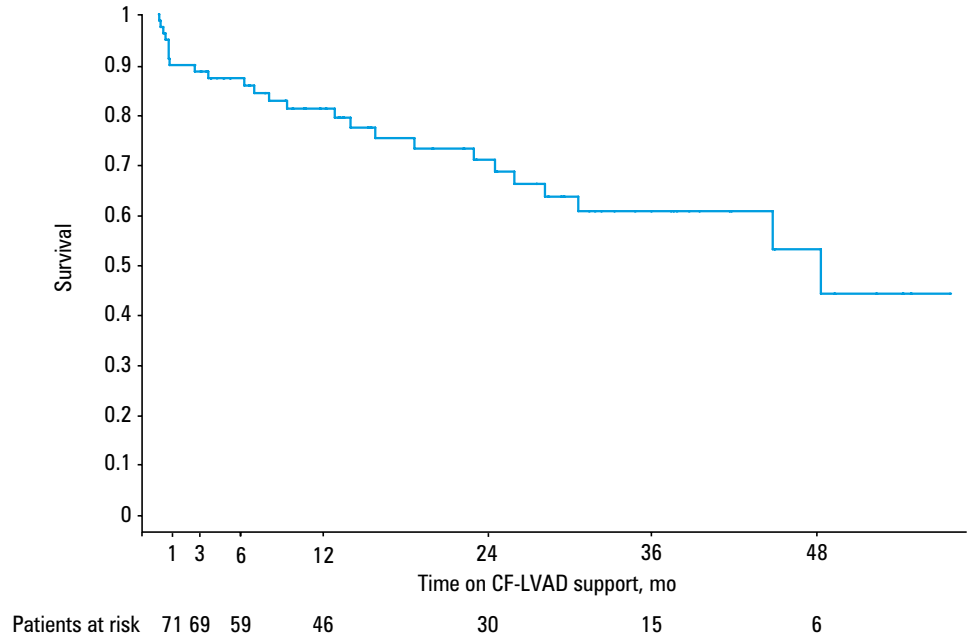
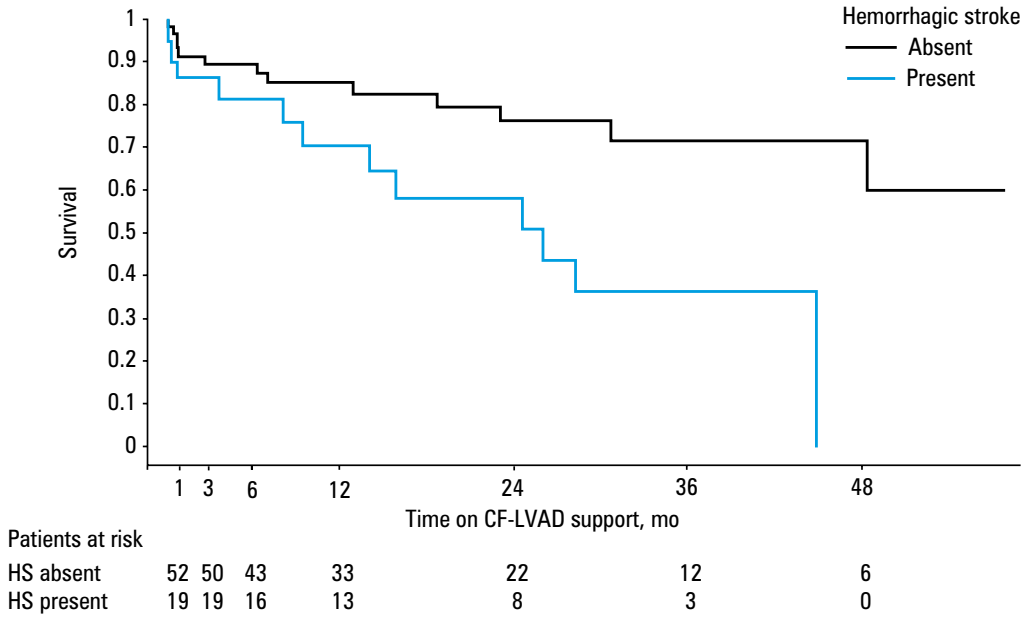


