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ORIGINAL ARTICLE

How does age affect outcomes after left ventricular assist device implantation: results from the PCHF-VAD registry

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Abstract

Aims Use of left ventricular assist devices (LVADs) in older patients has increased, and assessing outcomes in older LVAD recipients is important. Therefore, this study aimed to investigate associations between age and outcomes after continuous-flow LVAD (cf-LVAD) implantation.

Methods and results Cf-LVAD patients from the multicentre European PCHF-VAD registry were included and categorized into those <50, 50–64, and ≥65 years old. The primary endpoint was all-cause mortality. Among secondary outcomes were heart failure (HF) hospitalizations, right ventricular (RV) failure, haemocompatibility score, bleeding events, non-fatal thromboembolic events, and device-related infections. Of 562 patients, 184 (32.7%) were <50, 305 (54.3%) were aged 50–64, whereas 73 (13.0%) were ≥65 years old. Median follow-up was 1.1 years. Patients in the oldest age group were significantly more often designated as destination therapy (DT) candidates (61%). A 10 year increase in age was associated with a significantly higher risk of mortality (hazard ratio [HR] 1.34, 95% confidence interval [CI] [1.15–1.57]), intracranial bleeding (HR 1.49, 95% CI [1.10–2.02]), and non-intracranial bleeding (HR 1.30, 95% CI [1.09–1.56]), which was confirmed by a higher mean haemocompatibility score (1.37 vs. 0.77, oldest vs. youngest groups, respectively, $P = 0.033$). Older patients suffered from less device-related infections requiring systemic antibiotics. No age-related differences were observed in HF-related hospitalizations, ventricular arrhythmias, pump thrombosis, non-fatal thromboembolic events, or RV failure.

Conclusions In the PCHF-VAD registry, higher age was associated with increased risk of mortality, and especially with increased risk of major bleeding, which is particularly relevant for the DT population. The risks of HF hospitalizations, pump thrombosis, ventricular arrhythmia, or RV failure were comparable. Strikingly, older patients had less device-related infections.

Keywords Advanced heart failure; Left ventricular assist devices; Destination therapy; Survival; Age

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Introduction

Despite tremendous developments in heart failure (HF) therapy over the past decade, it is estimated that up to 10% of all HF patients have advanced HF.[1] Besides improvements in pharmacological therapy, mechanical options for advanced HF have become more readily available, with significant technological improvements.[2] The left ventricular assist device (LVAD) is an established treatment option for long-term mechanical circulatory support in advanced HF patients. This was to some extent facilitated by the growing mismatch between demand and availability of donor hearts, especially in Western Europe.[3] Additionally, more timely referral, improved patient selection, clinical experience, and technological advancement have improved outcomes after LVAD implantation, and LVADs are now more often used as destination therapy (DT) in older patients and those not deemed eligible or suited for heart transplantation.[4–10] Furthermore, the use of LVADs as bridge to transplant (BTT) has increased in older patients as well.[11] With the increasing use of LVADs and the expected number of patients who could benefit from LVAD support, risk stratification is essential for proper patient selection, especially in older patients. Several risk scores have been developed, but with improvements in LVAD technology and patient management, new insights into the impact of an aging LVAD population on the clinical management and outcomes are essential.[12,13] Moreover, outcomes other than mortality are particularly relevant for older recipients and DT, as they affect quality of life and costs. Therefore, this study aimed to assess the associations between age and cause-specific clinical outcomes after continuous-flow LVAD (cf-LVAD) implantation.

Methods

The methods and characteristics of the observational PCHF-VAD study have been described previously.[14] Briefly, cf-LVAD patients were included in 13 European HF tertiary referral centres, a collaborative of participants and alumni of the Postgraduate Course in Heart Failure (PCHF) of the Heart Failure Association of the European Society of Cardiology and the European Heart Academy, forming the PCHF-VAD registry. All participating centres acquired approval from the local ethics review boards (predominantly, a waiver of informed consent was obtained by the individual centres). The patient data were recorded and managed using REDCap (Research Electronic Data Capture) electronic data capture tools—a secure, web-based application, hosted at the University of Zagreb School of Medicine, serving as the data-coordinating centre.[15]

At the time of analysis, 583 patients who were implanted with a durable ventricular assist device between December 2006 and January 2020 were included in this registry. Patients with a pulsatile device (n = 4) or biventricular assist device (n = 11), as well as patients aged <18 years (n = 6), were excluded from this analysis, leaving 562 patients.

Patients were categorized into those younger than 50 years, patients between 50 and 64 years, and patients aged 65 years and older. The primary endpoint was all-cause mortality. Secondary outcomes were rates of heart transplantation, weaning from LVAD support, HF hospitalization, right ventricular (RV) failure (acute and chronic), LVAD-related infection requiring systemic antibiotics, non-fatal thromboembolic events, intracranial bleeding, non-intracranial bleeding, LVAD exchange, and haemocompatibility score (HCS).

