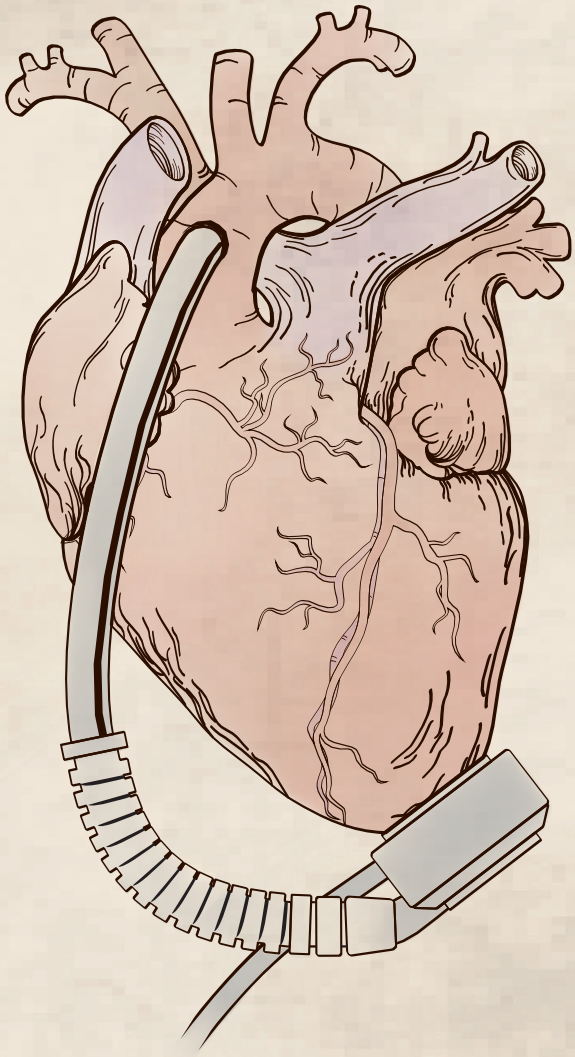
DURABLE
LEFT VENTRICULAR ASSIST DEVICE THERAPY
FOR END-STAGE HEART FAILURE

Optimizing selection criteria



YUNUS CAN YALÇIN

Stellingen
behorende bij het proefschrift:

Durable left ventricular assist device therapy for end-stage heart failure
''Optimizing selection criteria''

I. More stringent selection criteria, and optimal timing of LVAD implantation can help in preventing the onset of acute kidney injury. (this thesis)

II. Electromagnetic interference between ICD's and LVAD's remains an ongoing concern with the new HeartMate 3 device and ICD's from Biotronik and Medtronic. (this thesis)

III. The integrity of the aortic valve is crucial for the functioning of the LVAD and therefore concomitant aortic valve surgery should be scheduled based on individual patient characteristics. (this thesis)

IV. Sustained renal function improvement is seen in few LVAD patients and should therefore not be expected for the majority of patients. (this thesis)

V. Stringent selection criteria for the scheduling of LVAD implantation results in improving overall survival rates. (this thesis)

VI. The use of SGLT2 inhibitors in patients with advanced heart failure is an effective treatment modality to reduce cardiovascular death and cardiorenal adverse events. (EMPEROR trial, Packer et al, N Engl J Med 2020;383:1413-24)

VII. The use of LVAD therapy might negatively impact survival following subsequent heart transplantation, underlining the need for continuous optimization of patient selection criteria. (Truby et al., Circulation 2019;140:459-69)

VIII. The introduction of the HeartMate 3 has virtually rendered pump thrombosis an issue of the past. (MOMENTUM 3 trial, Mehra et al, N Engl J Med 2019;380:1618-27)

IX. The real-world data of HeartMate 3 implantations highlights the significant rates of major infections and right heart failure post implantation. (ELEVATE registry, Zimpfer et al, Eur Heart J 2020;41:3801-9)

X. In a select group of elderly patients (>65years), the utilization of LVAD therapy increases both quality of life as well as functional capacity. (Emerson et al., Journal of the American College of Cardiology 2021;78:883-94

