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ORIGINAL ARTICLE

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Survival and adverse events in patients with atrial fibrillation at left ventricular assist device implantation: an analysis of the European Registry for Patients with Mechanical Circulatory Support

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Key question

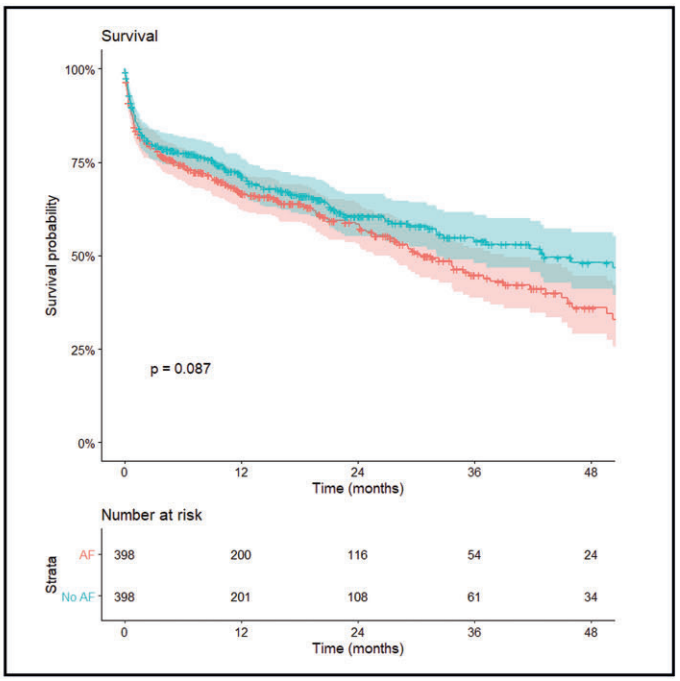
Does preimplant atrial fibrillation influence outcomes during left ventricular assist device support?

Key finding(s)

Patients with atrial fibrillation have a lower survival but it is not individually associated with a lower survival.

Take-home message

AF is not associated with a lower survival, AF patients with AF have worse outcomes during long-term LVAD support, indicating a sicker population.



Abstract

OBJECTIVES: Atrial fibrillation (AF) is a risk factor for mortality and cerebrovascular accidents (CVAs) and is common in patients with heart failure. This study evaluated survival and adverse events in patients with a left ventricular assist device (LVAD) and a history of AF in the European Registry for Patients with Mechanical Circulatory Support.

METHODS: Patients with a continuous-flow LVAD, AF or sinus rhythm (SR) and a follow-up were included. Kaplan–Meier analyses for survival (including a propensity-scored matched analysis), freedom from CVA, pump thrombosis, bleeding and a composite of pump thrombosis/CVA were performed. To correct for covariate imbalance, a Kaplan-Meier (KM) analysis was performed after propensity score (PS) matching the groups. Finally, a Cox regression was performed for predictors of lower survival.

RESULTS: Overall, 1821 patients (83% male) were included, with a median age of 57 years and a median follow-up of 13.1 months (interquartile range: 4.3–27.7). Preoperative Electrocardiogram (ECG) rhythm was AF in 421 (23.1%) and SR in 1400 (76.9%) patients. Patients with pre-LVAD AF had a lower ≤90-day (81.9% vs 87.1%, $P = 0.0047$) and 4-year (35.4% vs 44.2%, $P = 0.0083$) survival compared to SR. KM analysis with PS matching groups revealed a trend ($P = 0.087$) towards decreased survival. Univariable analyses confirmed pre-LVAD AF as a predictor for mortality, but the multivariable analysis did not. No difference in the rate of adverse events was found. An analysis of patients at 24 months revealed a higher rate of CVAs for pre-LVAD AF patients (77% vs 94.3%, $P < 0.0001$).

CONCLUSIONS: Patients with pre-LVAD AF undergoing LVAD implantation had a worse survival. However, after performing a multivariate analysis, and PS matching analysis, AF was no longer significant, indicating a worser preoperative condition in these patients. Concerning thrombo-embolic events, only patients with pre-LVAD AF alive beyond 24 months have a higher risk of CVAs.

Keywords: Heart failure • Left ventricular assist device • Atrial fibrillation • Mortality • Cerebrovascular accidents • Thromboembolic events

ABBREVIATIONS

AF	Atrial fibrillation
CI	Confidence interval
CVAs	Cerebrovascular accidents
EUROMACS	European Registry for Patients with Mechanical Circulatory Support
HF	Heart failure
HR	Hazard ratio
LVAD	Left ventricular assist device
PS	Propensity score
PT	Pump thrombosis
SR	Sinus rhythm
VAD	Ventricular assist device

INTRODUCTION

Left ventricular assist devices (LVADs) have become an accepted treatment modality in patients with end-stage heart failure (HF) [1]. Although LVADs provide a significant improvement in survival [2, 3], functional capacities and quality of life [4], their use is often accompanied by serious adverse events including cerebrovascular accidents (CVAs), pump thrombosis (PT) and major infections [5].

In the general population, atrial fibrillation (AF) is a known risk factor for mortality and morbidity, including CVAs [6]. It is estimated that ∼40% of patients with HF suffer from AF [7]. In patients with an LVAD, the presence of AF or atrial flutter is substantial with a reported prevalence ranging from 21% to 72% [8–10]. Several studies have reported outcomes after LVAD implantation of patients with preoperative AF compared to patients without AF, with conflicting results [8–12]. Multiple studies report a lower survival in patients with preoperative AF after LVAD implantation [9, 11], while others contradict this [8, 10, 12]. The studies are often restricted by the limited number of patients and their single-centre design.

Therefore, the aim of this study was to analyse the survival and adverse events in patients with an LVAD implantation with a history of AF compared with patients with sinus rhythm (SR) in the European Registry for Patients with Mechanical Circulatory Support (EUROMACS).

METHODS

The EUROMACS registry

EUROMACS is a registry of the European Association for Cardio-Thoracic Surgery [13]. It gathers data of patients implanted with a ventricular assist device (VAD) for scientific analyses. All relevant clinical, echocardiographic, haemodynamic and laboratory parameters were collected since January 2011. A protocol for data collection and data entry, including all relevant data for the registry, was provided to all participating centres before data entry was allowed. Details of the registry and data collection are described elsewhere in more detail [13].

Ethics statement

This study was approved by the institutional ethics committee of all respective participating centres, and all included subjects gave informed consent.

Data availability statement

All relevant data are available on request from the authors.

