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ORIGINAL ARTICLE

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Left ventricular assist device-related infections and the risk of cerebrovascular accidents: a EUROMACS study

Casper F. Zijderhand[a,b,†], Christiaan F.J. Antonides[b,†], Kevin M. Veen[b], Nelianne J. Verkaik[c], Felix Schoenrath [d,e], Jan Gummert[f], Petr Nemec [g], Béla Merkely[h], Francesco Musumeci [i], Bart Meyns [j], Theo M.M.H. de By[k], Ad J.J.C. Bogers [a] and Kadir Caliskan [b,*]

[a] Thoraxcenter, Department of Cardiothoracic Surgery, Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands
[b] Thoraxcenter, Department of Cardiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands
[c] Department of Medical Microbiology and Infectious Diseases, Erasmus MC, University Medical Center Rotterdam, Rotterdam, Netherlands
[d] Department of Cardiothoracic and Vascular Surgery, German Heart Center Berlin, Berlin, Germany
[e] DZHK (German Center for Cardiovascular Research), Partner Site Berlin, Berlin, Germany
[f] Clinic for Thoracic and Cardiovascular Surgery, Heart and Diabetes Center, NRW, Ruhr University Bochum, Bad Oeynhausen, Germany
[g] Department of Internal Cardiology Medicine, Marasyk University, Brno, Czech Republic
[h] Heart and Vascular Center, Semmelweis University, Budapest, Hungary
[i] Department of Heart and Vessels, Cardiac Surgery Unit and Heart Transplantation Center, S. Camillo-Forlanini Hospital, Roma, Italy
[j] Department of Cardiac Surgery, University Hospitals Leuven, Leuven, Belgium
[k] EUROMACS, European Association for Cardio-Thoracic Surgery (EACTS), Windsor, UK

* Corresponding author. Thoraxcenter, Department of Cardiology, Erasmus MC, University Medical Center Rotterdam, Dr. Molewaterplein 40, 3015 GD Rotterdam, Netherlands. Tel: +31-654937133; e-mail: dr.kcaliskan@outlook.com (K. Caliskan).

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Key question

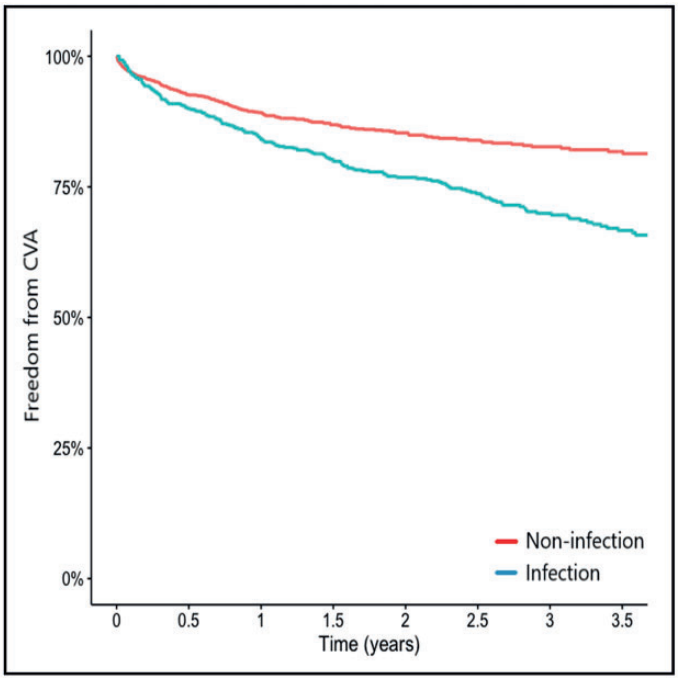
Does infection increase the risk of cerebrovascular accidents during left ventricular assist device support?

Key finding(s)

Both VAD-related and VAD-specific infection are associated with an increased risk of developing a CVA in LVAD supported patients.

Take-home message

This suggest the plausible need for proactive anticoagulation management in LVAD patients during infection.



†The first two authors contributed equally to this work.

Abstract

OBJECTIVES: In patients supported by a durable left ventricular assist device (LVAD), infections are a frequently reported adverse event with increased morbidity and mortality. The purpose of this study was to investigate the possible association between infections and thromboembolic events, most notable cerebrovascular accidents (CVAs), in LVAD patients.

METHODS: An analysis of the multicentre European Registry for Patients Assisted with Mechanical Circulatory Support was performed. Infections were categorized as VAD-specific infections, VAD-related infections and non-VAD-related infections. An extended Kaplan–Meier analysis for the risk of CVA with infection as a time-dependent covariate and a multivariable Cox proportional hazard model were performed.

RESULTS: For this analysis, 3282 patients with an LVAD were included with the majority of patients being male (83.1%). During follow-up, 1262 patients suffered from infection, and 457 patients had a CVA. Cox regression analysis with first infection as time-dependent covariate revealed a hazard ratio (HR) for CVA of 1.90 [95% confidence interval (CI): 1.55–2.33; $P < 0.001$]. Multivariable analysis confirmed the association for infection and CVAs with an HR of 1.99 (95% CI: 1.62–2.45; $P < 0.001$). With infections subcategorized, VAD-specific HR was 1.56 (95% CI: 1.18–2.08; P 0.002) and VAD-related infections [HR: 1.99 (95% CI: 1.41–2.82; $P < 0.001$)] remained associated with CVAs, while non-VAD-related infections ($P = 0.102$) were not.

CONCLUSIONS: Infection during LVAD support is associated with an increased risk of developing an ischaemic or haemorrhagic CVA, particularly in the setting of VAD-related or VAD-specific infections. This suggests the need of a stringent anticoagulation management and adequate antibiotic treatment during an infection in LVAD-supported patients.