XI. Whatever separates you from the truth, throw it away, it will vanish anyhow (Yunus Emre, 1228-1328, the Drop that Became the Sea)

Durable Left Ventricular Assist Device Therapy for End-stage Heart Failure

“Optimizing selection criteria”

By Yunus C. Yalçin

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Durable Left Ventricular Assist Device Therapy for End-stage Heart Failure

"Optimizing selection criteria"

Duurzame left ventricular assist device therapie voor eindstadium hartfalen
"Optimaliseren van selectiecriteria"

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus

Prof.dr. A.L. Bredenoord

and in accordance with the decision of the Doctorate Board.
The public defence shall be held on
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by

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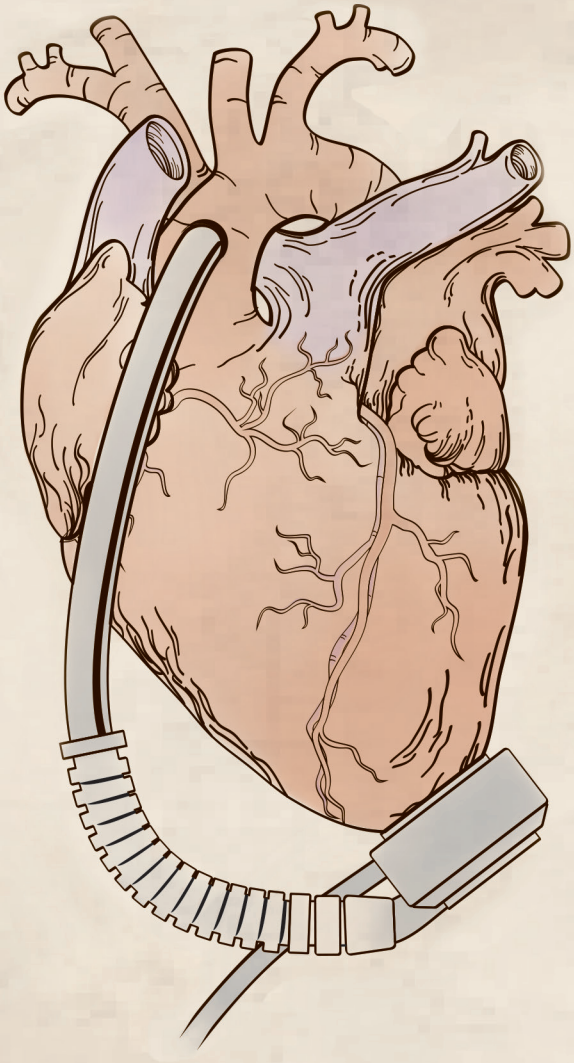
“A man sees in the world what he carries in his heart.”

– Johann Wolfgang Von Goethe - Faust.

Table of contents



Chapter I

Introduction, aims and outline of the thesis

Mechanically supporting the failing heart

Ever since the very first orthotopic heart transplantation the question remained how to treat patients with a failing heart most effectively.[1] Heart failure, meaning the inability of the heart to adequately supply the body with oxygen rich blood, has been described as being one of the leading causes of death in the developed world, with over 26 million people suffering from heart failure worldwide.[2] With the ever increasing age of the world population and the rapid urbanization of the world, the number of people suffering from heart failure worldwide will only rise in the future with predictions showing a 10% increase in prevalence by the year 2030.[3] While the advances of modern medicine have given us a plethora of treatment options, with the recent addition of sodium-glucose protein 2 (SGLT2) inhibitors and angiotensin receptor inhibitors (ARNI), many patients can be timely treated with optimal medical therapy.[4,5] However for those who develop refractory end-stage heart failure, only one final treatment remains, being heart transplantation. Orthotopic heart transplantation remains the gold standard in treating those suffering from medically refractory end-stage heart failure.[6,7] However, the scarcity of donor hearts remains a major limitation and has led to the development of the current generation of durable left ventricular assist devices (LVADs), with an increasing number of patients being treated worldwide.[8,9] LVAD therapy supports cardiac unloading, increases cardiac output and decreases right-sided congestion.[10,11] Initially, these devices had been developed as an alternative to treat patients on the waiting list for heart transplantation with a permanent intent. However, following the landmark study by Frazier et al in 1995, their use of an LVAD to bridge patients to a heart transplantation, showed great improvement in patient survival and rehabilitation.[12] The bridge-to-transplantation (BTT) indication has since saved many patients who otherwise were deemed too sick for heart transplantation. Following this success in several hospitals worldwide, the Erasmus MC University Hospital followed in 2000 with a pilot including the first-generation HeartMate LVAD. Subsequently, in 2006, the first LVAD implantation with the second-generation HeartMate II LVAD, in a woman suffering from myocarditis induced heart failure who was too sick for an urgent heart transplantation, was performed. This marked the beginning of a new era of advanced heart failure therapy at the Erasmus MC.

