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

Christiaan F.J. Antonides a, Yunus C. Yalcin a,b, Kevin M. Veen a, Rahatullah Muslem a, Theo M.M.H. De By a,c, Ad J.J.C. Bogers a, Finn Gustafsson d,e and Kadir Caliskan b,*

a Department of Cardio-Thoracic Surgery, Erasmus University Medical Center, Rotterdam, Netherlands
b Department of Cardiology, Erasmus University Medical Center, Rotterdam, Netherlands
c European Association for Cardio-Thoracic Surgery, EUROMACS, Windsor, UK
d Department of Cardiology, Rigshospitalet, Copenhagen, Denmark
e Department of Clinical Medicine, University of Copenhagen, Denmark

* Corresponding author. Department of Cardiology, Erasmus University Medical Center, Room Rg-431, Dr. Molewaterplein 40, 3015 GD Rotterdam, Netherlands. Tel: +31-681268158; e-mail: k.caliskan@erasmusmc.nl (K. Caliskan).

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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.

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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 worse preoperative condition in these patients. Concerning thromboembolic 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

| Acronym | Description |
|---------|-------------|
| 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, pump thrombosis (PT) and major infections [5].

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, pump thrombosis (PT) and major infections [5]. 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 AF undergoing LVAD implantation.
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 χ² test or Fisher’s exact test (if any of the expected cell sizes was <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.
| 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 (m²)  | 1.94 [1.79–2.1]        | 2.04 [1.84–2.15]              | <0.001  |
| Body mass index (kg/m²) | 22.2 [19.7–25.3]       | 23.5 [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 | 648 (66) | 305 (78) | <0.001 |
| CHA2DS2-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]          | 299 [237–443]                 | 0.487   |
| Total bilirubin (mg/dl) | 1.2 [0.8–2]            | 1.5 [0.9–2.1]                 | 0.969   |
| WBC (>10³/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 (>10⁹/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 regurgation   |                        |                               | 0.087   |
| Trivial–mild            | 652 (51)               | 178 (45)                      |         |
| Moderate–severe         | 461 (36)               | 172 (43)                      |         |
| Aortic regurgation      |                        |                               | 0.721   |
| Trivial–mild            | 402 (32)               | 124 (31)                      |         |
| Moderate–severe         | 51 (4)                 | 14 (4)                        |         |

Continued
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’.

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 heart 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.
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/m², \( P = 0.002 \)), 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, \( P = 0.008 \)). 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

Figure 2: Survival according to pre-implantation rhythm: atrial fibrillation versus sinus rhythm. Afib: atrial fibrillation.
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) CHA2DS2-VASc score based on the baseline data. Patients with pre-LVAD AF and a high CHA2DS2-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%) (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: 1.69 (1.21–2.37)], a history of COPD [HR: 1.32 (1.03–1.69, P = 0.029)], extracorporeal membrane oxygenation support pre-implant [HR 1.39 (1.02–1.90, P = 0.039)] and intubation before implant [HR 1.33 (1.02–1.75, P = 0.036)].

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/m²)   | 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 myocardal 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 (×10³/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.
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.
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 4: Survival according to pre-implantation rhythm atrial fibrillation versus sinus rhythm with propensity scoring matched groups. AF: atrial fibrillation.
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 CHA2DS2-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 CHA2DS2-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.

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