FIGURE 2 Survival of patients on continuous--flow left ventricular assist device (CF-LVAD) support depending on the incidence of hemorrhagic stroke (HS)



below 2, and above 3 were 0.54%, 0.34%, and 0.12%, respectively, for PT; 0.56%, 0.33%, and 0.11%, respectively, for IS; 0.56%, 0.35%, and 0.09%, respectively, for TIA; 0.47%, 0.4%, and 0.13%, respectively, for HS; 0.46%, 0.45%, and 0.09%, respectively, for GI bleeding; 0.5%, 0.43%, and 0.08%, respectively, for NB; as well as 0.44%, 0.41%, and 0.14%, respectively, for a group of deceased patients.

Mortality predictors in patients on left ventricular assist device support The univariable analysis revealed the following preimplantation conditions to be significant predictors of death: paroxysmal atrial fibrillation ($P = 0.047$), diabetes (0.03), and carotid artery disease (0.02). When postimplantation factors were considered, death correlated with bacteremia ($P = 0.01$), renal replacement therapy ($P = 0.002$), and the postoperative use of inotropes for RHF ($P = 0.046$). The lack of treatment with β-blockers, angiotensin II receptor antagonists, sildenafil, and protein pump inhibitors also correlated with mortality ($P \leq 0.001$, 0.002, 0.01, and 0.03 respectively). Mortality was associated with HS ($P \leq 0.001$) and bacteremia ($P = 0.01$), while no associations were observed for IS ($P = 0.59$), PT ($P = 0.35$), TIA ($P = 0.06$), GI bleeding ($P = 0.39$), NB ($P = 0.43$), and DLI ($P = 0.46$). When all analyzed AEs except HS and bacteremia were included in the analysis, no impact on survival was observed ($P = 0.09$). Survival curves depending on the incidence of a particular AE were compared using log-rank tests, which also showed poorer survival only for patients with HS ($P = 0.001$) or bacteremia ($P = 0.007$) (FIGURES 2 and 3). The Cox multivariable analysis also confirmed HS ($P = 0.027$; hazard ratio [HR], 2.7) and bacteremia ($P = 0.027$; HR, 2.8) to be independent

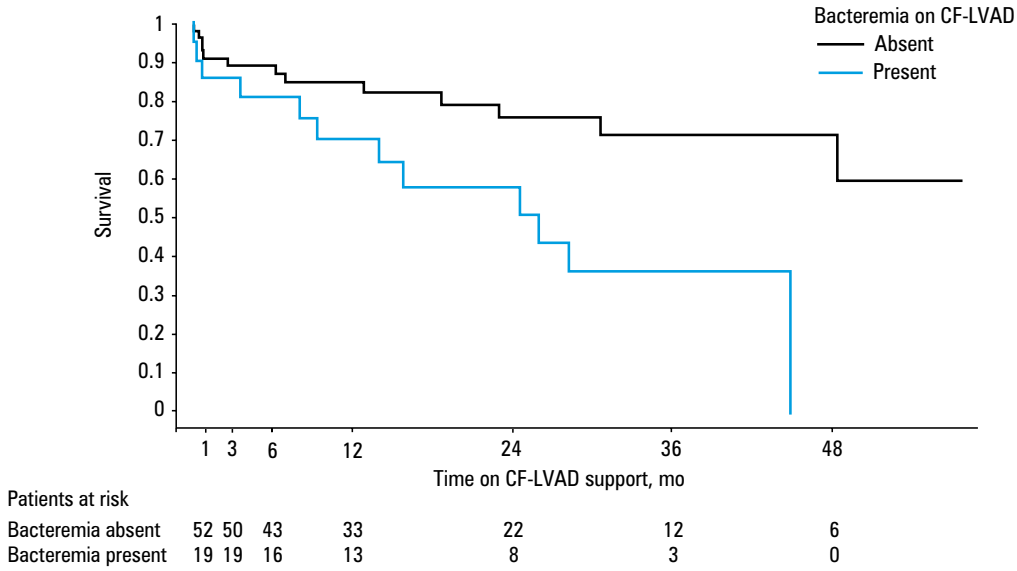


FIGURE 3 Survival of patients on continuous--flow left ventricular assist device (CF-LVAD) support depending on the incidence of bacteremia