Haemocompatibility score

In order to analyse the aggregate burden of haemocompatibility-related adverse events (HRAEs), the HCS was calculated for all patients. Each HRAE received a points score, based on its clinical relevance (Supporting Information, *Table S1*). The HCS was calculated for each patient by summing up all points associated with all HRAEs experienced by the patient during the follow-up period.[16]

Statistical analysis

Continuous data are expressed as mean value ± standard deviation or median and interquartile range [IQR], depending on the distribution of the data, and were compared by the ANOVA or the Kruskal–Wallis test. Categorical data are expressed as counts and percentages and were compared by the Pearson's χ^2 test. The probability of survival was calculated using the Kaplan–Meier method and was compared between age groups using the log-rank test. The hazard ratios (HRs) for the outcomes were assessed using Cox proportional hazards models and were calculated for a 10 year increase in age. For the survival analyses, the date of LVAD implantation was considered the index date. Follow-up duration was defined as time to last contact, heart transplantation, weaning from LVAD support, or death whichever occurred first.

In order to test whether age was independently associated with the outcomes, multivariable Cox proportional hazards

models were constructed. The associations between age and outcomes were adjusted for gender, INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) profile, baseline serum creatinine level, quartiles of LVAD implantation date, the need for mechanical circulatory support prior to LVAD surgery, and pre-LVAD vasopressor use.

Sensitivity analyses were performed to adjust the association between age and all-cause mortality for several baseline characteristics. The following baseline covariates, with <30% missing values, were tested in a forward stepwise Cox proportional hazards model: sex, cardiac implantable electronic device (CIED) status, heart rate, LVAD type, LVAD intention (BTT, bridge to decision [BTD], and DT), INTERMACS profile, aetiology of HF, known history of chronic kidney disease, atrial fibrillation/flutter, ventricular arrhythmias (VAs), significant VAs pre-LVAD, prior cardiac surgery, concomitant procedure with the LVAD implant, type of life support prior to LVAD, diuretic use, beta-blocker use, ivabradine use, mineralocorticoid receptor antagonist use, vasopressor use, ultrafiltration, type of mechanical ventilation, creatinine values, left ventricular internal dimension at end-diastole, and LVAD implant date quartile. The significant baseline covariates were then used in the Cox regression model for the secondary outcomes. Furthermore, an additional forward stepwise Cox proportional hazards model was constructed using the baseline covariates that differed significantly between the age groups. For both analyses, a significance level of 0.05 and 0.10 for entry and removal thresholds was used, respectively.

The numbers of missing values of the variables mentioned above are shown in Supporting Information, *Table S2*. Variables with <30% missing data were imputed using multiple imputation, whereas those with a larger proportion of missing data were not included in this analysis. If the missing variables showed a monotone pattern of missing values, the monotone method was used. Otherwise, an iterative Markov chain Monte Carlo method was used with a number of 10 iterations. A total of five imputations was performed, and the pooled data were analysed. The imputed data were only used for the multivariable analysis. An additional sensitivity analysis was performed to determine the consistency of the results. In this sensitivity analysis, patients were divided into tertiles according to their age at LVAD implantation. A two-sided *P*-value of 0.05 or lower was considered statistically significant. All statistical analyses were performed using Statistical Package for Social Sciences, Version 25.0 (SPSS Inc., Chicago, IL, USA).

Results

Of the 562 patients, 184 (32.7%) were younger than 50 years, 305 (54.3%) were aged 50 to 64 years, whereas 73 (13.0%) were 65 years or older. The baseline characteristics of the patients stratified by age are shown in *Table 1*. Older patients more often had a HeartMate 3 (HM3) device and more often received their LVAD as DT (61.1% vs. 3.4% as DT, 20.8% vs. 79.9% as BTT, and 18.1% vs. 16.7% as BTD for the oldest vs. youngest patient groups, respectively). Additionally, older patients had more advanced comorbidities and were less often implanted in an acute setting, which was indicated by a higher (less severe) mean INTERMACS profile.

Survival

Of the overall population, the median follow-up time on LVAD support was 1.1 [IQR 0.5–2.2] years. Non-significant differences in follow-up time between the age groups were observed (patients younger than 50 years: 1.2 [0.7–2.3], patients between 50 and 64 years: 1.1 [0.5–2.2], and patients aged 65 years or older: 1.4 [0.3–2.8], $P = 0.464$).

The time to event analysis for all-cause mortality is shown in *Figure 1A*. Patients aged 65 years or older had a significantly higher all-cause mortality than those aged 50–64 and <50 years (46.3% vs. 37.5% and 25.0%, respectively, $P = 0.03$). Pairwise comparison showed no significant survival differences between the 50–64 and ≥65 age groups. One-year mortality was notably higher in the oldest patient group, whereas the survival after the initial 12 months post-LVAD implantation was more comparable (*Figure 1B,C*). Furthermore, patients aged ≥65 years were significantly less often transplanted (14.3% vs. 55.9% and 70.5%, respectively, $P < 0.001$) and weaned from LVAD support (0% vs. 1.0% and 7.7%, respectively, $P = 0.021$) than those aged 50–64 and <50 years. A 10 year increase in age was significantly associated with a higher mortality risk (HR 1.34, 95% confidence interval [CI] [1.15–1.57]) and lower chance of heart transplant or weaning from LVAD (HR 0.90, 95% CI [0.80–1.01] and HR 0.63, 95% CI [0.35–1.16], respectively) after adjustment for sex, INTERMACS profile, baseline serum creatinine level, quartiles of LVAD implantation date, the need for mechanical circulatory support prior to LVAD surgery, and pre-LVAD vasopressor use (*Table 2*). The majority of deaths in all age groups were due to cardiovascular-related causes (Supporting Information, *Table S3*).