Following the success of the BTT indication a new indication, destination therapy (DT), took a more prominent role. This indication is suited in situations where LVAD therapy is the final treatment for end-stage HF, meaning a heart transplantation is no longer feasible for various reasons. Initially the BTT indication group outnumbered the DT group. However, the increasing need for heart transplantations and the rather stagnant availability of suitable donor hearts has made the DT indication far surpass the BTT indication.[13] It is important to note that this indication is based on the conditions at the time of implantation. While some LVAD patients may be BTT at the time of implantation, they subsequently can become a DT patient and never receive a donor heart. This while other patients who received an initial DT indication can be potentially transplanted. Moreover, recently published data shows similar adverse events in patients regardless of prior indication assignment.[14] This highlights the uncertainty, the unpredictability, and the need for more research regarding the outcomes following LVAD implantation in the battle against the grave prognosis of end-stage heart failure.

Current state of durable left ventricular assist device support

Recently, the durable LVAD support was startled by the decision of Medtronic to stop the distribution and sale of the HeartWare LVAD (HVAD), the first centrifugal continuous-flow LVAD.[15] This leaves Abbotts' HeartMate 3, the latest centrifugal continuous flow LVAD, as the only remaining major modality in the treatment of end-stage heart failure. While the decision of Medtronic is understandable, given the apparent issues of their device compared to the HeartMate 3, this leaves the future of LVAD support largely in the hands of a single device manufacturer.[16,17] Nonetheless, the HVAD was implanted in many patients worldwide and many of them are currently still supported by their device. Therefore, it remains important to continue the research of their respective outcomes and of those supported by the other device brands, including older generation LVAD's.

In recent years prior to the announcement of Medtronic, the outcomes of patients supported with the newer centrifugal continuous flow LVAD's were incrementally improving as centers became more experienced. Early reports of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) (report from 2008) and the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) (report from 2015) showed survival rates of 90% and 88.7% in the first month and 56% and 68.4% in the first year, respectively.[18,19] While these results were promising, the latest results in centrifugal implantations only show an increase in the survival rates, with INTERMACS (report from 2021) showing a 1 year survival rate of 82.3% and EUROMACS (report from 2021) showing a 1 year 72% rate.[8,20] This unequivocally shows the success of the recent LVAD devices to extend the survival of end-stage heart failure patients. However, survival is not the only outcome that patients care about. A patients' adverse event free survival and days out of hospital, while improved, remains burdensome with early and late onset right heart failure, tractus digestives bleedings, hemorrhagic and ischemic stroke and infections plaguing LVAD patients on the long-term support.[21,22]

Aims and outline of this thesis

The aim of this thesis is to investigate the outcomes of patients supported with durable LVAD therapy to improve upon these outcomes. Therefore, this thesis aims to identify, quantify, and predict the onset of adverse events associated with durable LVAD support. In order to be able to achieve this, data from the Erasmus MC, data from Johns Hopkins Hospital, data from the Medical University of South Carolina, as well as data form various international databases were analyzed.

