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ORIGINAL ARTICLE

Continuous-flow LVADs in the Nordic countries: complications and mortality and its predictors

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ABSTRACT

Objectives: The purpose of this study was to assess complications and mortality and its predictors, with continuous-flow left ventricular assist devices (CF-LVADs) in the Nordic Countries. **Design:** This was a retrospective, international, multicenter cohort study. **Results:** Between 1993 and 2013, 442 surgically implanted long-term mechanical assist devices were used among 8 centers in the Nordic countries. Of those, 238 were CF-LVADs (HVAD or HeartMate II) implanted in patients >18 years with complete data. Postoperative complications and survival were compared and Cox proportion hazard regression analysis was used to identify predictors of mortality. The overall Kaplan–Meier survival rate was 75% at 1 year, 69% at 2 years and 63% at 3 years. A planned strategy of destination therapy had poorer survival compared to a strategy of bridge to transplantation or decision (2-year survival of 41% vs. 76%, $p < .001$). The most common complications were non-driveline infections (excluding sepsis) (44%), driveline infection (27%), need for continuous renal replacement therapy (25%) and right heart failure (24%). In a multivariate model age and left ventricular diastolic dimension was left as independent risk factors for mortality with a hazard ratio of 1.35 (95% confidence interval (CI) [1.01–1.80], $p = .046$) per 10 years and 0.88 (95% CI [0.72–0.99], $p = .044$) per 5 mm, respectively. **Conclusion:** Outcome with CF LVAD in the Nordic countries was comparable to other cohorts. Higher age and destination therapy require particularly stringent selection.

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Heart failure; mechanical circulatory support; left ventricular assist device; outcomes

Introduction

Advanced therapies including treatment with left ventricular assist device (LVAD) and/or heart transplantation significantly improve outcomes in end-stage heart failure [1–4]. The use of implantable LVADs have steadily been increasing in the Western world, particularly since the introduction of continuous flow (CF) portable LVAD systems [5,6]. Two main pump techniques have been utilized: the axial flow pumps (HeartMate II (HMII) (Abbott Laboratories, Abbott Park, Illinois, USA), MicroMed DeBakey (MicroMed Cardiovascular, Inc.; Houston, Texas, USA), Jarvik 2000 (Jarvik Heart Inc. New York, NY, USA)) and the centrifugal pumps (HeartWare ventricular assist device (HVAD) (Medtronic, St. Paul, MN, USA), VentrAssist (Ventracor, Chatswood, NSW Australia, now out of the market) and HeartMate 3 (HM3) (Abbott Laboratories, Abbott Park, Illinois, USA)). The HMII and the HVAD have been tested in large clinical studies and have emerged as the most extensively used CF-LVADs [7–10]. Recently, a two-year follow-up of the HM3 was published [11].

In the USA, implantation rates and complications during LVAD support are followed thoroughly in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry since 2006 [6]. This registry now includes >22,000 patients from 185 participating hospitals and has been a valuable source for research regarding LVAD outcomes and complications in the USA. In 2009 The European Registry for Patients with Mechanical Circulatory Support (EUROMACS) was founded as an effort to collect the European experience as well [12]. In 2013 The International Society for Heart and Lung Transplantation (ISHLT) Mechanically Assisted Circulatory Support (IMACS) registry was initiated with the aim to create the global experience combining registries from the USA, Europe and Japan [5].

In an effort to fill the knowledge gap regarding use and outcomes of LVAD therapy and their predictors in the Nordic countries a registry was created in 2012 with the ambition to collect data from Denmark, Finland, Norway, Iceland and Sweden from 1993 to 2013. This report aims at

Table 1. Patient demographics and pre-implant characteristics.