Keywords: Heart failure • Left ventricular assist device • Infection • Cerebrovascular accidents • Thromboembolic events

ABBREVIATIONS

CVAs	Cerebrovascular accidents
CI	Confidence Interval
EUROMACS	European Registry for Patients Assisted with Mechanical Circulatory Support
HR	Hazard ratio
HF	Heart failure
HVAD	HeartWare Ventricular Assist Device
INTERMACS	Interagency Registry of Mechanically Assisted Circulatory Support
LVADs	Left ventricular assist devices

INTRODUCTION

Continuous-flow left ventricular assist devices (LVADs) have become an important modality, especially in the high income countries, in the treatment of end-stage heart failure (HF) as a bridge to transplantation, a bridge to candidacy or destination therapy. Given the shortage of suitable donor hearts, LVAD as destination therapy has become a viable treatment strategy in patients once all other therapeutic options have been exhausted [1]. However, long-term LVAD support has potential drawbacks, including the risk of cerebrovascular accident (CVA), bleeding and infection [1, 2]. The high rate of complications hampers the long-term survival of patients supported with a continuou-flow LVAD. The median long-term survival of patients with a donor heart is 15 years compared to median long-term survival on LVAD support of 5 years [3]. Infection is the most common cause of rehospitalizations with an incidence of 4.4 per 100 patients in 3 months and 24.0 in 12 months of LVAD support and continues to increase over time [1]. Therefore, major infection is the second leading cause of death in LVAD-supported patients [2].

Thromboembolic events are another notable complication in LVAD-supported patients and are significantly increased in patients with LVAD support [4]. Whereby, a CVA, both ischaemic and haemorrhagic, continues to be a major cause of morbidity and mortality [5, 6]. Interestingly, some small studies reported already the association between infections and CVA, where 51–63% of the patients had active infections at the time of CVA [7, 8]. An Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) study confirmed these findings with a higher prevalence of CVAs in patients with an active infection compared to patients without an active infection (18% vs 11%) [9]. Although these studies report a higher incidence of CVA in LVAD patients with an active infection, most studies were based on small single-centre cohort studies, lacked detailed data regarding the risk of CVA, type of infections and possible differentiation between ischaemic and haemorrhagic CVA. Furthermore, known risk factors for both infections and CVA, such as smoking, diabetes and atrial fibrillation, could potentially blur the potential interaction of the risk of a CVA and infections [10–12]. To investigate this, it is important to use a large patient database so these factors can be corrected in the analysis. Early recognition and proactive treatment of infections in LVAD patients along with meticulous anticoagulation management could lead to a decrease in infection-related CVAs. The aim of this study was therefore to evaluate the association between infections and CVAs in the European Registry for Patients with Mechanical Circulatory Support (EUROMACS), a multicentre registry with over 70 participating centres.

METHODS

Study design

A retrospective study was conducted in all patients who underwent an LVAD implantation using the EUROMACS data [2]. All patients aged ≥18 years with LVAD support were included. Exclusion criteria were patients aged <18 years or patients with a right ventricular assist device, single ventricular assist device, biventricular assist device, total artificial heart and a pulsatile device. Patients were censored at heart transplant or device explant.

Ethics statement

This study was approved by the institutional ethics committee of all respective participating centres in the EUROMACS, and all included subjects gave informed consent [13].

Data collection

All patients from May 2000 to April 2019, who met the inclusion criteria, were included in this study. Baseline characteristics before LVAD implantation include age, gender, body mass index, aetiology of HF, INTERMACS profile, preoperative condition and co-morbidities, electrocardiogram and echocardiogram were collected. Furthermore, perioperative data on device strategy, device type and intensive care unit stay were retrieved.

Outcomes

The primary outcome was the occurrence of CVA(s) in patients with infection(s) or without infection during LVAD support. Secondary end points included risk of CVA stratified by ischaemic or haemorrhagic after infection, survival, pump thrombosis and risk of neurological event(s) stratified by sort of infection.

Definitions

CVAs were defined using the INTERMACS definition. Ischaemic CVA is defined as a new acute neurological deficit associated with acute infarction on imaging. Symptomatic intracranial haemorrhage is defined as a new acute neurological deficit attributable to intracranial haemorrhage [14]. All infections, regardless of the severity, were subcategorized according to the International Society for Heart and Lung Transplantation definition as: non-VAD (Ventricular Assist Device) related—infections are not affected by the presence of the VAD and are unlikely related (i.e. lower respiratory tract infections and urinary tract infection); VAD related—infections that refer to those that can also occur in patients without VAD; however, there may be unique considerations in patients with VAD (i.e. endocarditis, mediastinitis and bloodstream infections); and VAD specific—infections that are specific to patients with VAD and are related to the device hardware and do not occur in non-VAD patients (i.e. driveline infections, pump or cannula infections and pocket infections) [15].

Statistics

Continuous data are presented as mean with standard deviation (Gaussian distribution) or median (interquartile range) (non-Gaussian distribution). Categorical data are presented as frequencies (percentage). The Fine and Gray method was used to calculate the cumulative incidence of CVA with death as competing risk. An infection occurs somewhere in follow-up; therefore, incorporating it as a baseline variable leads to a possible immortal time bias: a patient has to survive until an infection occurs. Infection was therefore used as a time-varying covariate. This implies that the covariate infection only is considered a variable after the first infection took place. Subsequently, it is not relevant to group the baseline variables on infection yes or no, since infection occurs somewhere in follow-up and is often of transient nature. To visualize the impact of time-varying covariates on outcomes, an extended Kaplan–Meier estimator was used to generate extended Kaplan–Meier curves presenting freedom of CVA [16]. A multivariable cox model was developed in order to investigate determinants associated with CVA. Determinants were prespecified, and no predictor selection attempts were undertaken. First post-LVAD infection was incorporated in the Cox proportional hazard model as a time-varying covariate [17]. Missing baseline data were imputed using multiple imputations by chained equations. All baseline variables with <20% missing values were imputed. Five imputed datasets were generated using 20 iterations each. Convergence and imputations were visually checked. Since missing data were low in the prespecified determinants (Supplementary Material, Table S1), analyses were done on the imputed first dataset. Statistical analyses were done in R (Version 4.1.2).