In **Chapter II** we reviewed the current available literature to assess the incidence, risk factors, management and possible novel treatments for acute kidney injury following LVAD implantation. Moreover, this review provides the contemporary insights and future perspectives on post LVAD implantation associated acute renal injury. In **Chapters III** and **IV,** we assessed the outcomes of patients with kidney and liver disease respectively. These multicenter studies include both European and American patients to analyze the respective available longitudinal data. **Chapter V** includes the investigation of a relatively new

phenomenon, being the electromagnetic interference in patients between their pacemaker/ICD's and their newly implanted LVAD's. While this interference was present in the older HeartMate II, this study includes the new HeartMate 3 as well. Furthermore, we investigated the impact of pre-operative atrial fibrillation on outcomes, including hemocompatibility-related adverse events, in LVAD patients in **Chapter VI**.

Chapter VII includes a review on the most frequent and debilitating adverse events; the driveline exit-site infection. This study reviews several wound care protocols and differences between several proposed techniques and their effectiveness in treating and preventing driveline infections. Next, in **Chapter VIII,** we discuss a case report on one of our patients who received intermittent Levosimendan infusions for his refractory right heart failure, a cumbersome and difficult treatable complication post LVAD especially in DT patients in whom there is no bailout of a heart transplantation.

Following, in **Chapters IX, X, XI, XII** and **XIII** we investigated several research questions pertaining to aortic valve (surgery) associated pathology and its impact on patients supported with an LVAD. We first started with our own observation of aortic root thrombosis in patients treated with an aortic valve replacement. The following chapters try to answer questions regarding predictions of outcomes following concomitant aortic valve surgery in LVAD patients. With the use of data from the International Registry for Mechanically Assisted Circulatory Support (IMACS), which contains data from the INTERMACS, EUROMACS and the Japanese JMACS and various individual hospitals, we aimed to answer these research questions. **Chapter XII** consists of a letter to the editor, which serves as the prelude to **Chapter XIII**. Herein, we discuss the onset of aortic regurgitation in patients supported with LVAD support. This chapter includes the use of mixed models and joint models to accurately predict the onset and subsequent impact of aortic regurgitation on survival in LVAD patients.

Lastly, in **Chapter XIV**, we assessed and evaluated our very own outcomes in the Erasmus MC. This study compared our one and half decade of experience with the HeartMate II vs the HeartMate 3.

Finally, in **Chapter XIV** we discuss the important findings and their respective roles in patient care. Furthermore, we will discuss the current landscape of LVAD therapy, current limitations, and future perspectives.

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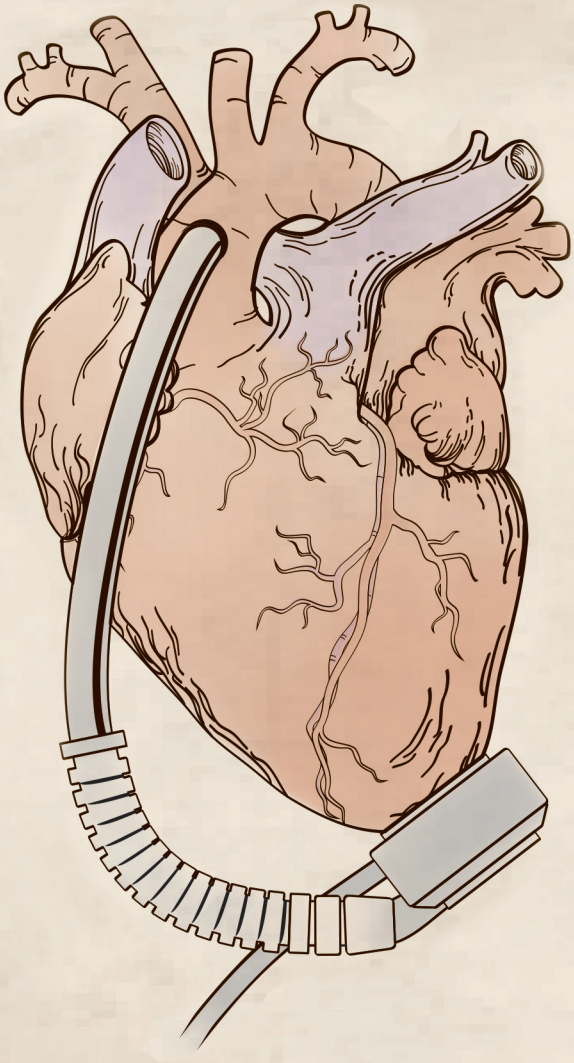