Factor	Category	All				BTT		
		All 244	DT 31	BTT 207	p-Value*	HMII 150	HVAD 57	p-Value*
Center (% within each device)	Copenhagen	62 (25.4%)	13 (41.9%)	49 (23.7%)	<.001	49 (32.7%)	0 (0.0%)	<.001
	Gothenburg	25 (10.2%)	2 (6.5%)	17 (8.2%)		17 (11.3%)	0 (0.0%)	
	Helsinki	13 (5.3%)	0 (0.0%)	13 (6.3%)		0 (0.0%)	13 (22.8%)	
	Lindkoping	26 (10.7%)	1 (3.2%)	25 (12.1%)		25 (16.7%)	0 (0.0%)	
	Lund	39 (16.0%)	0 (0.0%)	39 (18.8%)		31 (20.7%)	8 (14.0%)	
	Oslo	31 (12.7%)	1 (3.2%)	30 (14.5%)		0 (0.0%)	30 (52.6%)	
	Stockholm	32 (13.1%)	12 (38.7%)	20 (9.7%)		14 (9.3%)	6 (10.5%)	
	Uppsala	16 (6.6%)	2 (6.5%)	14 (6.8%)		14 (9.3%)	0 (0.0%)	
Age		54.1 (45.5, 61)	65.5 (62.9, 68.2)	52.3 (43.8, 58.9)	<.001	51.9 (43.2, 58.6)	54.5 (49.3, 59.8)	.14
Male Gender	Male	202 (82.8%)	28 (90.3%)	169 (81.6%)	.23	122 (81.3%)	47 (82.5%)	.85
Height (cm)		179 (173, 184)	180 (176, 184)	178 (172, 183)	.30	179 (173, 184)	177 (170, 183)	.23
Weight (kg)		81 (72, 93)	84 (74, 94)	81 (71, 93)	.61	81 (71, 95)	80 (71, 91)	.33
Destination Therapy		31 (12.7%)	31 (100.0%)	0 (0.0%)	n/a	150 (100.0%)	57 (100.0%)	
Diagnosis	ICM	96 (39.3%)	22 (71.0%)	73 (35.3%)	<.001	51 (34.0%)	22 (38.6%)	.43
	DCM	102 (41.8%)	5 (16.1%)	93 (44.9%)		66 (44.0%)	27 (47.4%)	
	Other	46 (18.9%)	4 (12.9%)	41 (19.8%)		33 (22.0%)	8 (14.0%)	
Disease duration	de novo	35 (14.3%)	0 (0.0%)	35 (16.9%)	.009	21 (14.0%)	14 (24.6%)	.22
	<6 months	52 (21.3%)	4 (12.9%)	46 (22.2%)		35 (23.3%)	11 (19.3%)	
	>6 months	148 (60.7%)	26 (83.9%)	118 (57.0%)		87 (58.0%)	31 (54.4%)	
Diabetes		41 (16.8%)	8 (25.8%)	32 (15.5%)	.15	24 (16.0%)	8 (14.0%)	.68
Stroke		15 (6.1%)	1 (3.2%)	13 (6.3%)	.49	6 (4.0%)	7 (12.3%)	.037
Hypertension		35 (14.3%)	8 (25.8%)	27 (13.0%)	.073	21 (14.0%)	6 (10.5%)	.41
Hb (g/l)		119 (104, 132)	122.5 (114, 133)	117 (103, 132)	.21	120 (104, 134)	110 (101, 124)	.022
Na (mmol/l)		136 (134, 139)	136.5 (134, 140)	136 (134, 139)	.62	136 (133, 139)	138 (134, 140)	.034
Bilirubin (μmol/l)		20 (12, 31)	19.5 (16, 28)	20 (11, 31)	.53	22 (12, 34)	18 (9, 24)	.039
Albumin (g/l)		32 (29, 36)	33 (29.5, 36)	32 (29, 36)	.91	33 (30, 36)	31 (27, 36)	.048
NT-pro-BNP (ng/l)		2505 (730, 6847)	3518 (1290, 7010)	2407 (681, 6683)	.56	2947 (1354, 7706)	1194 (446, 5850)	.017
GFR (ml/min)		64.1 (46.2, 85.5)	47.3 (34.7, 59.9)	70.5 (48.4, 88.7)	<.001	67.4 (48.4, 87.2)	72.0 (47.5, 96.0)	.47
Ejection frac- tion (%)		15 (10, 20)	15 (10, 20)	15 (10, 20)	.39	15 (10, 20)	15 (15, 20)	.073
LVIDd (cm)		6.9 (6.1, 7.8)	6.9 (6.5, 7.7)	6.9 (6, 7.8)	.92	6.9 (6.1, 7.8)	6.9 (6, 7.8)	.98
mPAP (mmHg)		35 (30, 41)	33.5 (29, 41)	35 (30, 42)	.78	37 (30, 44)	33 (28, 39)	.044
PCWP (mmHg)		25 (21, 30)	28 (24, 29)	25 (21, 30)	.40	25 (21, 31)	24 (20, 29)	.15
CI (l/min/m ²)		1.9 (1.5, 2.5)	1.84 (1.7, 2.1)	1.9 (1.5, 2.5)	.75	1.9 (1.5, 2.5)	1.9 (1.5, 2.5)	.99
PVR (WU)		2.5 (1.9, 3.9)	3.0 (2.3, 4.6)	2.5 (1.9, 3.8)	.14	2.6 (1.9, 3.9)	2.4 (1.7, 3.6)	.43
Prior Inotropes	Yes	113 (46.3%)	13 (41.9%)	100 (48.3%)	.37	73 (48.7%)	27 (47.4%)	.25
Prior IABP	Yes	55 (22.5%)	1 (3.2%)	53 (25.6%)	.004	22 (14.7%)	31 (54.4%)	<.001