Study design

The current study was approved by the EUROMACS committee of the EACTS. All durable LVAD implantations ($n = 4868$) between 2011 and July 2019 were available for analysis. Patients younger than 18 years and patients with a primary device other than an LVAD were excluded ($n = 1046$). Subsequently, all patients with a device other than a HeartMate II (Abbott, Lake Bluff, IL, USA), HeartMate 3 (Abbott) and HeartWare VAD (Medtronic, Minneapolis, MN, USA) ($n = 582$) and patients without a captured preoperative cardiac rhythm were excluded ($n = 179$). Finally, patients without any follow-up were not included in the analysis ($n = 405$). In total, 2609 patients were included for the analysis (see Fig. 1 for the overview of patient selection).

Definitions

This study explicitly studied preoperative cardiac rhythm and outcomes after LVAD implantations. Cardiac rhythms registered in EUROMACS are SR, paced rhythm, AF and atrial flutter. For this study, preoperative ECG rhythm of AF ($n = 380$) and atrial flutter ($n = 41$) were combined. AF in this study refers to both patients with AF and atrial flutter. No data on the duration of AF and the distinction between paroxysmal or sustained AF are available in EUROMACS.

Endpoints

The primary end point was early (≤90 days) and late (4-year) survival estimates following LVAD implantation for patients with pre-LVAD

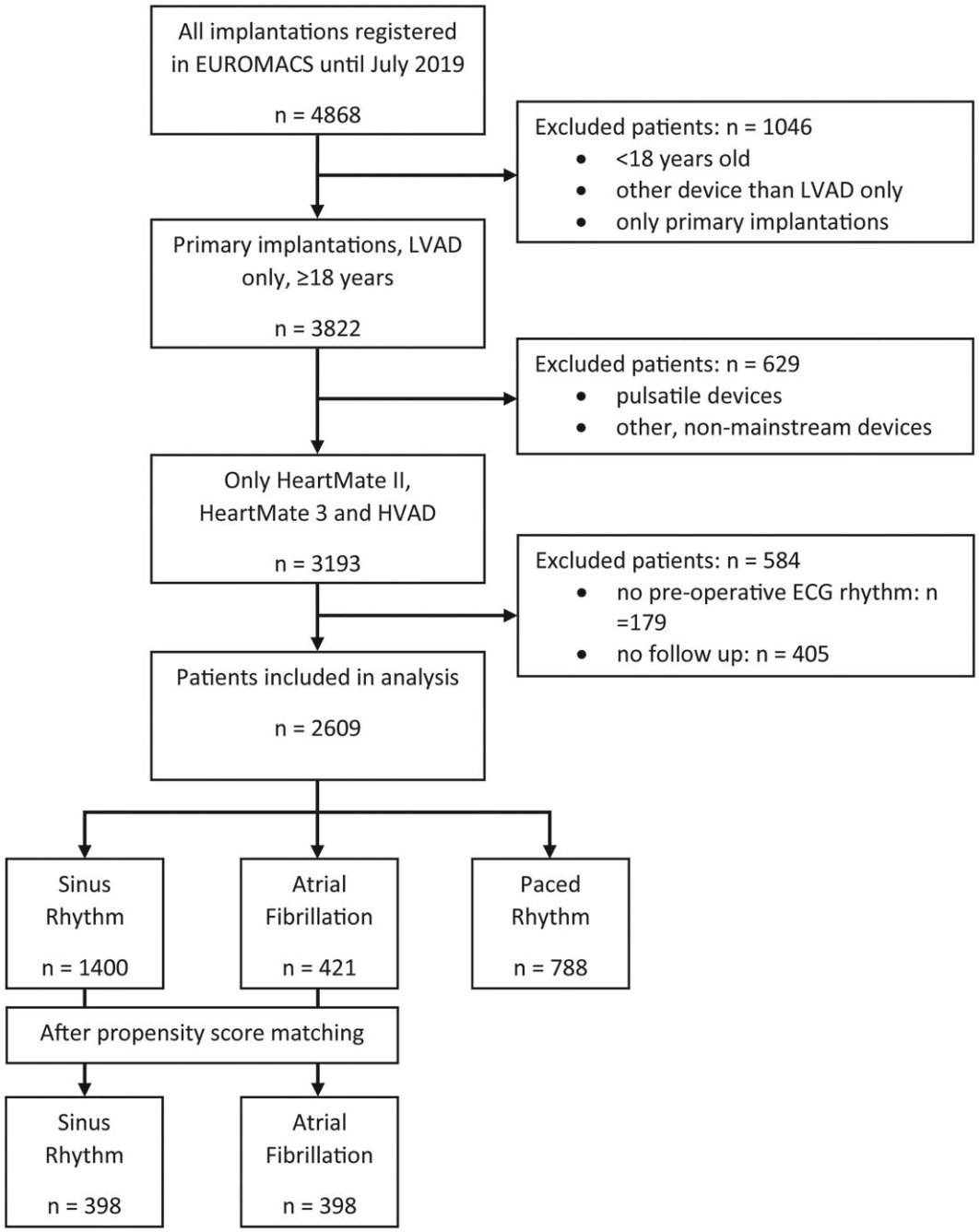


Figure 1: Flowchart of patient selection. EUROMACS: European Registry for Patients with Mechanical Circulatory Support; HVAD: HeartWare ventricular assist device; LVAD: left ventricular assist device.

AF and SR. Secondary end points were suspected or confirmed PT, CVA and bleeding. Finally, the freedom of a composite end point of thromboembolic events (including CVA and PT) was analysed.

Statistical analysis

Continuous parameters are expressed as median and interquartile range or as mean and 95% confidence interval (CI). Student's *t*-test or Mann–Whitney *U*-test according to the distribution of data were applied to test differences in baseline characteristics. The normality of data was assessed by performing the Shapiro–Wilk test. Categorical parameters were expressed as number and percentage and compared by χ^2 test or Fisher's exact test (if any of the expected cell sizes was $\leq$5) for association.

To reduce covariate imbalance a propensity score (PS) matching strategy was employed using the imputed dataset. The initial PS model contained all covariates, which differed significantly between the 2 groups (AF versus no AF). A 1:1 matching without replacement using a calliper set at 0.1 was applied. Covariate balance was assessed using standardized mean difference. A standardized mean difference below 0.1 after matching was considered good balance. If a covariate remained unbalanced after matching, it was added to the PS model to achieve satisfactory balance.