RESULTS

Baseline characteristics

In total, 3282 patients met the requirements and were included in the study. The median age was 56 years [interquartile range 47.0–63.0] and 83.1% were male. The predominant aetiology of HF was non-ischaemic heart disease (51.2%), and patients were mainly in INTERMACS class 2 (33.5%) or class 3 (27.6%) prior to implantation. Diabetes was present in 844 patients (26.7%) and a history of CVA was present in 186 patients (6.7%), of whom 169 (6.1%) were ischaemic and 17 (0.6%) were haemorrhagic. Bridge to transplantation was the most common device strategy (74.4%) and the device most frequently implanted was the HeartWare Ventricular Assist Device (HVAD) (Medtronic, Minneapolis, MN, USA) (50.8%) (Table 1).

Outcome after infection

During follow-up, 1262 (38.5%) patients experienced an infection. CVA was reported in 457 patients. The cumulative incidence of CVA in the overall population at 3 years was 14.8% [95% confidence interval (CI): 13.5–16.1; Supplementary Material, Fig. S1]. Cox regression with the first infection as a time-dependent covariate revealed a significant increased hazard ratio (HR) for CVA of 1.90 (95% CI: 1.55–2.33, $P < 0.001$) during infection in LVAD patients (Fig. 1). Furthermore, infection is significantly associated with ischaemic and haemorrhagic CVA, respectively, with an HR of 1.91 (95% CI: 1.43–2.56, $P < 0.001$; Fig. 2A) and an HR of 2.36 (95% CI: 1.77–3.16, $P < 0.001$; Fig. 2B). Pump thrombosis was comparable between the infection and non-infection groups with an HR of 0.85 (95% CI: 0.65–1.11, P 0.236; Fig. 3).

Infections subcategorized

Infections were subcategorized, according to the International Society for Heart and Lung Transplantation definition, as described in the 'Methods' section, as non-VAD related, VAD related and VAD specific. Non-VAD-related infections were not significantly associated with CVA [HR: 1.27 (95% CI: 0.95–1.69; $P = 0.102$]. However, both VAD-related and VAD-specific infections were significantly associated with the risk of a CVA, respectively, with an HR of 1.99 (95% CI: 1.41–2.82; $P < 0.001$) and an HR of 1.56 (95% CI: 1.18–2.08; $P = 0.002$) (Fig. 4).

Multivariable analysis

Multivariable analysis confirmed the significant association for risk of CVA during active infection with an HR of 1.99 (95%

Table 1: Baseline and clinical characteristics

	Overall
Number of patients	3282
Age, median [IQR]	56.0 [47.0, 63.0]
Male, *n* (%)	2728 (83.1)
Weight (kg), median [IQR]	79.0 [69.4, 90.0]
Height (cm), median [IQR]	176.0 [170.0, 181.0]
BMI, median [IQR]	25.6 [22.7, 28.9]
History of infection, *n* (%)	257 (9.1)
History of positive blood culture, *n* (%)	127 (5.4)
Diabetes, *n* (%)	837 (26.7)
Dialysis, *n* (%)	90 (2.9)
Smoking history, *n* (%)	2672 (66.6)
COPD, *n* (%)	304 (10.8)
History of neurological event (%), *n* (%)	
None	2485 (88.8)
CVA	186 (6.7)
ICB	17 (0.6)
TIA	108 (3.9)
Cardiac rhythm, *n* (%)	
Sinus	1422 (52.4)
Paced	801 (29.5)
Atrial fibrillation	430 (15.8)
Others	63 (2.3)
ICD in situ, *n* (%)	1762 (63.6)
ECMO, *n* (%)	344 (11.0)
LVEF (%), median [IQR]	19.0 [15.0, 22.0]
Aetiology, *n* (%)	
Ischaemic heart disease	1376 (48.8)
Non-ischaemic heart disease	1440 (51.2)
INTERMACS patient profile, *n* (%)	
1 Critical cardiogenic shock	470 (14.8)
2 Progressive decline	1067 (33.5)
3 Stable but inotrope dependent	878 (27.6)
4 Resting symptoms	567 (17.8)
5 Exertion intolerant	201 (6.3)
Device strategy (%), *n* (%)	
Bridge to transplant	2410 (74.4)
Destination therapy	599 (18.5)
Others	229 (7.1)
Device type (%), *n* (%)	
LVAD	3107 (94.7)
LVAD (+ temporary RVAD)	175 (5.3)
Device brand (%), *n* (%)	
HeartWare HVAD	1665 (50.8)
HeartMate II	1010 (30.8)
HeartMate 3	544 (16.6)
Other	59 (1.8)
ICU stay (days), median [IQR]	11.0 [5.0, 25.0]

BMI: body mass index; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; ECMO: extracorporeal membrane oxygenation; HVAD: HeartWare Ventricular Assist Device; ICB: intra-cranial bleeding; ICD: implantable cardioverter-defibrillator; ICU: intensive care unit; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; IQR: interquartile range; LVAD: left ventricular assist device; LVEF: left ventricular ejection fraction; RVAD: right ventricular assist device; TIA: transient ischaemic attack.