Competing event analysis showed that patients younger than 50 years died less often (19.0%) and were more often transplanted (56.4%) or weaned from LVAD support (4.2%) than patients aged 50–64 years (29.9%, 43.3%, and 0.7%, respectively) and patients aged 65 years or older (43.8%, 10.1%, and 0.0%, respectively) (*Figure 2*).

Secondary endpoints

LVAD-related infections that required systemic antibiotics occurred less often in older patients. As shown in the multivar-

Table 1 Baseline characteristics

	Overall population (n = 562)	Patients aged <50 years (n = 184)	Patients aged 50–64 years (n = 305)	Patients aged ≥65 years (n = 73)	P-value
Age, years	53 ± 12	39 ± 9	58 ± 4	68 ± 3	<0.001
Men	457 (81.3)	148 (80.4)	247 (81.0)	62 (84.9)	0.69
Geographical area					
North and West Europe (the Netherlands, Belgium, Germany, and Sweden)	373 (66.4)	138 (75.0)	204 (66.9)	31 (42.5)	<0.001
South and East Europe (Croatia, Poland, Lithuania, Italy, Spain, and Greece)	189 (33.6)	46 (25.0)	101 (33.1)	42 (57.5)	
Quartiles of date of LVAD implant					
1st quartile (6 Dec 2006 to 29 Oct 2012)	143 (25.4)	65 (35.3)	68 (22.3)	10 (13.7)	0.001
2nd quartile (30 Oct 2012 to 4 Aug 2015)	143 (25.4)	46 (25.0)	79 (25.9)	18 (24.7)	
3rd quartile (5 Aug 2015 to 16 Apr 2017)	139 (24.7)	43 (23.4)	77 (25.2)	19 (26.0)	
4th quartile (17 Apr 2017 to 28 Jan 2020)	137(24.4)	30 (16.3)	81 (26.6)	26 (35.6)	
ICD status					
No ICD	294 (53.3)	106 (58.2)	154 (51.5)	34 (47.9)	0.43
Primary prevention	180 (32.6)	53 (29.1)	99 (33.1)	28 (39.4)	
Secondary prevention	78 (14.1)	23 (12.6)	46 (15.4)	9 (12.7)	
CRT status					
No CRT	406 (74.1)	146 (83.4)	215 (71.7)	45 (61.6)	0.004
CRT-P carrier	14 (2.6)	4 (2.3)	7 (2.3)	3 (4.1)	
CRT-D carrier	128 (23.4)	25 (14.3)	78 (26.0)	25 (34.2)	
Heart rate, b.p.m.	83.3 ± 19.0	89.9 ± 21.7	81.3 ± 17.4	77.5 ± 15.1	<0.001
SBP, mmHg	99.5 ± 13.9	96.7 ± 13.5	100.5 ± 14.0	101.9 ± 13.8	0.009
DBP, mmHg	64.2 ± 10.9	64.4 ± 10.9	64.0 ± 11.0	64.2 ± 10.2	0.95
BMI, kg/m^2	25.9 ± 4.6	25.0 ± 5.0	26.5 ± 4.4	25.4 ± 4.6	0.003
LVAD type					
HeartMate II	265 (47.2)	104 (56.5)	135 (44.3)	26 (35.6)	<0.001
HeartWare HVAD	119 (21.2)	34 (18.5)	70 (23.0)	15 (20.5)	
HeartMate 3	157 (27.9)	44 (23.9)	90 (29.5)	23 (31.5)	
Other	21 (3.7)	2 (1.1)	10 (3.3)	9 (12.3)	
LVAD destination					
BTT	356 (66.8)	139 (79.9)	202 (70.4)	15 (20.8)	<0.001
BTD	90 (16.9)	29 (16.7)	48 (16.7)	13 (18.1)	
DT	87 (16.3)	6 (3.4)	37 (12.9)	44 (61.1)	
INTERMACS profile					
1	90 (16.5)	40 (22.7)	46 (15.4)	4 (5.6)	<0.001
2	150 (27.4)	57 (32.4)	82 (27.4)	11 (15.3)	
3	176 (32.2)	52 (29.5)	90 (30.1)	34 (47.2)	
4–7	131 (23.9)	27 (15.3)	81 (27.1)	23 (31.9)	
Aetiology of heart failure					
Dilated cardiomyopathy	247 (44.0)	110 (59.8)	107 (35.1)	30 (41.1)	<0.001
Ischaemic cardiomyopathy	256 (45.6)	44 (23.9)	176 (57.7)	36 (49.3)	
Other	59 (10.5)	30 (16.3)	22 (7.2)	7 (9.6)	
Comorbidities					
Arterial hypertension	128 (22.8)	21 (11.4)	82 (26.9)	25 (34.2)	<0.001
Diabetes mellitus	114 (20.3)	18 (9.8)	75 (24.6)	21 (28.8)	<0.001
Chronic kidney disease	137 (24.4)	19 (10.3)	91 (29.8)	27 (37.0)	<0.001
Coronary artery disease	139 (24.7)	26 (14.1)	91 (29.8)	22 (30.1)	<0.001
Prior MI	211 (37.5)	38 (20.7)	144 (47.2)	29 (39.7)	<0.001
Prior coronary revascularization	170 (30.2)	29 (15.8)	118 (38.7)	23 (31.5)	<0.001
COPD	44 (7.8)	3 (1.6)	30 (9.8)	11 (15.1)	<0.001
Atrial fibrillation/flutter	173 (30.8)	41 (22.3)	103 (33.8)	29 (39.7)	0.006
Ventricular arrhythmias	153 (27.2)	52 (28.3)	81 (26.6)	20 (27.4)	0.92
Cerebrovascular events	41 (7.3)	10 (5.4)	26 (8.5)	5 (6.8)	0.44
Prior cardiac surgery	75 (13.3)	19 (10.3)	45 (14.8)	11 (15.1)	0.34
Concomitant procedure with LVAD implant	99 (17.6)	27 (14.7)	56 (18.4)	16 (21.9)	0.34
MCS prior to LVAD implant					
None	401 (74.0)	120 (68.6)	219 (74.2)	62 (86.1)	0.33
ECMO	40 (7.4)	14 (8.0)	24 (8.1)	2 (2.8)	
Temporary LVAD	5 (0.9)	3 (1.7)	1 (0.3)	1 (1.4)	
Temporary RVAD	1 (0.2)	1 (0.6)	0 (0.0)	0 (0.0)	
Temporary BiVAD	2 (0.4)	1 (0.6)	1 (0.3)	0 (0.0)	
IABP	73 (13.5)	27 (15.4)	40 (13.6)	6 (8.3)	
Other	20 (3.7)	9 (5.1)	10 (3.4)	1 (1.4)	