Table 1: Baseline characteristics of patient with preimplantation sinus rhythm and atrial fibrillation

Baseline characteristic	Sinus rhythm (n = 1400)	Atrial fibrillation (n = 421)	P-Value
Demographics			
Age	54 [44–61]	58 [50–64]	<0.001
Male	1148 (82)	371 (88)	0.003
Body surface area (m^2)	1.94 [1.79–2.1]	2 [1.84–2.15]	<0.001
Body mass index (kg/m^2)	22.2 [19.7–25.3]	23 [20.5–25.7]	0.002
Primary diagnosis			0.137
Ischaemic	469 (35)	146 (36)	
Dilated	601 (45)	200 (49)	
Others	254 (19)	61 (15)	
Time since first cardiac diagnosis >2 years ago	848 (66)	305 (78)	<0.001
CHA_2DS_2-VASc score >3	191 (14)	72 (17)	0.077
NYHA class 4	607 (61)	201 (66)	0.143
INTERMACS patient profile			0.555
Profile 1	212 (15)	66 (16)	
Profile 2	416 (30)	139 (33)	
Profile 3	369 (27)	102 (24)	
Profile ≥4	395 (28)	112 (27)	
Comorbidities			
Diabetes	316 (23)	129 (31)	0.001
ICD therapy	799 (63)	246 (64)	0.679
Major myocardial infarction	262 (19)	80 (19)	0.985
Major infections	140 (10)	48 (12)	0.47
COPD	108 (8)	49 (12)	0.013
Symptomatic peripheral vascular disease	71 (6)	35 (10)	0.016
Neurologic event	135 (10)	48 (12)	0.264
Cancer, other than skin cancer	53 (4)	14 (4)	0.625
Smoking history	628 (46)	165 (40)	<0.001
Preoperative status			
Intra-aortic balloon pump	138 (10)	48 (12)	0.343
Extra corporeal membrane oxygenation	167 (12)	53 (13)	0.657
Intubation	219 (16)	63 (15)	0.691
Other VAD	67 (5)	10 (3)	0.033
Other surgical procedures	144 (11)	59 (14)	0.039
Need for ≥3 inotropes	138 (11)	48 (12)	0.665
Preoperative medication			
Amiodarone	395 (32)	154 (39)	0.006
Ace inhibitors	530 (42)	148 (38)	0.2
Beta-blockers	671 (54)	210 (53)	0.932
Phenprocoumon	76 (7)	25 (7)	0.992
Anticoagulant therapy	757 (60)	258 (65)	0.01
Antiplatelet therapy			0.019
Single therapy	354 (28)	104 (26)	
Dual therapy	105 (8)	17 (4)	
Blood chemistry			
MELD score	12.1 [7.8–16.4]	15.2 [10.6–20.5]	<0.001
Creatinine (μmol/l)	107 [85–141]	120 [92–163]	<0.001
ALT (U/l)	31 [19–71]	26 [17–54]	0.197
AST (U/l)	32 [22–68]	33 [23–76]	0.063
LDH (U/l)	308 [235–473]	298 [237–443]	0.487
Total bilirubin (mg/dl)	1.2 [0.8–2]	1.5 [0.9–2.1]	0.969
WBC ($\times 10^9$/l)	8.5 [6.7–11]	8.3 [6.5–11]	0.618
Haemoglobin (g/dl)	11.9 [10.3–13.6]	12.2 [10.7–13.9]	0.615
Platelets ($\times 10^9$/l)	207 [155–265]	199 [155–251]	0.121
INR	1.25 [1.1–1.5]	1.4 [1.2–2]	<0.001
PTT (s)	36 [28–45]	38 [30–46]	0.345
CRP (mg/l)	3 [1–9]	3 [1–8]	0.087
Echocardiography			
TAPSE	14 [12–17]	13 [12–16]	0.027
Ejection fraction grade <20%	743 (64)	238 (64)	0.974
Mitral regurgitation			0.574
Trivial–mild	498 (39)	171 (43)	
Moderate–severe	368 (50)	188 (47)	
Tricuspid regurgitation			0.087
Trivial–mild	652 (51)	178 (45)	
Moderate–severe	461 (36)	172(43)	
Aortic regurgitation			0.721
Trivial–mild	402 (32)	124 (31)	
Moderate–severe	51 (4)	14 (4)	

Continued

Table 1: Continued

Baseline characteristic	Sinus rhythm (n = 1400)	Atrial fibrillation (n = 421)	P-Value
RV dysfunction			0.834
Trivial–mild	244 (25)	78 (26)	
Moderate–severe	530 (54)	154 (52)	
Haemodynamic parameters			
Heart rate (bpm)	84 [72–97]	88 [75–103]	<0.001
Systolic blood pressure (mmHg)	100 [90–110]	100 [90–110]	0.494
Diastolic blood pressure (mmHg)	65 [30–71]	63 [57–70]	0.187
Mean blood pressure (mmHg)	81 [74–90]	81 [74–90]	0.925
Pulmonary artery systolic pressure (mmHg)	53 [40–65]	50 [40–60]	0.155
Pulmonary artery diastolic pressure (mmHg)	27 [33–20]	26 [20–32]	0.207
Mean pulmonary artery pressure (mmHg)	19 [2–37]	20 [5–35]	0.829
Right atrial pressure (mmHg)	11 [7–15]	12 [8–17]	0.187
Pulmonary artery wedge pressure (mmHg)	25 [19–31]	25 [18–30]	0.809

Continuous variables are depicted as median [interquartile range] and categorical variables as count (percentage).

ALT: alanine aminotransferase; AST: aspartate aminotransferase; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; ICD: implantable cardioverter-defibrillator; INR: international normalized ratio; INTERMACS: interagency registry for mechanically assisted circulatory support; LDH: lactate dehydrogenase; MELD: model for end-stage liver disease; NYHA: New York health association; PTT: partial thromboplastin time; RV: right ventricle; TAPSE: tricuspid annular plane systolic excursion; VAD: ventricular assist device; WBC: white blood cell.

Table 2: Perioperative and postoperative characteristics of patients with pre-implant sinus rhythm or atrial fibrillation

Baseline characteristic	Sinus rhythm (n = 1400)	Atrial fibrillation (n = 421)	P-Value
Device strategy			0.505
Possible bridge-to-transplantation	1056 (76)	297 (71)	
Destination therapy	229 (16)	78 (19)	
Bridge-to-recovery	24 (2)	9 (2)	
Rescue therapy	84 (6)	31 (7)	
Other	5 (0.3)	2 (0.5)	
Cardiopulmonary bypass time (min)	85 [63–113]	81 [62–113]	0.299
Time in operating room for implant (min)	240 [180–316]	231 [175–302]	0.041
Concomitant cardiac procedures			
PFO/ASD closure	49 (3.5)	22 (5.2)	0.115
CABG	18 (1.3)	3 (0.7)	0.441
Tricuspid valve repair	119 (8.5)	45 (10.7)	0.174
Aortic valve repair	13 (0.9)	3 (0.7)	0.777
Aortic valve replacement	49 (3.5)	15 (3.4)	1.000
Mitral valve repair	22 (1.6)	5 (1.2)	0.654
Mitral valve replacement	3 (0.2)	1 (0.2)	1.000
Concomitant temporary RVAD implant	76 (5.4)	23 (5.5)	0.978
Reoperation for cardiac tamponade/bleeding	212 (15.1)	70 (16.6)	0.545
Dialysis after implant	67 (4.8)	19 (4.5)	0.817
ICU stay (days)	11 [5–24]	13 [6–26]	0.139
Hospital stay (days)	17 [8–27]	14 [2–26]	0.025

Continuous variables are depicted as median [interquartile range] and categorical variables as count (percentage).