CI: 1.62–2.45; $P < 0.001$; Supplementary Material, Table S2). Furthermore, multivariable analysis confirmed the significant association for the risk of ischaemic or haemorrhagic CVA after infection, respectively, with an HR of 2.00 (95% CI: 1.48–2.71, $P < 0.001$; Supplementary Material, Table S3) and an HR of 2.42 (95% CI: 1.80–3.27, $P < 0.001$; Supplementary Material, Table S4). Multivariable analysis of the subcategorized infections confirmed the earlier mentioned findings with non-VAD related not significant associated with the risk of a CVA (HR 1.25, 95% CI: 0.93–1.68, $P = 0.144$). VAD-related and VAD-specific infections remained significantly associated with the increased risk of a CVA after multivariable analysis (respectively, HR 1.99, 95% CI: 1.39–2.85, $P < 0.001$ and HR 1.54, 95% CI: 1.15–2.06, $P = 0.003$; Supplementary Material, Table S3). Furthermore, patients with an HVAD showed more significantly more ischaemic CVA and infection after implantation than in other devices in the multivariable analysis (Supplementary Material, Tables S3 and S5). No violation of the proportional hazard assumption was detected with the Schoenfeld test, $P = 0.850$.

DISCUSSION

In this article, we analysed the association of an active infection and risk of CVA in patients supported with an LVAD in the large multicentre EUROMACS using contemporary analyses with infection as a time-dependent covariate. The main findings were that infections, in particular VAD-related and VAD-specific infections, are significantly associated with an increased risk of both ischaemic and haemorrhagic CVAs. The multivariable analysis confirmed the highly significant association with an HR of 1.99 ($P < 0.001$). This implies the plausible clinical relevance, with timely and adequate treating the patients with an active infection, and concomitant stringent management of the anticoagulation regime to prevent an ischaemic of haemorrhagic CVA during an active infection.

In our study, infections occurred in 38.5% of the patients after LVAD implantation. This observation is consistent with what is known from the current literature, i.e. 35–42% [9, 18]. Infections in patients supported by an LVAD, and in particular bloodstream infections, have previously been suggested as a significant risk factor for both ischaemic and haemorrhagic CVAs [7, 8, 19, 20]. However, clinical temporal association of infections leading to a CVA and sample size were limited in these studies. With contemporary analyses, with infection as time-varying covariate in an extended Kaplan–Meier, we were able to calculate and visualize the risk of a CVA during or after an active infection. The overall incidence of CVA was 14.8% at 3 years, with most patients having an ischaemic CVA, which is in concordance with previous studies (18%) [9]. Our study revealed that, in particular, patients with a VAD-related or VAD-specific infection have an increased risk of developing a CVA. Earlier studies showed that the majority of VAD-related infections are bloodstream infections, while driveline infections are described as the predominant type of VAD-specific infection [21]. Interestingly, local infections, such as a driveline infection, are less likely to result in systemic activation of the inflammatory system but have the same influence on the risk of CVAs [22]. Particularly, bloodstream infections are linked to coagulation system activation, thereby an increased risk of CVA [23, 24]. Our study did not show a difference in the risk of pump-thrombosis between patients with or without an infection. This is in concordance with earlier studies and might be a result of more small thrombus formation, which could more easily transport throughout the LVAD [25]. Patients with an HVAD had an elevated risk of both ischaemic CVA and this is described earlier which contributed to the recent production stop of the HVAD [26].

During septic infections, the blood is hypercoagulable, and platelets are activated; these mechanisms contribute to tissue ischaemia and necrosis of organs [27, 28]. Therefore, proposed mechanisms could trigger a CVA during or short after infection, which includes platelet activation and aggregation,