Chapter II

Acute kidney injury following left ventricular assist device implantation; Contemporary insights and future perspectives

Yalcin YC, Bunge JJH, Guven G, Muslem R, Szymanski M, den Uil CA, Hesselink DA, Topkara VK, Manintveld OC, Colombo PC, Bogers AJJC, Caliskan K

J Heart Lung Transplant. 2019;38(8):797-805

Abstract

Currently, an increasing number of patients with end-stage heart failure are being treated with left ventricular assist device (LVAD) therapy, as bridge-to-transplantation, bridge-to-candidacy, or destination therapy (DT). Potential life-threatening complications may occur, specifically in the early postoperative phase, which positions LVAD implantation as a high-risk surgical procedure. Acute kidney injury (AKI) is a frequently observed complication after LVAD implantation and is associated with high morbidity and mortality. The rapidly growing number of LVAD implantations necessitates better approaches of identifying high risk patients, optimizing perioperative management, and preventing severe complications such as AKI. This holds especially true for those patients receiving an LVAD as DT, who are typically older (with higher burden of co-morbidities) with impaired renal function and at increased postoperative risk. Herein we outline the definition, diagnosis, frequency, pathophysiology, and risk factors for AKI in LVAD patients. We also review possible strategies to prevent and manage AKI in this patient population.

Introduction

Currently, an increasing number of patients with end-stage heart failure (HF) benefit from durable left ventricular assist device (LVAD) therapy.(1) However, LVAD implantation remains a high-risk surgical procedure associated with life-threatening complications, especially in the early postoperative phase that are associated with early postoperative mortality.(2) The 1-year survival for patients receiving contemporary LVAD support ranges between 80% and 83% based upon data from the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) and Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS).(1, 3)

Acute kidney injury (AKI) is a frequent complication following LVAD implantation and is associated with increased morbidity and mortality.(4-7) With rapidly growing number of LVAD implantations, there is a need to enhance identification of high risk patients, improve perioperative management and possibly prevent AKI and other life-threatening complications.

This review outlines the definition, diagnosis, and incidence of AKI after LVAD implantation, and the diagnostic and prognostic role for novel biomarkers. Furthermore, we review the pathophysiology, risk factors and the impact on outcomes of postoperative AKI. Finally, we outline possible prevention and management strategies of AKI following LVAD implantation. This review will focus mainly on contemporary continuous flow devices, however, will include studies that used a combination of pulsatile and continuous flow devices.

Definition, diagnosis, and incidence of post LVAD AKI

Since 2012, three main definitions of AKI have been used in the cardiac surgery population (Table 1). The most common clinical sign of AKI is a progressive decrease in renal excretory function, which results in a) oliguria or anuria, b) accumulation of several products of nitrogen metabolism including creatinine and urea, c) metabolic acidosis, and d) electrolyte abnormalities. The KDIGO criteria is recommended due to its comprehensive definition, ensuring a robust diagnosis.(8)

Contemporary studies investigating AKI after LVAD implantation have solely relied on (an) increase (in) serum creatinine or need for renal replacement therapy (RRT) in diagnostic formulations. This is most likely due to the retrospective nature of most of these studies, which often lack data on urinary output. However, relying solely on (an increase of) serum creatinine for the diagnosis of AKI can be problematic, especially in critically ill patients. End-stage HF patients who are LVAD candidates, tend to endure muscle wasting, sarcopenia and cachexia resulting in lower creatinine concentration, underestimating the underlying compromised renal function (a limitation that could be possibly overcome by the use of muscle independent biomarkers).(9) Furthermore, volume overload in the decompensated state of heart failure, before LVAD implantation, as well as positive fluid balances in the perioperative phase, can partially obscure an increase of serum creatinine due to dilution.(10)

Table 1. A comparison of the 3 widely used definitions of AKI. These include the RIFLE (risk, injury, failure, loss, end-stage), AKIN (acute kidney injury network) and KDIGO (kidney disease improving global outcomes) criteria.