ASD: atrial septal defect; CABG: coronary artery bypass grafting; ICU: intensive care unit; PFO: patent foramen ovale; RVAD: right ventricular assist device.

Kaplan–Meier curves stratified by cardiac rhythm were constructed for the evaluation of survival in the first 4 years after LVAD implantation. Differences were compared by log-rank test. A multivariable Cox proportional hazards analysis was performed for the identification of parameters associated with lower survival. Missing data were handled by performing multiple imputations, which was only performed for the baseline variables used in the univariable and multivariable analyses. If variables had too much missing data (>50%), they were excluded from the analysis (see Supplementary Material, Table S1 for percentages missing for each baseline variables). However, the majority of the used variables had <10% missing values. A total of 5 rounds of imputations were performed and the data were pooled according to Rubin's rules. Variables were included in the multivariable models if P-value was ≤0.20 in the univariable analysis and deemed to be relevant to the outcome. All multivariable models were constructed using the enter method, including all variables at once. The Cox proportional hazard assumptions were graphically assessed and were not violated. Two-tailed $P < 0.05$ was considered statistically significant.

Analyses were performed using SPSS statistical software package, version 26.0 for Mac (SPSS Inc., IBM company, Chicago, IL, USA) or R-studio [Core Team (2017), R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/] with the package 'survival' and 'match'.

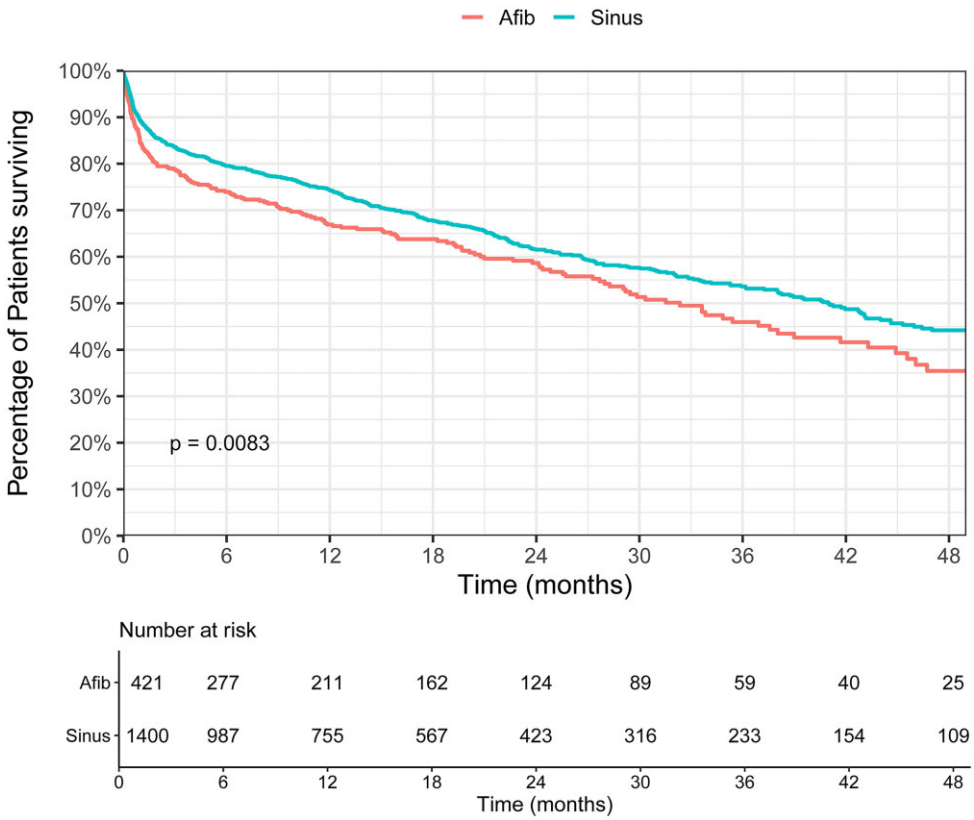


Figure 2: Survival according to pre-implantation rhythm: atrial fibrillation versus sinus rhythm. Afib: atrial fibrillation.

RESULTS

Patient population

In total, 2609 patients met the requirements for inclusion in the current study. The mean age was 54 ± 12 years with 85% being male. The most frequent aetiology of HF was dilated cardiomyopathy (46%). The most prevalent LVAD strategy was bridge-to-transplantation/bridge-to-candidacy (74%), with HeartWare LVAD as the most frequently implanted device in 1378 (52.8%) patients, followed by 780 (29.9%) HeartMate II patients and 451 (17.3%) HeartMate 3 patients.

Baseline characteristics

Overall, 3 groups of cardiac rhythm were identified within the registry: SR ($n = 1400$), paced rhythm ($n = 788$) and AF ($n = 421$). A baseline comparison between the SR, paced rhythm and AF group was performed. The paced rhythm population was highly heterogeneous, which was evident in the baseline characteristics comparison (Supplementary Material, Table S2). Moreover, because information about the indication for pacing or the underlying rhythm was not stated in EUROMACS, those patients were omitted from any further analysis. When comparing patients with SR to patients with AF before LVAD implantation, patients with a history of AF were older (58 vs 54 years, $P < 0.001$), had a higher body mass index (23 vs 22.2 kg/m^2, $P = 0.002$), were more likely to have a longer duration (>2 years) of cardiac disease (65.1% vs 50.9%, $P < 0.001$) and had worse baseline renal function (creatinine 107 vs 120 µmol/l, $P < 0.001$) (Table 1). In most other aspects, the patient groups were comparable (Table 1).

Perioperative and postoperative outcomes

Overall, perioperative results between the groups were comparable, with similar rates of concomitant cardiac procedures, implantation of temporary right VAD and requirement for dialysis after implantation. Only median time in the operating room (240 min for SR vs 231 min for AF, $P = 0.041$) and hospital stay in days (17 for SR vs 14 for AF, $P = 0.025$) were significantly different (Table 2).