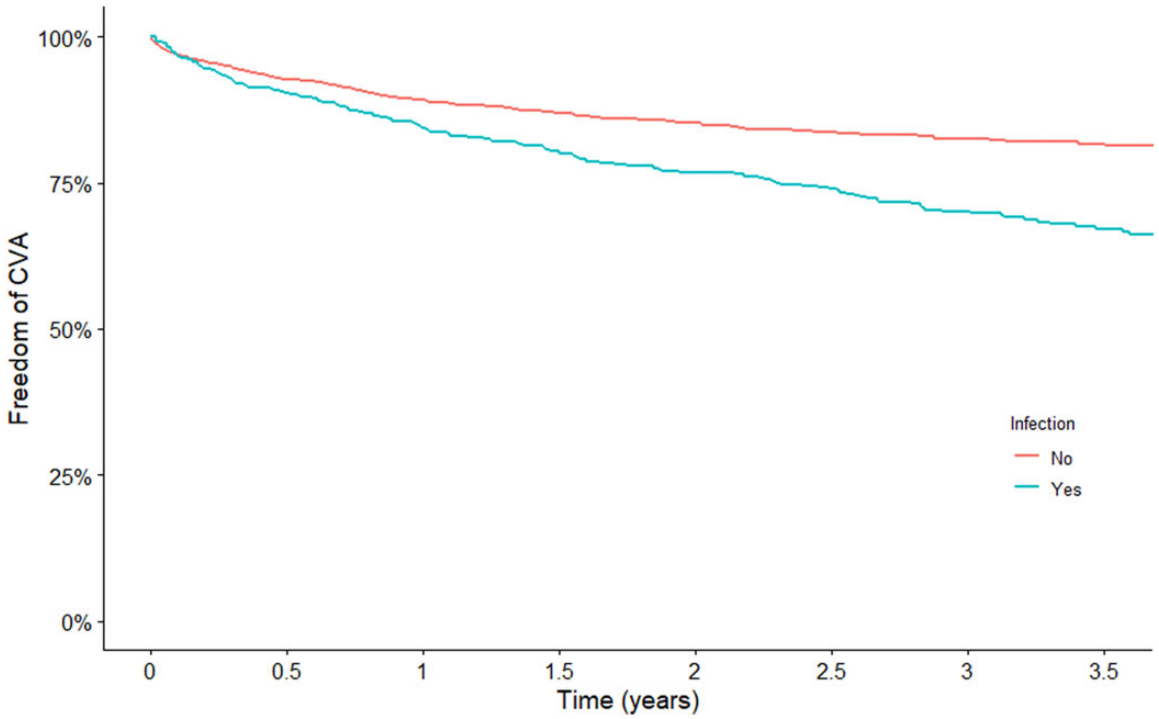


Figure 1: Freedom from all-cause (ischaemic and haemorrhagic) cerebrovascular accidents in an extended Kaplan–Meier with infection as time-varying covariate.

inflammation-induced thrombosis, impaired endothelial function, infection provoked cardiac arrhythmias and dehydration-induced thrombosis [29, 30]. Another adverse effect of continuous-flow LVAD support is shear stress on blood components and endothelial dysfunction [31, 32]. This could lead to aggravating the ubiquitous existent acquired von Willebrand disease and thereby increase haemorrhagic events which is a major cause of morbidity [33]. Furthermore, subclinical microthromboembolisms to the brain could probably as well transform into a secondary haemorrhagic CVA [34]. Both of these factors, a septic infection and shear stress, could probably explain the incremental risk of bleeding and thereby CVA. Our study implies that, given association between VAD-related and VAD-specific infections with the increased risk of ischaemic and haemorrhagic CVA, it is essential to treat infections as early and aggressively as possible and concomitantly, proactive anticoagulation management. However, radical treatment of infections remains very challenging because of possible formation of biofilm on the prosthetic material involved. To date, there are no appropriate evidence-based antimicrobial treatment guidelines in LVAD patients. Therefore, further studies should focus on the development of a protocolized diagnostic and treatment approach, not only for the treatment of infection but also to reduce the risk of concomitant CVA.

Adequate antithrombotic therapy in LVAD patients is important in the prevention of thrombotic or haemorrhagic events. Maintaining an INR value between the aimed therapeutic range of 2.0 and 3.0 tends to be crucial to prevent these complications [34]. This could be challenging given the quality of anticoagulation therapy is often lower than expected [35]. Furthermore, LVAD patients often have coexisting morbidity, which could potentially increase the risk of thrombotic and/or haemorrhagic complications [36]. Such comorbidities include atrial fibrillation, congestive right-sided HF, renal failure, pulmonary circulation disorders, liver disorders and coagulopathy and are known to be predictors of an increased risk of a CVA after infection [37]. Our study adjusted for most, available, comorbidities with the multivariable analysis and concluded that active infection remained significant associated with risk of CVA during LVAD support. Interestingly, atrial fibrillation during long-term LVAD support is a known significant risk factor for CVA [38]. However, after adjusting for atrial fibrillation in our study, infection was still significantly associated with the elevated risk of CVA. To reduce the risk of haemorrhagic complications during LVAD support, a new preliminary study suggests maintaining much lower INR values between 1.5 and 1.9 [39]. Therewith, exposure to any antibiotic agent (in particular, co-trimoxazole and rifampicin) is associated with an increased risk of bleeding due to anticoagulation derangements requiring even more hospitalizations [40]. At the moment, little is known about other options for optimizing the anticoagulation therapy, such as anti-platelet therapy and strict anticoagulant monitoring; this will be an interesting topic for the near future. The elevated risk of CVA in LVAD patients with an active infection suggests that attention should be paid to maintain anticoagulation in the therapeutic range, especially when the patient is suffering from an infection. Understanding these differences is critical in timely diagnoses and thereby providing management interventions with scientifically proven guidelines.

Limitations

This EUROMACS study has certain limitations that should be considered while interpreting the results. Due to the retrospective nature of this study, the number of data fields captured is limited. It is possible that not all infections or CVAs were captured, which could lead to outcome missing data. This could result in a possible underestimation of these outcomes; however, the EUROMACS regularly