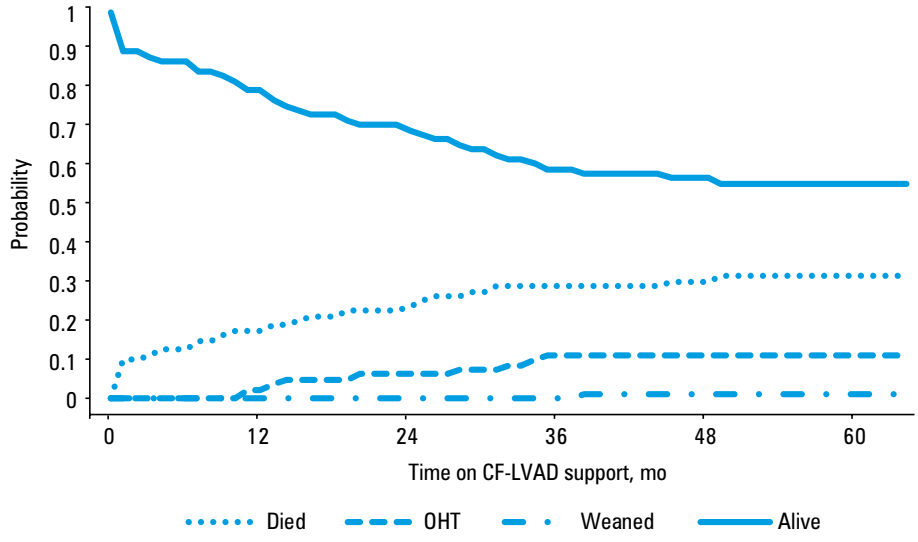


FIGURE 4 Competing outcomes of patients on continuous-flow left ventricular assist device (CF-LVAD) support
Abbreviations: OHT, orthotopic heart transplant

predictors of mortality among LVAD-related AEs. The remaining AEs did not show any significant impact on mortality (for PT, $P = 0.083$ [HR, 0.33]; for IS, $P = 0.62$ [HR, 1.4]; for GI bleeding, $P = 0.66$ [HR, 0.79]; for NB, $P = 0.6$ [HR, 0.72]; and for DLI, $P = 0.06$ [HR, 0.38]).

The type of CF-LVAD, the INTERMACS profile 1–3 versus 4–7, age group, and HF before implantation were also analyzed, but no differences in survival were observed ($P = 0.84$, $P = 0.73$, $P = 0.38$, and $P = 0.25$, respectively).

The major outcomes of CF-LVAD therapy such as OHT, pump explantation due to heart regeneration, death, or staying alive on LVAD support were depicted in FIGURE 4 as competing outcomes over time.

DISCUSSION Our study investigated short- and long-term outcomes in heart transplant candidates bridged with CF-LVAD support, with a special focus on the timing of LVAD-related AEs and associated mortality risk. The number of CF-LVAD implantations gradually increases worldwide owing to good survival rates. However, despite a continuous improvement of technology, morbidity and mortality rates are significant, especially when considering older generations of ventricular assist devices. The knowledge of survival data, predictors of mortality, and AEs during LVAD support facilitates the search for preventive measures and the choice of the best strategy for individual patients.[5]

Our study demonstrated survival rates (early and late) that ranged in between those reported in the EUROMACS and INTERMACS registries (30 days, 88% and 95%, respectively; 1 year, 69% and 81%, respectively; 2 years, 55% and 70%, respectively; and 3 years, 44% and 59%, respectively).[5,11] Our results are also in agreement with the recently published IMACS registry (ISHLT Mechanically Assisted Circulatory Support), including 13 000 patients implanted with CF-LVAD, which reported the 1- and 6-month survival rates of 95% and 86%, respectively. It is also in line with a study by Tsiouris et al,[12,13] including 200 patients (mean duration of LVAD support, 581 days), who reported the 30-day, 6-month, as well as 1-, 2-, 3-, and 4-year survival rates of 94%, 96%, 78%, 71%,

62%, and 45%, respectively (as compared with 90%, 87%, 81%, 71%, 61%, and 53%, respectively, in our study).