(*Continues*)

Table 1 (continued)

	Overall population (n = 562)	Patients aged <50 years (n = 184)	Patients aged 50–64 years (n = 305)	Patients aged ≥65 years (n = 73)	P-value
Medications					
Diuretic	454 (91.0)	130 (86.1)	254 (91.4)	70 (100.0)	0.003
Beta-blocker	299 (64.4)	85 (63.0)	171 (65.8)	43 (62.3)	0.79
ACEi/ARB	213 (44.9)	67 (47.5)	120 (45.6)	26 (37.1)	0.34
MRA	315 (72.1)	78 (62.9)	180 (73.2)	57 (85.1)	0.004
Ivabradine	45 (10.9)	13 (10.9)	24 (10.3)	8 (12.7)	0.87
Inotrope	305 (66.6)	99 (72.8)	166 (65.4)	40 (58.8)	0.11
Laboratory values					
Creatinine, μmol/L	127.1 ± 56.0	123.9 ± 68.1	127.4 ± 50.9	132.5 ± 45.5	0.56
Bilirubin, μmol/L	24.3 ± 20.5	27.8 ± 21.1	23.7 ± 21.8	19.4 ± 11.3	0.02
Echocardiographic data					
LVIDd, mm	70.7 ± 12.5	69.1 ± 12.4	71.3 ± 13.1	72.0 ± 10.2	0.14
LVEF, %	19.4 ± 7.5	19.0 ± 8.7	19.3 ± 7.1	20.4 ± 6.0	0.42

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BiVAD, biventricular assist device; BMI, body mass index; BTD, bridge to decision; BTT, bridge to transplant; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CRT-D, CRT-defibrillator; CRT-P, CRT-pacing; DBP, diastolic blood pressure; DT, destination therapy; ECMO, extracorporeal membrane oxygenation; HVAD, HeartWare Ventricular Assist Device; IABP, intra-aortic balloon pump; ICD, implantable cardioverter defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal dimension at end-diastole; MCS, mechanical circulatory support; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; RVAD, right ventricular assist device; SBP, systolic blood pressure.

iable analysis, an increase of 10 years was associated with a significantly lower risk of infection (HR 0.88, 95% CI [0.77–0.99]; *Table 2*).

A 10 year increase in age was associated with a higher risk of intracranial (HR 1.49, 95% CI [1.10–2.02]) and non-intracranial bleedings (HR 1.30, 95% CI [1.09–1.56]; *Table 2*). The risk of incident atrial fibrillation or flutter was higher in older patients (HR 1.38, 95% CI [1.11–1.73]). The risk of non-fatal thromboembolic events was numerically but not significantly higher with increasing age. No significant differences in the rates of HF-related hospitalizations, VAs, pump thrombosis, or RV failure were observed between the age groups (*Table 2*).