DT: destination therapy; BTT: bridge to transplantation; ICM: ischemic cardiomyopathy; NICM: non-ischemic cardiomyopathy; Hb: hemoglobin; Na: sodium; NT-pro-BNP: nN-terminal-pro-brain natriuretic peptide; LVIDd: left ventricular internal diameter in end diastole; CI: cardiac index; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; WU: Wood units; IABP: intra-aortic balloon pump.

*p-Values are for comparison of the percentage of patients with each event, as determined by the Pearson's chi-squared test or for the comparison of continuous variables using the Kruskal-Wallis test.

describing patient outcomes, complications and its predictors during CF-LVAD support in the Nordic countries.

Methods

Data for patients receiving LVADs in Denmark (Copenhagen), Finland (Helsinki), Norway (Oslo), and Sweden (Gothenburg, Linköping, Lund, Stockholm and Uppsala) from 1993 to 2013 were retrospectively collected. Non-implantable, temporary LVADs, pulsatile LVADs, BiVADS, and patients <18 years were excluded from this study. The patients were stratified according to implantation strategy (bridge to transplant (BTT) vs. destination therapy (DT) and according to the type of LVAD that was implanted, HMII vs. HVAD. The study complied with the Declaration of Helsinki and each local research ethics committee approved of the study. Individual patient informed consent was not required for this data review.

Statistical analysis

Baseline data are presented as median and interquartile range (IQR) for continuous variables and percentages for categorical data. Differences in baseline characteristics and complications were assessed using Kruskal-Wallis test with *post hoc* analysis with Dunn's test with Bonferroni correction for multiple comparisons for continuous data. Pearson's chi-squared test was used to compare categorical data between the groups. Patient survival was analyzed using the Kaplan-Meier method and the log-rank test was used to compare survival between groups. Competing risk curves were created using cumulative incidence functions and competing risk regression were performed according to the method of Fine and Gray. Cox proportional hazard model was used to assess predictors for mortality. All variables significantly associated with mortality in the univariate model were included in the multivariate model (age, DT vs. BTT, atrial fibrillation, platelets, GHFR, left ventricular internal diameter in end diastole (LVIDd) and). Patients were censored at transplant or device explant for recovery.

In multivariable analysis multiple imputation assuming multivariate normal distribution (MVN) was used for continuous variables using the Markov Chain Monte Carlo (MCMC) procedures. Data analysis was done using Stata/SE 14.2 for Mac (StataCorp, TX, USA). Overall a 2-sided p -value of $<.05$ was considered significant.

Results

Patient demographics

Between 1993 and 2013, 442 temporary and durable surgically implanted mechanical circulatory support devices were used and entered in the registry from 8 centers in the Nordic countries. Of those, 284 were durable CF LVADs implanted in patients >18 years. We excluded 39 patients implanted with miscellaneous devices (22 VentrAssist, 10 MicroMed DeBakey and 7 Jarvik2000) and 6 patients with missing data and performed a retrospective analysis in the remaining 238 patients.

The baseline characteristics for all patients are described in Table 1. Overall, patients were 54.1 IQR(45.4–61.0) years old and 83% were males. The majority of patients were in INTERMACS profile 3 (31%) (Figure 1) and the intention with the implant was BTT in 85%. When comparing DT vs. BTT there was a difference in the center preference for type of device ($p < .001$). As expected, patients implanted as DT vs. BTT were older (65.5 IQR[62.9–68.2] vs. 52.3[43.8–58.9], $p < .001$), were more likely to have a history of ischemic cardiomyopathy ($p < .001$) with a longer disease duration ($p < .01$), had poorer renal function ($p < .001$) and were less likely to be on a balloon pump at the time of implant ($p < .01$) (Table 1).