Table 1 Comparison of **RIFLE**, **AKIN** and **KDIGO** criteria				
	RIFLE	**AKIN**	**KDIGO**	**Urine Output**
Definition of AKI	SCr increase within 7 days and sustained for 24 hours	SCr increase within 48 hours	SCr increase within 48 hours or within 7 days	
Stages of AKI				
Stage 1 (RIFLE = Risk)	SCr increase 1.5-1.9 times baseline	SCr increase 1.5-1.9 or ≧0.3 mg/dL increase	SCr increase ≧0.3 mg/dL within 48 hours or 1.5-1.9 times baseline within 7 days	UO < 0.5 mL/kg/h for 6 hours
Stage 2 (RIFLE = Injury)	SCr increase 2.0-2.9 times baseline	SCr increase ≧2.0-3.0 times baseline	SCr increase 2.0-2.9 times baseline in 7 days	UO < 0.5 mL/kg/h for 12 hours
Stage 3 (RIFLE = Failure)	SCr increase ≧3.0 times baseline or SCr increase ≧ 4 mg/dL (with an acute rise ≧0.5 mg/dL)	SCr increase ≧3 times baseline or SCr increase ≧ 4 mg/dL (with an acute rise ≧0.5 mg/dL) or need for RRT	SCr increase ≧3.0 times baseline or SCr increase ≧ 4 mg/dL or need RRT	UO < 0.3 mL/kg/h for 24 hours or anuria for 12 hours
(RIFLE = Loss)	Need RRT for >4 weeks			
(RIFLE = End-Stage)	Need RRT for >3 months			

Abbreviations: RIFLE: risk, injury, failure, loss, end-stage, AKIN: acute kidney injury network, KDIGO: kidney disease improving global outcomes, SCr: Serum Creatinine, UO: Urine output, RRT: renal replacement therapy

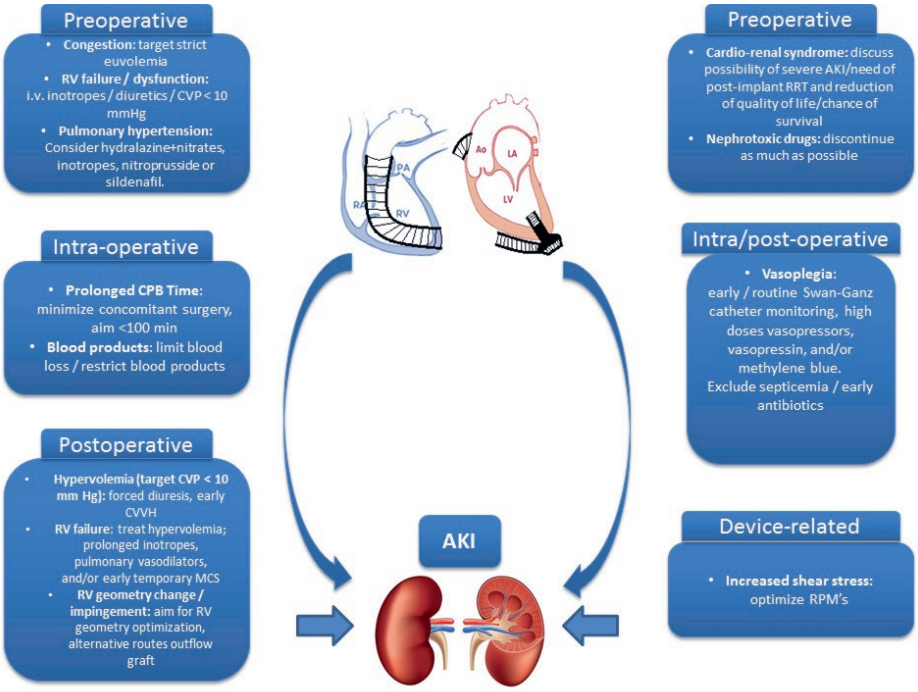
The reported incidence of AKI following LVAD implantation ranges between 11% and 45% in the LVAD population.(4-6, 11-13) However, we recently reported that post-operative AKI is evident in as many as 70% of patients.(7) This broad range reflects variability in definitions of AKI as well as differences in the LVAD population among these studies. This critical limitation hampers the ability to compare and to interpret these results. Nonetheless, AKI following LVAD implantation is regarded as a frequent and life-threatening complication, especially when associated with pre-, and post-operative right-sided ventricular failure (RVF).(14)