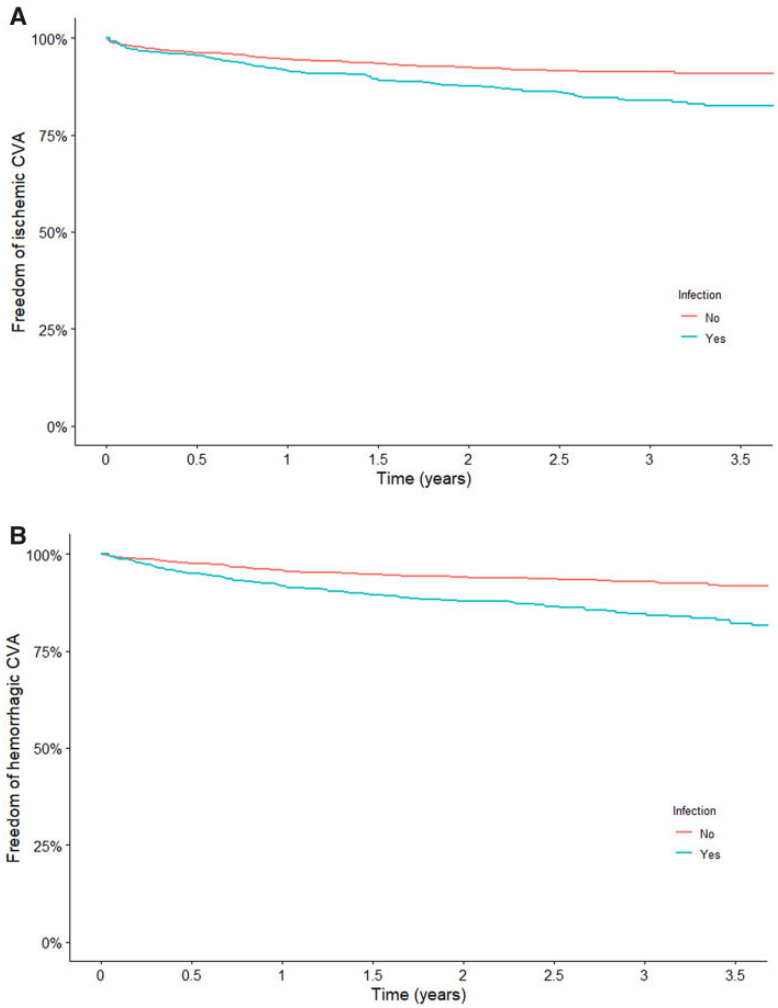


Figure 2: (**A**) Freedom from ischaemic cerebrovascular accident in an extended Kaplan–Meier with infection as time-varying covariate. The red line represents the non-infection group, and the blue line represents the infection group. (**B**) Freedom from haemorrhagic cerebrovascular accident in an extended Kaplan–Meier with infection as time-varying covariate.

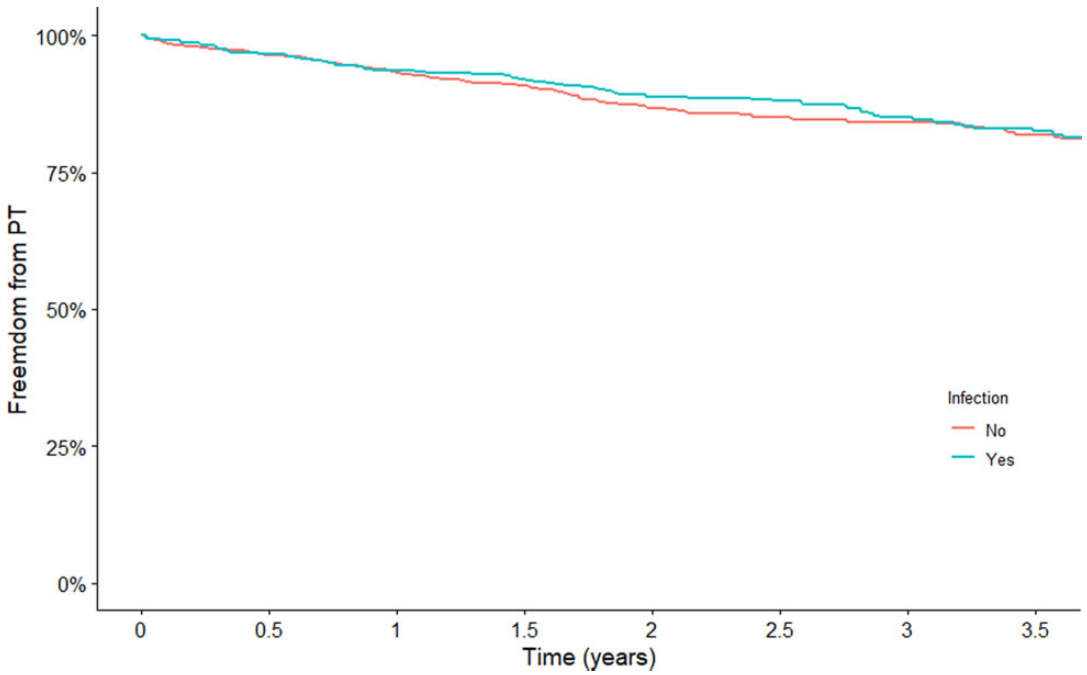


Figure 3: Freedom from pump thrombosis in an extended Kaplan–Meier with infection as time-varying covariate.

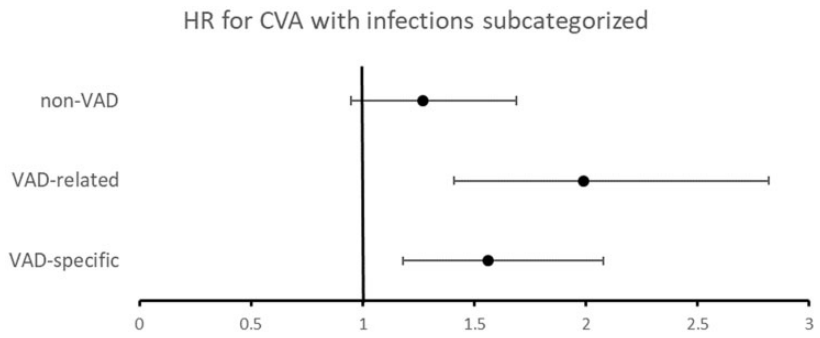


Figure 4: Forest plot of hazards ratios for the subcategories (non-VAD related, VAD related and VAD specific) of infection and cerebrovascular accident. *X*-axis represents the hazards ratios with confidence interval.

checks data input and audits participating centres for data quality and completion. Furthermore, due to the large multicentre database design, specific details of infection including pathogens or INR values at the time of infection are missing. This is an important issue for future research. Finally, we used multiple imputations to account for randomly missing baseline data. Incremental improvements in LVAD therapy led to a reduced incidence of CVA. The used historic data relate the incidence of infection and CVA occurring with devices used at that time.