In the study by Tsiouris et al,[13] the mean length of hospital stay was 21 days and 11 days in the intensive care unit, which is comparable with the results reported by Starling et al[14] but slightly shorter than in our study group. The discrepancy probably results from the severe condition of patients before implantation and the lack of a rehabilitation unit in our institution at the time the majority of patients were implanted. Therefore, the rehabilitation period in our study had been included in the implantation hospital stay.

Multiorgan failure, RVF, and stroke posed the greatest risk of death according to the INTERMACS data, while the EUROMACS registries reported multiorgan failure and infections.[5,11,15,16] Stroke remained the leading cause of death in our cohort (13.9%). On the other hand, multiorgan failure was often secondary to cerebral insult and resulted in patient death in 5.1% of cases, which is much lower when compared with the above registries.

A recent stroke analysis of the INTERMACS database revealed that prognosis for HS was significantly worse than for IS and that the first HS posed a higher risk of another stroke.[17] In some smaller studies, survival rates after stroke were higher, although long-term mortality risk in patients with stroke was twice as high as that in stroke-free individuals.[18] Our results showed high mortality rates for HS, which may be related to a relatively long time of LVAD support, more comorbidities, and a more advanced stage of HF at LVAD implantation, as expressed by a higher rate of patients with INTERMACS profile 1 in our population. Relatively low in-hospital and ambulatory plasma INR levels were probably not associated with a higher rate of HS. However, further studies are needed to explore this issue.

Our cohort also represents early experience in ventricular assist device placement, as indicated by 12.7% of patients undergoing implantation due to cardiogenic shock (INTERMACS 1), which is probably associated with a more limited access to short- or mid-term left ventricular support devices in earlier years. In the sixth INTERMACS report (9112 patients), early mortality was higher in patients with INTERMACS profiles 1–2 as compared with those with profiles 3–4, with infection and multiorgan failure found to be the major causes of death.[15,19] Yet, in our study, no significant differences were observed between INTERMACS profiles 1–3 and 4-6 regarding early and late outcomes. However, we did not assess every INTERMACS profile because profile 2 or 3 was found in almost 60% of our patients and other groups were less numerous. In future studies, when our LVAD population becomes larger, we are planning to assess survival according to the INTERMACS profile, especially INTERMACS 1.

Kumar et al[20] identified ischemic etiology as an independent predictor of mortality in patients with CF-LVAD. Our study found that only some of the factors discussed above had an impact on mortality.

In the latest IMACS report, infection and bleeding each affected over one-third of patients. In our study, GI bleeding and NB occurred at a similar rate, but LVAD-related infections affected more patients.[12]

According to Patel et al,[21] CF-LVAD is the "second hit" causing bleedings in predisposed patients, such as those with severe HF and acquired von Willebrand syndrome. In their study, epistaxis was strongly associated with GI bleeding. Such a relation was not investigated in our group, but it would be interesting to identify predictors and possible relationships of these types of bleeding in future studies. Tsiouris et al[13] reported that the most frequent AE was GI bleeding (21%), followed by RVF (19%) and stroke (15%). In our study, RVF was less frequent probably due to a careful selection of patients before LVAD implantation. In another study, the incidence of GI bleeding was 23.9% and it was correlated with chronic kidney disease.[22] A lower incidence of GI bleeding in our study is probably due to the fact that we used extensive diagnostic measures before implantation. Endoscopy of at least the upper GI tract was performed in all possible candidates, and proton pump inhibitors were used in most patients after implantation.