Haemocompatibility score

The mean HCS was significantly higher in older LVAD patients (patients younger than 50 years: 0.77 ± 1.46, patients between 50 and 64 years: 1.09 ± 1.91, and patients aged 65 years or older: 1.37 ± 1.93, P = 0.033; *Figure 3*). The differences between the three groups were most prominent in Tier I and Tier IIIB.

Sensitivity analysis

In addition to categorizing patients into the pre-specified age groups, the study population was stratified into tertiles by age. In the first tertile (T1), patients aged 50 years or younger were included, the second tertile (T2) included patients between 50.1 and 60.1 years, whereas the third tertile (T3) consisted of patients aged 60.2 years or older. The baseline characteristics are shown in Supporting Information, *Table S4*, and differences between the age groups were similar to those observed in the main analysis. As reported in the main analysis, older LVAD patients had a higher risk of all-cause mortality, atrial fibrillation/flutter, and non-intracranial bleedings and lower chance of heart transplantation, weaning from LVAD support, and device-related infections (Supporting Information, *Table S5*). The mean HCS was significantly higher in Tier III compared with Tier I and Tier II (Supporting Information, *Figure S1*).

Figure 1 Kaplan–Meier plots of time to all-cause mortality for (A) the complete follow-up period, (B) the first year post-LVAD implantation, and (C) the period starting 1 year post-LVAD implantation. LVAD, left ventricular assist device.

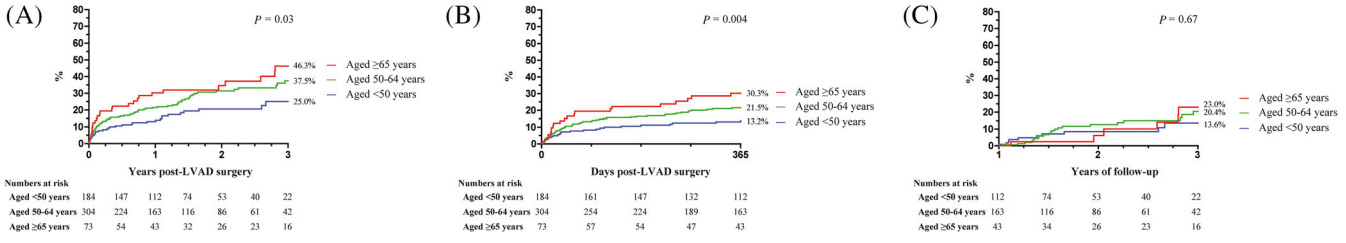

Table 2 Numbers and hazard ratios for the endpoints

	Number of patients with an event (total n = 562)	Patients aged <50 years with an event (n = 184)	Patients aged 50–64 years with an event (n = 305)	Patients aged ≥65 years with an event (n = 73)	P-value	Hazard ratios	
						HR [95% CI] Unadjusted (per 10 years)	HR [95% CI] Adjusted[a] (per 10 years)
All-cause mortality	156 (27.8)	36 (19.6)	91 (29.8)	29 (39.7)	0.002	1.29 [1.11–1.50]	1.39 [1.12–1.72]
HF hospitalization	108 (20.8)	33 (19.9)	63 (22.3)	12 (17.4)	0.63	1.07 [0.91–1.26]	1.06 [0.89–1.25]
RV failure	116 (21.4)	33 (19.1)	73 (24.7)	10 (13.9)	0.089	1.05 [0.89–1.24]	1.07 [0.90–1.27]
Atrial fibrillation/flutter	79 (14.8)	16 (9.4)	47 (16.1)	16 (22.5)	0.022	1.38 [1.11–1.73]	1.35 [1.07–1.71]
Ventricular arrhythmia	155 (28.4)	45 (25.9)	95 (31.8)	15 (20.5)	0.11	1.03 [0.90–1.19]	1.00 [0.87–1.16]
LVAD-related infections requiring AB	188 (34.6)	76 (44.2)	96 (32.2)	16 (21.9)	0.002	0.86 [0.77–0.97]	0.88 [0.77–0.99]
Non-intracranial bleeding	118 (22.1)	29 (17.1)	68 (23.2)	21 (29.6)	0.081	1.30 [1.09–1.53]	1.30 [1.09–1.56]
Intracranial bleeding	46 (8.6)	9 (5.2)	31 (10.5)	6 (8.5)	0.14	1.46 [1.08–1.96]	1.49 [1.10–2.02]
Pump thrombosis	41 (7.6)	11 (6.4)	25 (8.5)	5 (7.0)	0.70	1.07 [0.82–1.40]	0.98 [0.75–1.29]
Non-fatal thromboembolic events	56 (10.4)	13 (7.6)	33 (11.2)	10 (13.9)	0.27	1.19 [0.94–1.51]	1.19 [0.93–1.53]
Weaning from LVAD	9 (1.6)	7 (3.8)	2 (0.7)	0 (0.0)	0.014	0.50 [0.30–0.81]	0.63 [0.35–1.16]
LVAD exchange	22 (4.1)	12 (7.0)	10 (3.4)	0 (0.0)	0.03	0.70 [0.51–0.95]	0.69 [0.49–0.98]
Heart transplantation	218 (38.8)	97 (52.7)	115 (37.7)	6 (8.2)	<0.001	0.83 [0.75–0.93]	0.90 [0.80–1.01]

AB, antibiotics; CI, confidence interval; HF, heart failure; HR, hazard ratio; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; RV, right ventricular.