When comparing the BTT groups receiving HMII or HVAD there was a difference in the center preference for type of device ($p < .001$). Baseline laboratories were also different between HMII vs. HVAD; hemoglobin (120 IQR[104–134] vs. 110 IQR[101–124], $p < .05$), sodium (136 IQR[133–139] vs. 138 IQR[134–140], $p < .05$) bilirubin (22 IQR[12–34] vs. 18 IQR[9–24], $p < .05$, NT-pro-BNP (2947 IQR[1354–7706] vs. 1194 IQR[446–5850],

Figure 1. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles for the different pump types. There were no differences between the groups ($p = .22$ by Pearson's chi-squared test).

$p < .05$). There were no differences in pre-implant echocardiography or invasive hemodynamics. However, fewer patients in with HMII had pre-implant intra-aortic balloon pump (IABP) compared to patients with HVAD (15% vs. 54%, $p < .01$). INTERMACS profiles were similar between the groups ($p = \text{NS}$) (Table 1).

Overall patient survival

The patients were followed for a median of 195 IQR[74–514] days. The overall Kaplan–Meier (KM) estimate of survival was 75% (95% CI [69–81%]) at one year, 69% (95% CI [59–76%]) at two years and 63% (95% CI [50–73%]) at three years (Figure 2(A)). Patients with a planned destination therapy (DT) had worse survival than patients with planned BTT with a one- and two-year survival of 54% (95% CI [36–70%]) and 41% (95% CI [23–59%]) for DT vs. 79% (95% CI [71–84%]) and 76% (95% CI [67–83%]) ($p < .001$ by log-rank test) for BTT (Figure 2(B)). Furthermore, there was no difference in survival when comparing INTERMACS profiles (INTERMACS 1–3 vs. INTERMACS 4–7) ($p = \text{NS}$ by log-rank test) or when comparing the time era for pump implantation

Figure 2. (A) Kaplan–Meier survival curves over three years for the overall population. (B) Kaplan–Meier survival curves over three years stratified by planned destination therapy (DT) or bridge to transplant (BTT). Patients were censored at transplant or device explant for recovery.

(2001–2007 vs. 2008–2010 vs. 2011–2013) ($p = \text{NS}$ by log-rank test).

Competing outcomes in the BTT patients

Overall competing outcomes curves for patients implanted as BTT ($n = 207$) are shown in Figure 3(A) and competing outcomes stratified according to type of device in Figure 3(B,C). In the whole group median time to transplant was 189 IQR[123–370] days. In a competing risk regression analysis there were no association with device type (HVAD vs.

HMII) and risk for either mortality ($p = .31$) or chance for transplantation ($p = .86$).

Adverse events

The frequencies of major adverse events are presented in Table 2. Overall, the most common complications were non-driveline infections (excluding sepsis) (44%), driveline infection (27%), need for continuous renal replacement therapy (CRRT) (25%) and right heart failure (24%). When comparing DT vs. BTT; re-operation (36% vs. 18%, $p < .05$) sepsis (39% vs. 17%, $p < .01$), stroke (32% vs. 8%, $p < .01$) GI-bleeding (36% vs. 8%, $p < .01$) and non-driveline infections (58% vs. 32%, $p < .01$) was more common in DT patients vs. BTT patients (Table 2). When comparing adverse events in BTT patients with HMII vs. HVAD there were no significant differences.

Risk factors for mortality

Univariate risk factors for mortality were age (1.49, 95% CI [1.16–1.91] per 10 patient year, $p = .002$), DT as implantation strategy (2.59, 95% CI [1.48–4.55] for DT vs. BTT, $p < .001$), atrial fibrillation (1.75 95% CI [1.04–2.93] for yes vs. no, $p = .035$), platelet count (0.79 , 95% CI [0.66–0.94] per $50 \times 10^9/\text{l}$, $p = .007$), glomerular filtration rate (GFR) (0.86 , 95% CI [0.78–0.95] per 10 ml/min, $p = .003$) and left ventricular internal diameter in end diastole (LVIDd) (0.88 , 95% CI [0.78–0.99] per 5 mm, $p = .035$). In a multivariate model using multiple imputation, age and LVIDd was left as independent risk factors with a HR of 1.35 (95% CI [1.01–1.80], $p = .046$) per 10 years and 0.88 (95% CI [0.72–0.99], $p = .044$) per 5 mm respectively.