Early and late survival

The median follow-up time after LVAD implantation was 13.1 months (interquartile range: 4.3–27.7 months). Early survival (≤90 days) was significantly lower in patients with AF (81.9% vs 87.1%; $P = 0.0047$) as well as the survival at 4 years (35.4% vs 44.2%; $P = 0.0083$) (Fig. 2). Causes of death were predominantly multi-organ failure (18.1%), CVAs (14.4%), sepsis (11.8%) and infection (9.5%) (Supplementary Material, Table S3). An exploratory univariable Cox regression analysis (Supplementary Material, Table S4) for factors associated with mortality yielded over 25 potential covariates with a P-value of ≤0.20 (Table 3) including INTERMACS patient profiles 1 and 2, ischaemic heart disease and the treatment with an extracorporeal membrane oxygenator prior to LVAD implantation. Moreover, pre-LVAD AF was significantly associated with mortality with a hazard ratio (HR) of 1.25 (95% CI: 1.06–1.47, P-value = 0.008). In the multivariable analysis, however, pre-LVAD AF was not significantly associated with mortality with a HR of 1.19 (95% CI: 0.95–1.32, $P = 0.189$) (Table 3). Only the following variables remained significantly ($P < 0.05$) associated with mortality: an increase in age per year [HR: 1.02

Table 3: Univariable and multivariable cox regression analyses of predictors of inferior survival

Baseline characteristics	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	*P*-Value	Hazard ratio (95% CI)	*P*-Value
Age	1.023 (1.017–1.029)	<0.001	1.02 (1.01–1.03)	<0.001
AF at baseline	1.25 (1.06–1.47)	0.008	1.10 (0.91–1.32)	0.331
Body mass index (kg/m^2)	1.01 (1.00–1.03)	0.105	1.00 (0.98–1.02)	0.862
Primary diagnosis				
Ischaemic	1.41 (1.21–1.63)	<0.001	1.23 (1.04–1.45)	0.017
Non-ischaemic	Ref		Ref	
INTERMACS				
Profile 1	1.73 (1.40–2.15)	<0.001	1.69 (1.21–2.37)	0.002
Profile 2	1.21 (0.99–1.46)	0.053	1.19 (0.95–1.49)	0.129
Profile 3	0.93 (0.76–1.15)	0.512	0.99 (0.79–1.25)	0.941
Profile ≥4	Ref		Ref	
Comorbidities				
Diabetes mellitus	1.30 (1.11–1.53)	0.001	0.95 (0.74–1.22)	0.690
COPD	1.42 (1.14–1.78)	0.002	1.32 (1.03–1.69)	0.029
Major myocardial infarction	1.25 (1.05–1.50)	0.013	0.93 (0.74–1.17)	0.542
Symptomatic peripheral vascular disease	1.50 (1.10–2.05)	0.012	1.03 (0.73–1.46)	0.865
Smoking history	1.15 (0.95–1.40)	0.154	1.04 (0.85–1.27)	0.712
Preoperative condition				
Intubation	1.62 (1.35–1.94)	<0.001	1.33 (1.02–1.74)	0.036
Intra-aortic balloon pump	1.19 (0.95–1.50)	0.122	0.96 (0.74–1.24)	0.743
Other surgical procedures	1.59 (1.29–1.96)	<0.001	1.22 (0.95–1.56)	0.123
Extra corporeal membrane oxygenation	1.79 (1.47–2.20)	<0.001	1.39 (1.02–1.90)	0.039
Antiplatelet therapy				
None	Ref		Ref	
Single therapy	1.15 (0.97–1.37)	0.086	0.98 (0.80–1.20)	0.844
Dual therapy	0.89 (0.67–1.19)	0.436	0.70 (0.50–0.99)	0.042
Blood chemistry				
Creatinine (μmol/l)	1.003 (1.002–1.004)	<0.001	1.002 (1.000–1.004)	0.063
LDH (U/l)	1.000 (1.000–1.001)	0.023	1.000 (1.000–1.000)	0.904
Total bilirubin (mg/dl)	1.030 (1.010–1.049)	0.003	1.021 (1.000–1.044)	0.052
WBC ($\times 10^9$/l)	1.013 (0.997–1.029)	0.104	0.985 (0.964–1.006)	0.167
INR	1.08 (0.99–1.17)	0.097	1.04 (0.857–1.26)	0.699
PTT (s)	1.006 (1.002–1.009)	<0.001	1.001 (0.996–1.005)	0.803
Haemodynamic parameters				
Systolic blood pressure (mmHg)	1.08 (0.99–1.17)	0.097	1.004 (0.993–1.015)	0.442
Heart rate (bpm)	0.997 (0.99–1.00)	0.162	1.000 (0.995–1.004)	0.996

AF: atrial fibrillation; CI: confidence interval; COPD: chronic obstructive pulmonary disease; INR: international normalized ratio; INTERMACS: interagency registry for mechanically assisted circulatory support; LDH: lactate dehydrogenase; PTT: partial thromboplastin time; Ref: reference; WBC: white blood cell.

(95% CI: 1.01–1.03)], primary diagnosis of ischaemic cardiomyopathy [HR: 1.23 (95% CI: 1.04–1.45)], INTERMACS patient profile 1 [HR: 1.59 (95% CI: 1.19–2.11)], a history of COPD [HR: 1.32 (95% CI: 1.03–1.69, $P = 0.029$)], extracorporeal membrane oxygenation support pre-implant [HR 1.39 (95% CI: 1.02–1.90, $P = 0.039$)] and intubation before implant [HR 1.33 (95% CI: 1.02–1.75, $P = 0.036$)].

Propensity score matching

For the PS matching, patients were matched in a 1:1 fashion for over 40 variables This yielded 398 patients in each group. The standardized mean difference before and after matching for all variables is shown in Fig. 3 and Supplementary Material, Table S5. After matching, a KM analysis did not show a statistically significant difference in mortality between patients with pre-LVAD AF and SR ($P = 0.087$) (Fig. 4).

Adverse events

Comparing freedom from CVA between the groups with pre-LVAD AF and SR revealed that there was a trend, although not statistically significant, for lower rate of CVA-free survival in the AF group after 4 years (65.0% for AF vs 80.2% for SR, $P = 0.099$) (Fig. 5A). This trend towards a higher rate of CVA in the AF group was apparent from 24 months and onwards. To further review this trend, a conditional analysis for all patients still at risk at 24 months was performed. This revealed a statistically significant difference in freedom from CVA (77%) in the AF group, compared to the SR group (94.3%; $P < 0.001$; Fig. 5B). A Cox proportional hazards model confirmed this finding with a HR of 0.99 (95% CI: 0.70–1.41) for the first 2 years and a HR of 4.01 (2.05–7.87) for the follow-up from 2 years and onwards. An exploratory assessment of the baseline of patients still at risk after 24 months showed similar differences between the AF and SR groups as the complete baseline (Supplementary Material, Table S6). Finally, groups were divided into patients with a low (≤3) or high (>3) CHA_2DS_2-VASc score based on the baseline data. Patients with pre-LVAD AF and a high CHA_2DS_2-VASc score had a significantly higher rate of CVA (44% vs 69%, $P = 0.001$) (Supplementary Material, Fig. S1).