[a]Adjusted for gender, INTERMACS profile, serum creatinine level, quartiles of date of LVAD implantation, mechanical circulatory support prior to LVAD surgery, and pre-LVAD vasopressor use.

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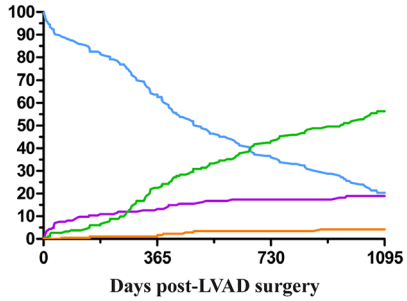
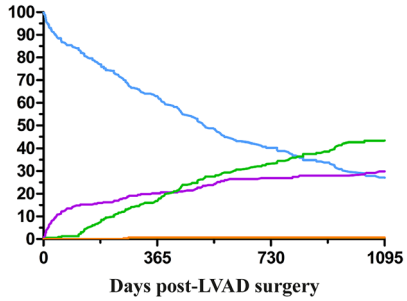
Figure 2 Competing event analysis for (A) patients aged <50 years, (B) patients aged 50–64 years, and (C) patients aged ≥65 years. HTx, heart transplantation; LVAD, left ventricular assist device.

(A)



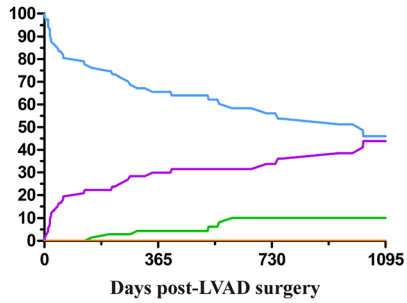
% alive with LVAD support	100	82.0	63.7	46.4	35.9	28.8	20.4
% died	0	10.9	12.6	16.8	17.4	17.4	19.0
% with HTx	0	6.03	22.5	33.3	43.2	49.6	56.4
% weaned from LVAD support	0	1.10	1.10	3.48	3.48	4.21	4.21

(B)



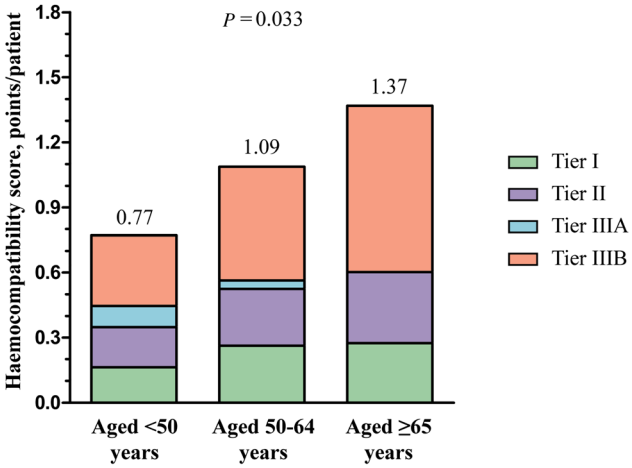
% alive with LVAD support	100	76.9	62.9	48.8	40.3	33.8	27.2
% died	0	15.9	20.2	23.9	27.0	28.0	29.9
% with HTx	0	7.47	16.8	27.7	33.1	38.6	43.3
% weaned from LVAD support	0	0	0.72	0.72	0.72	0.72	0.72

(C)



% alive with LVAD support	100	76.2	65.7	62.2	56.1	53.8	46.0
% died	0	22.3	29.9	31.5	33.8	36.1	43.8
% with HTx	0	1.44	4.41	6.24	10.1	10.1	10.1
% weaned from LVAD support	0	0	0	0	0	0	0

Figure 3 Haemocompatibility score according to age.



Additional assessment of the associations between age and outcomes adjusted for the covariates that were selected in a forward stepwise Cox regression model provided results comparable with the fixed model (Supporting Information, *Tables S6* and *S7*).

Discussion

In this large European multicentre study of cf-LVAD recipients, higher age was associated with an increased risk of all-cause mortality after LVAD implantation. Older LVAD patients more often suffered from intracranial and non-intracranial bleedings, which was also consistent with a higher mean HCS in comparison with younger patients. This is an important consideration for patient selection at higher age, especially in the case of DT. Strikingly, older patients less often suffered from device-related infections requiring systemic antibiotics. We provided numerous additional analyses of associations between age and cause-specific outcomes.