Discussion

Survival after implantation of CF LVAD was comparable to other cohorts in this retrospective analysis of patients from eight centers in four Nordic countries. The 1-year survival was 75%. This can be compared to the latest reported survival from the eighth INTERMACS report where the 1 year survival was 81% for CF LVADs pump implanted from 2008 [6]. In the latest EUROMACS registry the 1-year survival for LVADs implanted from 2011 to 2016 was lower and reported at 69% [13]. The patients in our study received their LVADs from 2001 to 2013 and thus represent a more historic cohort. However, in the INTERMACS report there is no difference in survival between patients with CF LVADs implanted before 2010 compared to pumps implanted from 2014–2017. Survival in BTT patients treated with the either HMII or HVAD were not different. Furthermore, there was a large variation in the preferred device type among the different centers but study site was not a predictor for mortality.

The largest obstacles to a more widespread use of LVADs are the burden of complications, particularly complications related to bleeding and thrombosis. Stroke is one of the major complications after LVAD implantation and

Figure 3. (A) Competing risk curves over 2 years for the overall bridge to transplant (BTT) population. Competing risk curves over one year for the HeartMate II (HMII) (B) and HVAD (C) pumps. At any point in time, the sum of the proportions for each outcome equals 1.

Table 2. Adverse events following pump implantation.

Factor	All					BTT				
	DT (n = 31)					BTT (n = 207)				
	All (n = 244) 244	No. of patients (%)	Events /patient-yr	No. of patients (%)	Events /patient-yr	p-Value*	HMII (n = 150)	no. of patients (%)	events /patient-yr	HVAD (n = 57)
N										
Reoperation	48 (21.3%)	11 (35.5%)	0.22	37 (17.9%)	0.19	.04	23 (15.3%)	14 (25.0%)	0.14	0.47
CRRT	56 (25.2%)	10 (32.2%)	0.20	46 (22.2%)	0.23	.27	31 (20.7%)	15 (26.8%)	0.19	0.50
Sepsis	48 (22.5%)	12 (38.7%)	0.24	36 (17.4%)	0.18	<.01	26 (17.3%)	10 (17.9%)	0.16	0.33
Stroke 14 days	6 (2.8%)	2 (6.5%)	0.04	4 (1.9%)	0.02	.16	2 (1.3%)	2 (3.6%)	0.01	0.07
Stroke	26 (12.3%)	10 (32.3%)	0.20	16 (7.7%)	0.08	<.01	10 (6.7%)	6 (10.7%)	0.06	0.20
GI bleeding	27 (13.9%)	11 (35.5%)	0.22	16 (7.7%)	0.08	<.01	10 (6.7%)	6 (11.3%)	0.06	0.20
Other Bleeding	25 (13.0%)	4 (12.9%)	0.08	21 (10.1%)	0.11	.57	13 (8.7%)	8 (15.4%)	0.08	0.27
Thromboembolic event	17 (7.7%)	4 (12.9%)	0.08	13 (6.3%)	0.07	.21	10 (6.7%)	3 (5.4%)	0.06	0.10
Pump Thrombosis	17 (7.6%)	3 (9.7%)	0.06	14 (6.8%)	0.07	.60	12 (8.0%)	2 (3.6%)	0.07	0.07
Right Ventricular Failure	54 (24.4%)	10 (33.3%)	0.20	44 (21.3%)	0.22	.22	34 (22.7%)	10 (17.9%)	0.20	0.33
Driveline Infection	52 (26.9%)	7 (22.6%)	0.14	45 (21.7%)	0.23	.79	34 (22.7%)	11 (20.8%)	0.20	0.24
Non-driveline Infection	84 (44.4%)	18 (58.1%)	0.36	66 (31.9%)	0.34	<.01	43 (28.7%)	23 (45.1%)	0.26	0.77
Device Failure	23 (11.9%)	4 (12.9%)	0.08	18 (8.7%)	0.09	.34	12 (8.0%)	7 (13.0%)	0.07	0.23
Pump Exchange	11 (5.7%)	0 (0.0%)	0.00	11 (5.3%)	0.06	.21	7 (4.7%)	4 (7.4%)	0.04	0.13

CRRT: continuous renal replacement therapy; GI: gastrointestinal.