CONCLUSION

Our findings imply that infection is associated with an increased risk of developing an ischaemic or haemorrhagic CVA in LVAD-supported patients. Furthermore, subcategorized infections including VAD-related and VAD-specific infections are associated with a significantly increased risk of both ischaemic and haemorrhagic CVA. This study suggests the plausible need for proactive anticoagulation management and adequate antibiotic treatment in LVAD patients with an active infection.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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Conflict of interest: none declared.

Data Availability Statement

All relevant data are available on request from the authors.

Author contributions

Casper F. Zijderhand: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Validation; Visualization; Writing—original draft; Writing—review & editing. **Christiaan F.J. Antonides:** Conceptualization; Data curation; Formal analysis; Methodology; Validation; Visualization; Writing—original draft; Writing—review & editing. **Kevin M. Veen:** Data curation; Formal analysis; Methodology; Writing—original draft; Writing—review & editing. **Nelianne J. Verkaik:** Writing—original draft; Writing—review & editing. **Felix Schoenrath:** Writing—review & editing. **Jan Gummert:** Writing—review & editing. **Petr Nemec:** Writing—review & editing. **Béla Merkely:** Writing—review & editing. **Francesco Musumeci:** Writing—review & editing. **Bart Meyns:** Writing—review & editing. **Theo M.M.H. de By:** Project administration; Writing—review & editing. **Ad J.J.C. Bogers:** Conceptualization; Methodology; Project administration; Writing—review & editing. **Kadir Caliskan:** Conceptualization; Methodology; Project administration; Writing—review & editing.

Reviewer information

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REFERENCES

[1] Teuteberg JJ, Cleveland JC, Jr., Cowger J, Higgins RS, Goldstein DJ, Keebler M *et al.* The Society of Thoracic Surgeons Intermacs 2019 annual report: the changing landscape of devices and indications. Ann Thorac Surg 2020;109:649–60.

[2] de By T, Schoenrath F, Veen K, Mohacsi P, Stein J, Alkhamees K *et al.* The European Registry for Patients with Mechanical Circulatory Support of the European Association for Cardio-Thoracic Surgery: third report. Eur J Cardiothorac Surg 2022;62:ezac032. doi: 10.1093/ejcts/ezac032.

[3] Zijlstra LE, Constantinescu AA, Manintveld O, Birim O, Hesselink DA, Thiel R *et al.* Improved long-term survival in Dutch heart transplant patients despite increasing donor age: the Rotterdam experience. Transpl Int 2015;28:962–71.

[4] Shrode CW, Draper KV, Huang RJ, Kennedy JL, Godsey AC, Morrison CC *et al.* Significantly higher rates of gastrointestinal bleeding and thromboembolic events with left ventricular assist devices. Clin Gastroenterol Hepatol 2014;12:1461–7.

[5] Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED et al Seventh INTERMACS annual report: 15,000 patients and counting. J Heart Lung Transplant 2015;34:1495–504.

[6] Frontera JA, Starling R, Cho SM, Nowacki AS, Uchino K, Hussain MS et al Risk factors, mortality, and timing of ischemic and hemorrhagic stroke with left ventricular assist devices. J Heart Lung Transplant 2017;36:673–83.

[7] Cho SM, Hassett C, Rice CJ, Starling R, Katzan I, Uchino K. What causes LVAD-associated ischemic stroke? Surgery, pump thrombosis, antithrombotics, and infection. ASAIO J 2019;65:775–80.