Several studies have previously investigated the effects of age on LVAD survival, but our results provide insights into a contemporary LVAD cohort in the European setting.[17–22] Earlier INTERMACS and IMACS analyses also found higher age to be associated with an increased mortality risk.[18,19,22,23] Similar findings were observed by several other studies[18,21] although some smaller single-centre studies reported no significant survival differences.[17,20] However, these earlier studies mainly included patients from the United States and consisted mostly of older types of LVADs. In our study, the mortality risk was highest in the oldest patient group, but the risk appeared to be upfront with similar risk of mortality

beyond 12 months. Interestingly, older patients were in less severe INTERMACS profile prior to LVAD implantation, yet had a higher mortality. This may be partially explained by other factors such as higher rates of comorbidities and frailty. However, despite the increased mortality risk, the overall survival of older patients on LVAD support was still acceptable, in particular after the first year. Therefore, LVAD implantation could be considered in carefully selected elderly patients.

Interestingly, the number of patients aged ≥65 years implanted with an LVAD increased over recent years. This may partially be explained by the expanded indications for DT in Europe as well as the advent of the HM3 after the successful MOMENTUM 3 trial, which showed similar favourable effects of the HM3 for patients aged ≥65 years.[6] The HM3 has been approved for DT for several years and is increasingly being used for said indication in older patients, which is also reflected in our study as the proportion of implanted HM3 devices was largest in the oldest patient category. The use of BTT LVAD has also increased in older patients in the recent years, suggesting that general acceptance of older patients for both DT and BTT indications is increasing.[10,11]

Bleeding and pump thrombosis are among the most common adverse events post-LVAD implantation. These are especially disabling in the DT setting, with the potential long-term risk of repeated hospitalizations and reduced quality of life. The MOMENTUM 3 trial showed a lower risk of bleeding, stroke, and pump thrombosis for the HM3 as compared with the HeartMate II (HMII), underscoring the importance of studying age-related effects in the present era.[6] In our study, a 10 year increase in age was associated with a higher risk of both intracranial and non-intracranial bleedings (HR 1.49 and HR 1.30, respectively). The risk of non-fatal thromboembolic events was slightly higher, although not significant, in older patients, despite a higher prevalence and higher risk of incident atrial fibrillation in older patients. No differences were found with respect to the occurrence of pump thrombosis. The clinical HCS was developed to analyse the burden of haemocompatibility-related LVAD events.[16] We found that the mean HCS was significantly higher in older patients (1.37 vs. 0.77, P = 0.033). With the detrimental effects of a stroke especially at older age during LVAD support, we believe this is an important finding that warrants further research in methods to assess overall bleeding risk in elderly LVAD patients. One could imagine a cutoff point above which bleeding risk is deemed too high in order to prevent disabling events during LVAD support. Analyses from the INTERMACS and IMACS database reported higher risks of gastrointestinal bleeding for patients aged ≥70 and ≥75 years.[18,22,23] These results suggest more vigilant monitoring for bleeding risk of elderly LVAD recipients. Reports on age-related stroke risk, on the other hand, are conflicting.[18,20,22] Given the time points at which the studies were undertaken, it is likely that, compared with our study, very few patients in the previous studies received an HM3 LVAD. Furthermore, differences in study populations are important as one study only investigated DT patients, whereas another study only found age to be associated with higher stroke risk in the DT, but not the BTT, patients.[20,23]

Besides haemocompatibility-related complications, device-related infections are a major cause of morbidity and mortality, often requiring hospitalization for long courses of intravenous antibiotics.[24] We found a significantly lower risk of LVAD-related infections among older patients (HR 0.88, 95% CI [0.78–0.99]), which underscores earlier work.[17,18,20,25] This finding is rather interesting because the immune system of older people is often impaired compared with younger people. A possible explanation might be that younger patients exhibit a more (pro)active lifestyle that includes more exercise and can easily lead to manipulation or irritation of the driveline causing infection or that younger patients may be less careful in their driveline and general post-LVAD care, a potential pattern also observed after heart transplantation.[26] Furthermore, based on the INTERMACS profiles and proportion of patients on mechanical circulatory support prior to LVAD implant, it seems plausible that younger patients more often had their LVAD implanted in an acute setting and were therefore at higher risk of developing a driveline infection. Lastly, elderly LVAD patients had a lower body mass index (BMI) than the middle age group, which has also been associated with a lower risk of driveline infections.[25,27]

Perspectives

To the best of our knowledge, this is the first study to investigate associations between age and detailed cause-specific clinical outcomes in a large multinational European population of contemporary cf-LVAD patients. LVAD DT is becoming more important and is expected to increase to similar numbers as BTT in Europe, especially with aging populations with otherwise high life expectancies in wealthy countries. Several studies have reported on age-related risks post-LVAD implantation. However, these studies almost exclusively incorporated data on US patients. The differences in HF and LVAD management between the United States and Europe make it difficult to extrapolate earlier findings to the current European setting. Furthermore, most studies were conducted in an earlier era in which the older HMII (axial-flow) and HeartWare Ventricular Assist Device (HVAD) were mostly used. The current study contains a significant number of patients with an HM3, which is the predominant and contemporary ventricular assist device in Europe after the successful MOMENTUM 3 trial, and particularly since the recent withdrawal of HVAD from the market. Our study therefore adds significantly to current literature and provides valuable in-

sights into contemporary European LVAD management in older recipients.