The rate of other coagulation related events was also compared between the pre-LVAD AF and SR groups. First, the freedom from PT was not significantly different between pre-LVAD AF (79.7%) and SR (76.1%) patients at 48 months ($P = 0.28$) (Supplementary Material, Fig. S2). Freedom from bleeding showed a trend towards more events in the AF group (69.9%)

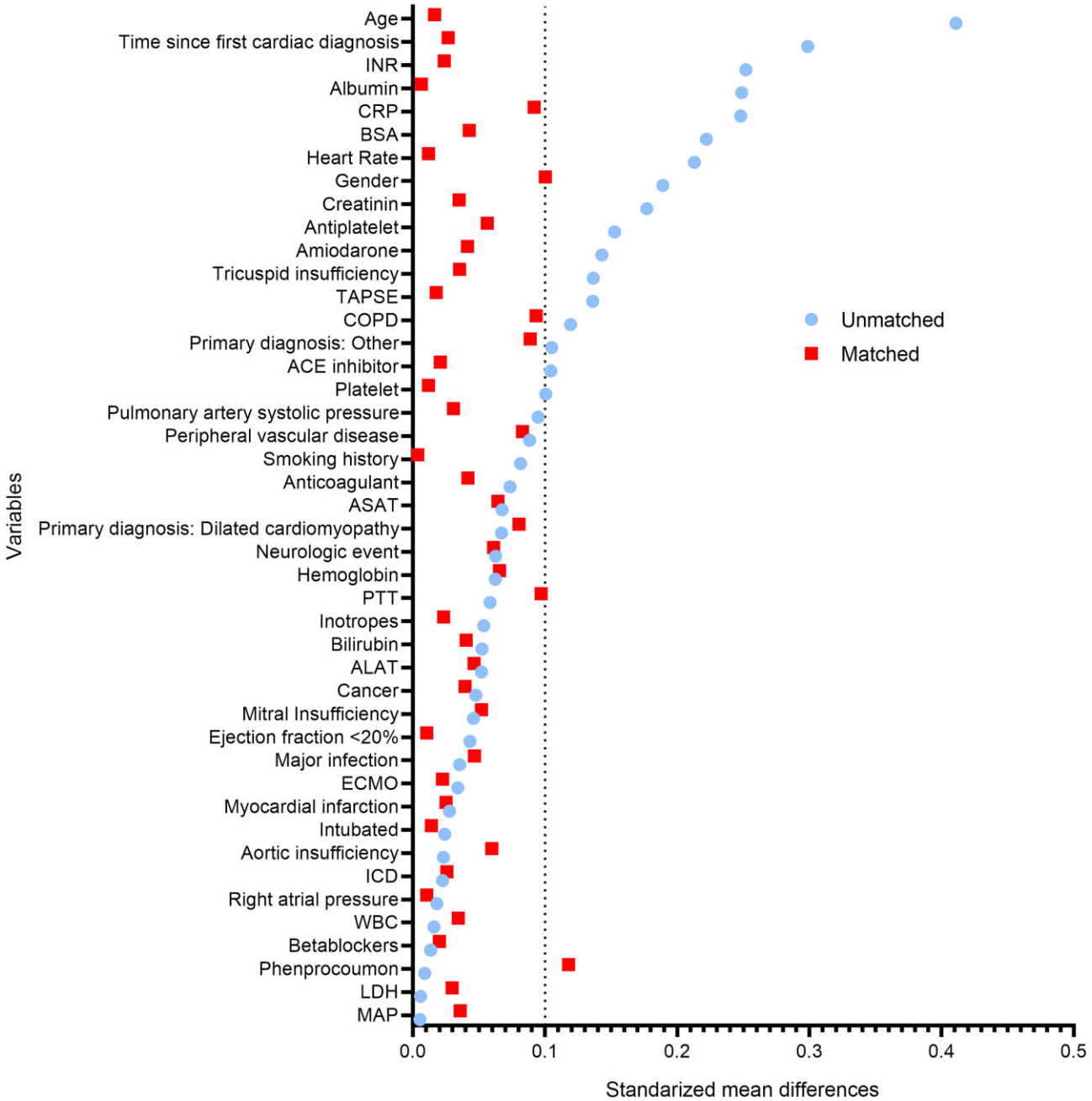


Figure 3: Standardized mean difference between patients with pre-left ventricular assist device atrial fibrillation and sinus rhythm, before and after propensity score matching. BSA: body surface area; COPD: chronic obstructive pulmonary disease; CRP; C-reactive protein; ECMO: extracorporeal membrane oxygenation; ICD: implantable cardioverter-defibrillator; INR: international normalized ratio; PTT: partial thromboplastin time; TAPSE; tricuspid annular plane systolic excursion; WBC: white blood cell count.

compared to the SR group (79.4%) ($P = 0.077$) (Supplementary Material, Fig. S3). Finally, the freedom from the composite end point of the thromboembolic events CVA and PT was performed and did not reveal a significant difference between the groups (55.7% for pre-LVAD AF vs 61.0% for SR, $P = 0.71$) (Supplementary Material, Fig. S4).

DISCUSSION

In this study, we reviewed if preoperative AF impacts survival and adverse events during LVAD therapy, as it is a well-known risk factor for cardiovascular events in the general population. Although the survival was significantly lower for patients with AF compared to SR, preoperative AF was not independently significantly associated with a lower survival in the multivariable model of this study. A PS matching analysis confirmed the overall results, indicating that AF itself is not primarily associated with worse outcomes. Also, when comparing freedom from adverse events between the AF and SR groups, no overall significant differences for freedom from CVA, PT, bleeding and the composite end point of thromboembolic events were observed. However, a conditional analysis for patients at risk at long term (>24 months) did reveal a significantly higher rate of CVA for patients with AF.