*p-Values are for the percentage of patients with each event, as determined by Pearson's chi-squared test.

the incidence of stroke has been reported to be between 8–30% in clinical trials and is associated with increased mortality [6,8–11]. In the present cohort the incidence of stroke was 12%. There were more strokes in the DT group compared to the BTT group. However, within the BTT group there were no differences between the two pump types. The incidences of pump thrombosis was low and comparable to that of recently reported in clinical trials [9,14]. Bleeding is the most frequent complication leading to re-hospitalization after LVAD implantation. In particular gastro-intestinal bleeding (GIB) is frequent and occurred in 15% to over 30% of the patients in recent clinical trials [9,14]. The overall incidence of GIB in the present study were low, probably because of a shorter duration of support and younger age compared to other reports, but there was a clear increased risk in the DT cohort which further emphasizes the fragility of this patient group.

A planned strategy of DT was only used in 13% in the present study and patients with DT had a clearly lower long-term survival. However, DT was not an independent predictor of mortality in our study, probably partly explained by age being in the model but also the low number of patients with DT resulting in a wide confidence interval. Although destination therapy has proven effective in randomized trials [3,9,14] and is accepted by most guidelines [15,16] and payers, the widespread use of destination therapy has been questioned in several settings [17,18]. The Randomized Evaluation of VAD InterVEntion before Inotropic Therapy (REVIVE-IT) trial aimed to extend LVAD use to patients with an estimated 25–30% mortality at one year, corresponding to roughly INTERMACS 5-7 [19]. REVIVE-IT was stopped due to concerns over high rates of reported pump thrombosis with the study pump (the HMII), whether clinical equipoise was present, and slow enrolment [19]. Public funding for destination therapy is accepted in Denmark and Finland and was accepted in 2014 in Norway. However, in Sweden it was used variably and a health technology assessment concluded that there was insufficient evidence of net clinical benefit and importantly, cost effectiveness to justify public acceptance. Indeed, the clinical practice guidelines from the Swedish Board of Health and Welfare uniquely take cost effectiveness into account, and recommend DT LVAD only in the research setting (i.e. not accepted for routine clinical use) [20]. Instead, a randomized trial of CF LVAD (HM3) vs. optimal medical care was launched in Sweden (SweVAD, clinicaltrials.gov NCT02592499), testing the hypothesis that DT LVAD improves outcomes in INTERMACS 2–6.

Higher age, atrial fibrillation, low GFR, low platelet count, small LVIDd and DT vs. BTT all predicted mortality in a univariate model. Atrial fibrillation may have done so by increasing the risk for stroke. However, only age and LVIDd were independent predictors of mortality in the multivariate models. These factors are well-known but non-modifiable risk factors for mortality, and the combination of higher age and DT having worse outcomes further highlights and may in part explain the continued lack of widespread acceptance and implementation of LVAD [21].

The present study is rather small and more accurate models with better predictive capacity based on larger study populations have been previously published [22,23].

Reduced complications and mortality will likely be required before LVAD use gains widespread acceptance and implementation. This can be accomplished through improved technology and improved patient selection [24]. As recently reported in the MOMENTUM trial of HM3, there were no events of pump thrombosis leading to reoperation or removal of the device and a reduced incidence of stroke, even though disabling stroke were similar, in the group treated with HM3 [11]. Transcutaneous energy transmission and fully implantable systems would be major advances probably leading to fewer complications and wider acceptance. Finally, most HF therapy is cost effective and widely available and an expectation of net benefit is sufficient to justify use. In contrast, advanced HF therapy in the form of heart transplantation and LVAD are scarce and/or expensive and detailed assessment of risk and benefit and the expected net benefit may need to be not just present but also sizable to justify use [25].

Conclusion

In the present study, mortality and morbidity after continuous flow LVAD in the Nordic countries were acceptable and comparable to other studies. Higher age was associated with worse outcomes and as LVAD technology and use continue to evolve, destination therapy and LVAD use in higher age will be important areas for further research.