[8] Akin S, Soliman OI, Constantinescu AA, Akca F, Birim O, Domburg RT et al Haemolysis as a first sign of thromboembolic event and acute pump thrombosis in patients with the continuous-flow left ventricular assist device HeartMate II. Neth Heart J 2016;24:134–42.
[9] Shah P, Birk SE, Cooper LB, Psotka MA, Kirklin JK, Barnett SD *et al.* Stroke and death risk in ventricular assist device patients varies by ISHLT infection category: an INTERMACS analysis. J Heart Lung Transplant 2019;38:721–30.
[10] Pan B, Jin X, Jun L, Qiu S, Zheng Q, Pan M. The relationship between smoking and stroke: a meta-analysis. Medicine (Baltimore) 2019;98:e14872.
[11] Carey IM, Critchley JA, DeWilde S, Harris T, Hosking FJ, Cook DG. Risk of infection in type 1 and type 2 diabetes compared with the general population: a matched cohort study. Diabetes Care 2018;41:513–21.
[12] Sandercock P, Bamford J, Dennis M, Burn J, Slattery J, Jones L *et al.* Atrial fibrillation and stroke: prevalence in different types of stroke and influence on early and long term prognosis (Oxfordshire community stroke project). BMJ 1992;305:1460–5.
[13] de By TM, Mohacsi P, Gummert J, Bushnaq H, Krabatsch T, Gustafsson F *et al.*; EUROMACS members. The European Registry for Patients with Mechanical Circulatory Support (EUROMACS): first annual report. Eur J Cardiothorac Surg 2015;47:770–6; discussion 6–7.
[14] Acharya D, Loyaga-Rendon R, Morgan CJ, Sands KA, Pamboukian SV, Rajapreyar I *et al.* INTERMACS analysis of stroke during support with continuous-flow left ventricular assist devices: risk factors and outcomes. JACC Heart Fail 2017;5:703–11.
[15] Hannan MM, Husain S, Mattner F, Danziger-Isakov L, Drew RJ, Corey GR *et al.*; International Society for Heart and Lung Transplantation. Working formulation for the standardization of definitions of infections in patients using ventricular assist devices. J Heart Lung Transplant 2011;30:375–84.
[16] Smith AR, Goodrich NP, Beil CA, Liu Q, Merion RM, Gillespie BW *et al.* Graphical representation of survival curves in the presence of time-dependent categorical covariates with application to liver transplantation. J Appl Stat 2019;46:1702–13.
[17] Kleinbaum DG, Klein M. Extension of the Cox proportional hazards model for time-dependent variables. Statistics for Biology and Health 2011;1:241–88.
[18] Zinoviev R, Lippincott CK, Keller SC, Gilotra NA. In full flow: left ventricular assist device infections in the modern era. Open Forum Infect Dis 2020;7:1–8.
[19] Trachtenberg BH, Cordero-Reyes AM, Aldeiri M, Alvarez P, Bhimaraj A, Ashrith G *et al.* Persistent blood stream infection in patients supported with a continuous-flow left ventricular assist device is associated with an increased risk of cerebrovascular accidents. J Card Fail 2015;21:119–25.
[20] Yoshioka D, Sakaniwa R, Toda K, Samura T, Saito S, Kashiyama N *et al.* Relationship between bacteremia and hemorrhagic stroke in patients with continuous-flow left ventricular assist device. Circ J 2018;82:448–56.
[21] Nienaber JJ, Kusne S, Riaz T, Walker RC, Baddour LM, Wright AJ *et al.*; Mayo Cardiovascular Infections Study Group. Clinical manifestations and management of left ventricular assist device-associated infections. Clin Infect Dis 2013;57:1438–48.
[22] Cagliostro B, Levin AP, Fried J, Stewart S, Parkis G, Mody KP *et al.* Continuous-flow left ventricular assist devices and usefulness of a standardized strategy to reduce drive-line infections. J Heart Lung Transplant 2016;35:108–14.
[23] Lindsberg PJ, Grau AJ. Inflammation and infections as risk factors for ischemic stroke. Stroke 2003;34:2518–32.
[24] Levi M, Keller TT, van Gorp E, ten Cate H. Infection and inflammation and the coagulation system. Cardiovasc Res 2003;60:26–39.
[25] Najjar S, Slaughter M, Pagani F, Starling R, McGee E, Eckman P *et al.*; HVAD Bridge to Transplant ADVANCE Trial Investigators. An analysis of pump thrombus events in patients in the HeartWare ADVANCE bridge to transplant and continued access protocol trial. J Heart Lung Transplant 2014;33:23–34.
[26] Cho S, Mehaffey J, Meyers S, Cantor R, Starling R, Kirklin J *et al.* Cerebrovascular events in patients with centrifugal-flow left ventricular assist devices: propensity score–matched analysis from the Intermacs registry. Circulation 2021;144:763–72.
[27] Yaguchi A, Lobo FL, Vincent JL, Pradier O. Platelet function in sepsis. J Thromb Haemost 2004;2:2096–102.
[28] Zeerleder S, Hack CE, Wuillemin WA. Disseminated intravascular coagulation in sepsis. Chest 2005;128:2864–75.
[29] D' Atri LP, Schattner M. Platelet toll-like receptors in thromboinflammation. Front Biosci (Landmark Ed) 2017;22:1867–83.
[30] Bartoli CR, Zhang DM, Hennessy-Strahs S, Kang J, Restle DJ, Bermudez C. Clinical and in vitro evidence that left ventricular assist device-induced von Willebrand factor degradation alters angiogenesis. Circ Heart Fail 2018;11:e004638.
[31] Scardulla F, Pasta S, D'Acquisto L, Sciacca S, Agnese V, Vergara C *et al.* Shear stress alterations in the celiac trunk of patients with a continuous-flow left ventricular assist device as shown by in-silico and *in vitro* flow analyses. J Heart Lung Transplant 2017;36:906–13.
[32] Meyer AL, Malehsa D, Bara C, Budde U, Slaughter MS, Haverich A *et al.* Acquired von Willebrand syndrome in patients with an axial flow left ventricular assist device. Circ Heart Fail 2010;3:675–81.
[33] Rocha EA, Rocha F, Deliberalli I, de Andrade JBC, Ricarte IF, Singhal AB *et al.* Cerebral microembolism in intracerebral hemorrhage: a prospective case-control study. Neurocrit Care 2021;34:547–56.
[34] Nassif ME, LaRue SJ, Raymer DS, Novak E, Vader JM, Ewald GA *et al.* Relationship between anticoagulation intensity and thrombotic or bleeding outcomes among outpatients with continuous-flow left ventricular assist devices. Circ Heart Fail 2016;9.
[35] Sage W, Gottiparthy A, Lincoln P, Tsui SSL, Pettit SJ. Improving anticoagulation of patients with an implantable left ventricular assist device. BMJ Open Qual 2018;7:e000250.
[36] Uriel N, Pak SW, Jorde UP, Jude B, Susen S, Vincentelli A *et al.* Acquired von Willebrand syndrome after continuous-flow mechanical device support contributes to a high prevalence of bleeding during long-term support and at the time of transplantation. J Am Coll Cardiol 2010;56:1207–13.
[37] Shao IY, Elkind MSV, Boehme AK. Risk factors for stroke in patients with sepsis and bloodstream infections. Stroke 2019;50:1046–51.
[38] Antonides CFJ, Yalcin YC, Veen KM, Muslem R, de By TMMH, Bogers AJJC *et al.* 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. Eur J Cardiothorac Surg 2022;61:1164–75.
[39] Netuka I, Ivak P, Tucanova Z, Gregor S, Szarszoi O, Sood P *et al.* Evaluation of low-intensity anti-coagulation with a fully magnetically levitated centrifugal-flow circulatory pump-the MAGENTUM 1 study. J Heart Lung Transplant 2018;37:579–86.
[40] Baillargeon J, Holmes HM, Lin YL, Raji MA, Sharma G, Kuo YF. Concurrent use of warfarin and antibiotics and the risk of bleeding in older adults. Am J Med 2012;125:183–9.