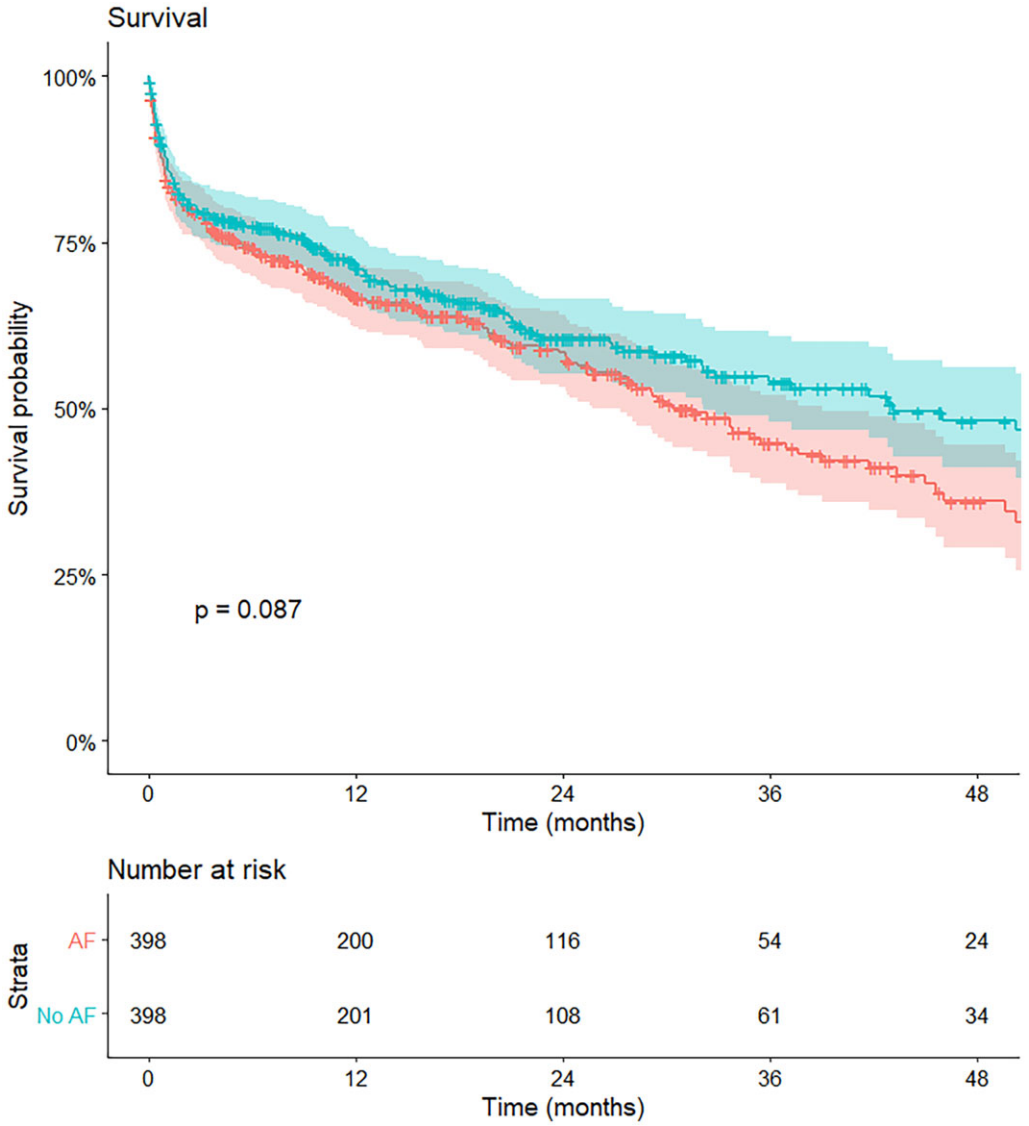


Figure 4: Survival according to pre-implantation rhythm atrial fibrillation versus sinus rhythm with propensity scoring matched groups. AF: atrial fibrillation.

Since the results of the previous studies were conflicting, the current study, with data from the large European multicentre, 'real-world' registry data, set out to elucidate the consequence of preoperative AF for outcomes during LVAD support. Deshmukh *et al.* [9] analysed a cohort of 331 patients, with 53.8% suffering from any form of atrial arrhythmias, and found atrial tachycardia to be a significant predictor of lower survival in a multivariate model. However, several baseline characteristics, including pre-operative circulatory support and INTERMACS patient profile, which are well-established risk factors for worse outcome, were not included in the multivariable analysis. Contrarily, another study of 389 patients (31% with AF) found no significant association between AF and decreased survival but did find 1 for thromboembolic events, which was upheld in the multivariable analysis. However, the baseline comparison and the variables used in the regression models were quite restricted [11]. A recent study of Pedde *et al.* included 769 patients [with a noticeably high percentage (72.6%) of patients with AF] and found similar results to our study. Preoperative AF was a predictor of mortality in the univariable but not in the multivariable analysis [8]. The largest study to date is from the North American INTERMACS registry, which included 3909 patients (27.3% with AF). The outcomes of the study were relatively comparable to our study, with AF being a univariable predictor for mortality, but not a significant predictor for worse survival in the multivariable model. AF was also not associated with an increased risk of the composite of thrombo-embolic events [10]. Therefore, AF is more likely to be a clinical marker of sicker patients with probably a longer duration of heart disease and more comorbidities, as is seen in the differences in baseline characteristics between the groups.

Interestingly, when the outcomes of the AF and SR groups were inspected more closely, there was a clear trend visible for the freedom of CVAs from 24 months and onwards. The conditional analysis from 24 months and onwards did demonstrate a highly statistically significant difference for the freedom from CVAs between the SR and AF groups. An exploratory review of the baseline of patients still at risk at 24 months did not reveal any noticeable difference compared to the complete group of AF and SR patients. A possible cause of the increase in the number of CVAs after 24 months in the AF group as compared to the SR group could be a higher risk of thrombo-embolism from the left atrial auricle, although the current study does not provide direct evidence for this.