Limitations

Our analysis was limited by several factors mostly inherent to the study design. First of all, due to the non-randomized design, confounding might have biased our results. Even after adjusting for possible confounders, residual confounding cannot be excluded. Furthermore, selection bias and missing data, which we tried to limit by using multiple imputation methods, may have affected our results. Furthermore, the proportion of patients older than 65 years was relatively small, which may have influenced analysis of the secondary outcomes. Lastly, additional data on anticoagulation use, such as time in therapeutic range, were not available.

Conclusions

Although age was associated with increased risk of mortality and bleeding events, the clinical outcomes of older patients after cf-LVAD implantation were acceptable. Reflecting on the poor prognosis of end-stage HF patients and the fact that survival of elderly patients is by definition impaired due to advanced comorbidities and frailty, we suggest that age alone should not be a contra-indication for LVAD DT, which is consistent with European consensus recommendations. However, one should be aware of the increased risk of bleeding with a complicated clinical course post-LVAD implantation when selecting older patients. Future studies of anticoagulation regimens might also aid in better tailoring of these therapies in the elderly population, possibly allowing for less aggressive anticoagulation, particularly in the setting of a very low thrombosis rate in the newest generation HM3 LVAD.

Conflict of interest

N.J. reports personal fees and non-financial support from Servier, personal fees from Teva Pharmaceutical Industries, Krka, Sanofi Genzyme, Boehringer Ingelheim, Bayer, non-financial support from Abbott, outside the submitted work. A.C.P. reports personal fees from Novartis, Bayer, Vifor, Astra-Zeneca, outside the submitted work. I.P. reports grants and personal fees from Boehringer Ingelheim, personal fees from Teva Pharmaceutical Industries, Servier, Krka, Corvia, personal fees and non-financial support from Novartis, Pfizer, Bayer, Sandoz, Abbott, Sanofi Aventis, outside the submitted work. A.J.F. reports personal fees from Alnylam, Bayer, Boehringer Ingelheim, Fresenius, Imedos Systems, Medtronic, MSD, Mundipharma, Pierre Fabre, Pfizer, Roche, Vifor, Zoll, grants and personal fees from AstraZeneca, Novartis, outside the submitted work. L.H.L. reports personal fees from Merck, Bayer, Pharmacosmos, Abbott, Medscape, Myokardia, Sanofi, Lexicon, Radcliffe cardiology, grants and personal fees from Vifor-Fresenius, AstraZeneca, Boehringer Ingelheim, Novartis, grants from Boston Scientific, outside the submitted work. D. M. reports personal fees from Boehringer Ingelheim, Bayer, Pfizer, Novartis, AstraZeneca, Novo Nordisk, Teva, Servier, outside the submitted work. F.R. has not received personal payments by pharmaceutical companies or device manufacturers in the last 3 years (remuneration for the time spent in activities, such as participation as steering committee member of clinical trials and member of the Pfizer Research Award selection committee in Switzerland, were made directly to the University of Zurich). The Department of Cardiology (University Hospital of Zurich/University of Zurich) reports research-, educational- and/or travel grants from Abbott, Amgen, Astra Zeneca, Bayer, Berlin Heart, B. Braun, Biosense Webster, Biosensors Europe AG, Biotronik, BMS, Boehringer Ingelheim, Boston Scientific, Bracco, Cardinal Health Switzerland, Corteria, Daiichi, Diatools AG, Edwards Lifesciences, Guidant Europe NV (BS), Hamilton Health Sciences, Kaneka Corporation, Kantar, Labormedizinisches Zentrum, Medtronic, MSD, Mundipharma Medical Company, Novartis, Novo Nordisk, Orion, Pfizer, Quintiles Switzerland Sarl, Sahajanand IN, Sanofi, Sarstedt AG, Servier, SIS Medical, SSS International Clinical Research, Terumo Deutschland, Trama Solutions, V-Wave, Vascular Medical, Vifor, Wissens Plus, ZOLL. The research and educational grants do not impact on F.R.'s personal remuneration. M.C. reports grants and personal fees from Novartis, grants from Abbott, personal fees from GE Healthcare, Bayer, Boehringer-Ingelheim, AstraZeneca, Teva Pharmaceutical Industries, Sanofi, LivaNova, non-financial support from Corvia, personal fees and non-financial support from Pfizer, outside the submitted work. J.J.B. reports personal fees from Abbott, outside the submitted work. All other authors have no conflict of interest to disclose.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Haemocompatibility score according to age tertile.
Table S1. Classification of haemocompatibility score.
Table S2. Number (percentage) of missing data.

Table S3. Causes of death.
Table S4. Baseline characteristics according to age tertiles.
Table S5. Numbers of patients reaching the endpoints according to age tertiles.
Table S6. Sensitivity analysis: numbers and hazard ratios for the endpoints assessed in a forward stepwise multivariable Cox proportional hazards model.
Table S7. Sensitivity analysis: numbers and hazard ratios for the endpoints assessed in a forward stepwise multivariable Cox proportional hazards model with baseline covariates that differed significantly between the age groups.

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