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References

- [1] Dellgren G, Geiran O, Lemström K, et al. Nordic Thoracic Transplant Study Group. Three decades of heart transplantation in Scandinavia: long-term follow-up. *Eur J Heart Fail.* 2013;15:308–315.
- [2] Lund LH, Khush KK, Cherikh WS, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-fourth Adult Heart Transplantation Report—2017; focus theme: allograft ischemic time. *J Heart Lung Transplant.* 2017;36:1037–1046.
- [3] Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med.* 2001;345:1435–1443.
- [4] Gustafsson F, Rogers JG. Left ventricular assist device therapy in advanced heart failure: patient selection and outcomes. *Eur J Heart Fail.* 2017;19:595–602.
- [5] Kirklin JK, Cantor R, Mohacsi P, et al. First Annual IMACS Report: a global International Society for Heart and Lung Transplantation Registry for Mechanical Circulatory Support. *J Heart Lung Transplant.* 2016;35:407–412.
- [6] Kirklin JK, Pagani FD, Kormos RL, et al. Eighth annual INTERMACS report: special focus on framing the impact of adverse events. *J Heart Lung Transplant.* 2017;36:1080–1086.
- [7] Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med* 2009;361:2241–2251.
- [8] Aaronson KD, Slaughter MS, Miller LW, et al. Use of an intra-pericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. *Circulation.* 2012;125:3191–3200.
- [9] Rogers JG, Pagani FD, Tatooles AJ, et al. Intrapericardial left ventricular assist device for advanced heart failure. *N Engl J Med.* 2017;376:451–460.
- [10] Pagani FD, Miller LW, Russell SD, et al. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. *J Am Coll Cardiol.* 2009;54:312–321.
- [11] Mehra MR, Goldstein DJ, Uriel N, et al. Two-year outcomes with a magnetically levitated cardiac pump in heart failure. *N Engl J Med.* 2018;378:1386–1395.
- [12] de By TMMH, Mohacsi P, Gummert J, et al. The European Registry for Patients with Mechanical Circulatory Support (EUROMACS): first annual report. *Eur J Cardiothorac Surg.* 2015;47:770–776.
- [13] de By TMMH, Mohacsi P, Gahl BZ, et al. The European Registry for Patients with Mechanical Circulatory Support (EUROMACS) of the European Association for Cardio-Thoracic Surgery (EACTS): second report. *Eur J Cardiothorac Surg.* 2017;53:309–316.
- [14] Mehra MR, Naka Y, Uriel N, et al. A fully magnetically levitated circulatory pump for advanced heart failure. *N Engl J Med.* 2017;376:440–450.
- [15] Feldman D, Pamboukian SV, Teuteberg JJ, et al. The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: executive summary. *J Heart Lung Transplant.* 2013;32:157–187.
- [16] Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation.* 2017;136:e137–e161.
- [17] Breathett K, Allen LA, Ambardekar AV. Patient-centered care for left ventricular assist device therapy: current challenges and future directions. *Curr Opin Cardiol.* 2016;31:313–320.

- [18] Kirklin JK. The role of mechanical circulatory support as destination therapy for ambulatory heart failure. *Glob Cardiol Sci Pract.* 2016;2016:e201624.
- [19] Pagani FD, Aaronson KD, Kormos R, et al. The NHLBI REVIVE-IT study: understanding its discontinuation in the context of current left ventricular assist device therapy. *J Heart Lung Transplant.* 2016;35:1277–1283.
- [20] Socialstyrelsen. Nationella riktlinjer för hjärtsjukvård. Stockholm: Socialstyrelsen; 2015 Oct:1–120.
- [21] Lund LH, Trochu J-N, Meyns B, et al. Screening for heart transplantation and left ventricular assist system: results from the ScREEning for advanced Heart Failure treatment (SEE-HF) study. *Eur J Heart Fail.* 2018;20:152–160.
- [22] Loghmanpour NA, Kanwar MK, Druzdzal MJ, et al. A new Bayesian network-based risk stratification model for prediction of short-term and long-term LVAD mortality. *ASAIO J.* 2015; 61:313–323.
- [23] Cowger J, Sundareswaran K, Rogers JG, et al. Predicting survival in patients receiving continuous flow left ventricular assist devices: the HeartMate II risk score. *J Am Coll Cardiol.* 2013; 61:313–321.
- [24] Lund LH, Matthews J, Aaronson K. Patient selection for left ventricular assist devices. *Eur J Heart Fail.* 2010;12: 434–443.
- [25] Lund LH. Optimizing outcomes after heart transplantation. *Eur J Heart Fail.* 2018;20:395–397.