The PREVENT multicenter study[23] (Prevention of HeartMate II Pump Thrombosis Through Clinical Management) reported a PT rate of up to 8.9% in the first 6 months of follow-up, although full adherence to optimal implantation techniques, heparin bridging, and pump speed recommendations resulted in a significantly lower risk of PT (1.9%). In that study, no significant difference in survival depending on PT was found, which is in line with our study. In a meta-analysis including over 28 000 patients, PT occurred in 10.6%.[24] Our data show higher PT rates, which is probably related to a heterogeneity of pump types and a relatively long LVAD support. The number of PT events could probably be reduced with routine diagnostic tests prior to surgery that identify lupus anticoagulant, heparin-induced thrombocytopenia antibodies, factor V Leiden, protein C or antithrombin III deficiency, as well as antiphospholipid syndrome. However, some of the above tests were routinely introduced in our institution in 2017, so they were not performed in patients implanted earlier.[25]

There are few studies comparing survival and AEs in different types of CF-LVADs. As the majority of patients in our institution were implanted with HVAD, we focused on this analysis, although a preliminary assessment of the events per patient-year for various CF-LVADs showed the best results for HM3. Stulak et al[26] compared outcomes between HM2 and HVAD and reported a trend for a higher incidence of DLI in patients

implanted with HM2 as well as a higher incidence of stroke (especially in patients with ischemic HF implanted with HVAD), although the total number of patient-years for HM2 was over 5-fold higher than for HVAD.

In the MOMENTUM 3 study (Thoratec Corporation MOMENTUM 3, Multicenter Study of MagLev Technology in Patients Undergoing MCS Therapy With HeartMate 3™ IDE Clinical Study Protocol) including 294 patients and comparing the rates of major AEs between HM3 and HM2, RVF occurred in 29.8% and 24.6% of cases, respectively; any bleeding, in 33.1% and 39.1%; any cardiac arrhythmia, in 31.1% and 37.7%; HS, in 2.6% and 5.8%; IS in 5.3% and 6.5%; disabling stroke, in 6% and 5.8%; DLI, in 1.9% and 6.5%; and GI bleeding, in 15.9% and 15.2%.[27,28] In future studies, once we enroll more patients implanted with HM3, we are also planning to compare the outcomes of different types of CF-LVAD and surgical implantation techniques.

Another interesting issue in patients on CF-LVAD support is the urgency status for OHT. In our study, the analysis of severe AEs revealed that most of them occurred in the second year of LVAD support. This may indicate that OHT should probably be considered after the first year of support before the majority of AEs occur, except for patients after HS or after an episode of bacteremia, who should probably be considered earlier because of poor prognosis.

Survival data observed in our study show that CF-LVAD support is now close to OHT in terms of the 1-year survival rate, which was 82.4% according to a National Health Service report[29] and nearly 88% to 90% according to a study by Mancini et al.[30]

In our study, only 1 of the 79 patients (1.3%) recovered and was weaned from the device, which is consistent with the results of larger studies, reporting cardiac recovery in 1.3% of patients.[31] Recovery should probably be more actively and systemically promoted by medical therapy intensification and pump speed adjustment in order to achieve it in a larger number of patients.

Except for clinical factors affecting survival, it would be extremely valuable to search for biochemical markers associated with mortality during CF-LVAD support, as shown by Szczurek et al[32] in a study of non-LVAD population awaiting OHT.

Our results show that efforts should be made to reduce the rates of postoperative infections, bleeding, and stroke. At our institution, we have already taken some measures, such as the introduction of novel mini-invasive implantation techniques and left atrial appendage closure together with strict INR monitoring, blood pressure management, and early treatment of infections.

Limitations Our study had several limitations. First, as a retrospective, observational, nonrandomized single-center study including a relatively small sample size, it had insufficient statistical power. Moreover, some perioperative data were not available, mostly for patients who underwent implantation outside our institution. In addition, the INR analysis included early postoperative measurements as well as those taken during temporary warfarin withdrawal for various reasons. Ambulatory self-measured INR levels were not available and were not included in this analysis.

Conclusions In patients with end-stage HF, CF-LVAD support improves survival. Despite the numerous benefits of CF-LVAD, the frequency of AEs remains substantial, although most of them occur after 1 year of LVAD support. Adverse events do not have a significant impact on mortality, except for HS and bacteremia. Preimplantation patient selection and treatment of AEs should focus on reducing the incidence and burden of AEs for further improvement of survival. Novel devices seem to overcome these shortcomings, but larger studies are needed to support these findings.

CORRECTIONS

This article was corrected on October 29, 2020. The list of corrections is available at www.mp.pl/paim.

ARTICLE INFORMATION

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