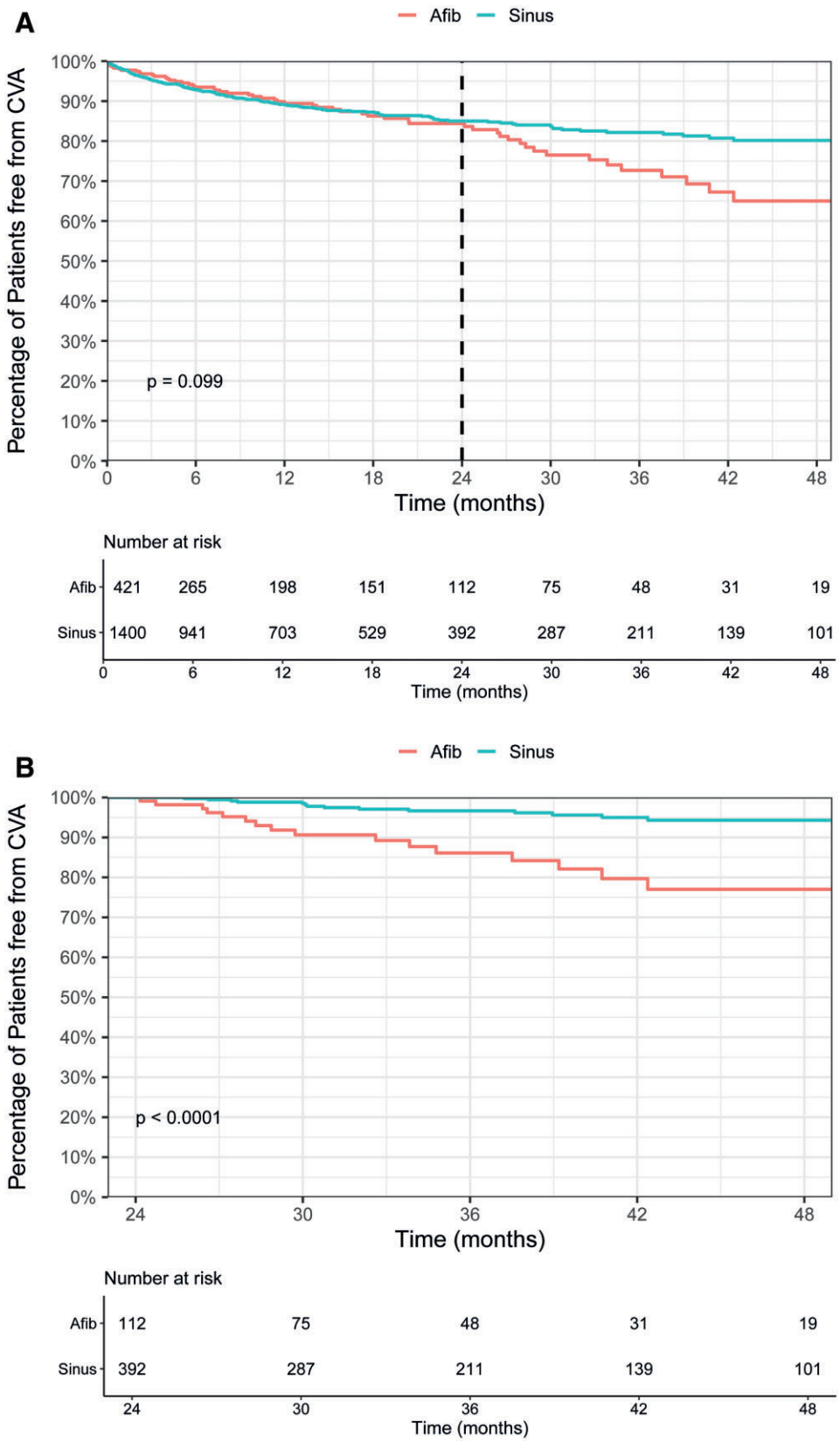


Figure 5: Freedom from cerebrovascular accident according to pre-implantation atrial fibrillation versus sinus rhythm. (**A**) 0–48 months freedom from cerebrovascular accident. (**B**) Conditional analysis after 24 months for freedom from cerebrovascular accident according to pre-implantation atrial fibrillation and sinus rhythm. Afib: atrial fibrillation; CVA: cerebrovascular accident.

Finally, all patients on vitamin K antagonists will inevitably have multiple periods of sub-therapeutical international normalized ratio (reported to be higher than 50% of the time [14]), which might result in an increased risk of thrombo-embolic events.

In the population with AF, the CHA_2DS_2-VASc score, primarily developed for non-VAD patients, is a tool often used to assess the risk of stroke and thromboembolic complications [15]. In concordance with another study, the CHA_2DS_2-VASc provided a significant discriminatory tool and showed that AF patients with a score of >3 had a significantly higher rate of CVA [16]. This score, however, is based on preoperative baseline characteristics and all patients have at least a score of 1, due to the fact that one of the criteria is congestive HF [15]. Moreover, due to the lack of data, preoperative hypertension, was not scored.

It is important to note that this study investigated the outcomes according to pre-implantation cardiac rhythm. Although there was a substantial group of patients with preoperative AF, it is unclear whether these patients had pre-existent or new-onset AF, and if they had paroxysmal or persistent AF. In addition, cardiac rhythm of patients during LVAD support is only scarcely captured and not readily available to analyse from the EUROMACS registry. Moreover, the specific details of the use of anticoagulation and antiplatelet therapy while being supported by an LVAD are also merely scarcely available within the registry's follow-up data. These could be major confounders that the current study could not address. A prospective study that accurately tracks these variables, including other known risk factors (e.g. blood pressure [17]), during LVAD support, would be valuable. This will allow to precisely analyse the possible contribution of cardiac rhythm to adverse events of patients supported by an LVAD.

Limitations

Some limitations should be taken into consideration. First, this study is based on the data of a large international multicentre database. Although EUROMACS regularly monitors its data completion and validity, the inclusion of some erroneous data cannot be ruled out completely. Furthermore, to correct the Cox regression models for missing data, missing data were imputed, although the percentage of data missing of the variables used was limited (max <50%) (Supplementary Material, Table S1). Finally, a substantial fraction of the patients had no data on preoperative cardiac rhythm ($n = 179$) or had the designation paced ($n = 788$). For both groups, it is unclear what the preoperative rhythm was, since pacing can be applied for a plethora of rhythm abnormalities, and the details of this are currently not captured in EUROMACS.

CONCLUSION

In this large European, multicentre registry study, patients with preoperative AF had a significantly lower survival compared with patients with SR. However, AF was not independently associated with lower survival as shown by the Cox regression and PS matching. Therefore, AF is probably more a marker of sicker patients with a worse pre-implant condition. Furthermore, freedom from thromboembolic events and bleeding did not differ significantly between the AF and SR groups, except for the risk of CVA at long-term follow-up. These findings are in concordance with recent studies, but the influence of cardiac rhythm during LVAD support to thromboembolic events and survival remains to be elucidated.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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Author contributions

Christiaan F.J. Antonides: Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing—original draft; Writing—review & editing. Yunus C. Yalcin**:** Data curation; Formal analysis; Methodology; Writing—original draft; Writing—review & editing. **Kevin M. Veen:** Formal analysis; Methodology. **Rahatullah Muslem:** Methodology; Writing—review & editing. **Theo M.M.H. De By:** Data curation; Investigation; Writing—review & editing. **Ad J.J.C. Bogers:** Methodology; Resources; Writing—review & editing. **Finn Gustafsson:** Conceptualization; Formal analysis; Methodology; Writing—original draft; Writing—review & editing. **Kadir Caliskan:** Conceptualization; Data curation; Methodology; Supervision; Writing—original draft; Writing—review & editing.

Reviewer information

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