Role of (novel) biomarkers of AKI

Recent research has focused on identifying new biomarkers that could predict AKI prior to serum creatinine concentration escalation, the latter being a harbinger sign of sustained damage. Neutrophil gelatinase-associated lipocalin (NGAL), plasma Cystatin-C (CyC) and kidney injury molecule-1 (KIM) have been suggested to predict the development of AKI.(15, 16) Of the aforementioned, only NGAL and Cystatin-C have been assessed in the LVAD population.(17) However, only NGAL showed a promising correlation with irreversible renal dysfunction. NGAL is a protein expressed in the kidney and is an essential component of the antimicrobial innate immune system.(18) Sumida et al. reported that perioperative increase of plasma NGAL predicts the development of severe AKI requiring RRT following LVAD implantation. Furthermore, a subsequent decrease in plasma NGAL concentration predicts

renal recovery from RRT in LVAD patients.(19) However, NGAL was unable to discriminate between non-RRT AKI and no AKI. Biomarkers other than NGAL such as liver fatty acid-binding protein (L-FABP) and interleukin (IL) 18 have been associated with tubular damage yet have never been assessed in the LVAD population.(20) Furthermore, understanding the microvascular derangement during AKI is essential for future development of biomarkers and therapeutics in this complex disease. Microparticles could play a significant role, providing information of imminent AKI before other conventional parameters are elevated. (21) Microparticles are one of the first observable (and measurable) mediators in the renal damage cascade. The early detection of these microparticles could benefit patients who are in the earliest stage of renal damage by adjusting therapy accordingly.

Although the aforementioned approaches appear promising for the early diagnosis of AKI, more prospective studies are needed to validate their clinical role in the prevention and management of postoperative AKI.



Pathophysiology, etiology and risk factors of AKI in LVAD patients

Up to 30% of patients undergoing cardiac surgery experience postoperative AKI.(22) Several factors have been suggested to contribute to the development of postoperative AKI, such as changes in renal perfusion, oxygenation and systemic activation of the inflammatory cascade.(23-26) In addition, prolonged hypoperfusion of vital organs due to postoperative low cardiac output syndrome and vasoplegia, may further reduce renal function.(27)

Lastly, the use of nephrotoxic drugs, (such as vancomycin and some diuretics) which are frequently administered, are associated with AKI.(28-30) Their mechanisms include tubular toxicity, allergic interstitial nephritis and/or vasoconstriction. However, the aforesaid pathways manifest themselves disparately among patients, suggesting that patient specific characteristics also represent a considerable role in the development of AKI (Figure 1).

Preoperative factors

End-stage HF patients often encounter acute-on-chronic or chronic renal failure, the titular 'cardiorenal syndrome', due to venous congestion, and/or forward failure.(31) Pre-implant severe renal dysfunction is associated with an increased rate of mortality.(32) Systemic circulation of inflammatory mediator(s) of end-stage HF patients is speculated to be conductive to decreased renal function prior to LVAD and the onset of AKI. Nonetheless, the clinical significance of this issue has yet to be determined.(33)

Furthermore, a significant subset of patients in addition encounter co-morbidities such as diabetes mellitus, and hepatic dysfunction and metabolic syndrome, which are all associated with the development of AKI.(7, 34-37) We have recently reported that patients with proteinuria pre-LVAD implantation were at a high risk to develop postoperative AKI.(37, 38) Therefore, routine nephrological evaluation, including urinalysis and ultrasound, should be considered in the pre-implant work-up in patients with significant renal failure (e.g. eGFR <60 ml/min). Renal ultrasound should exclude post-renal obstruction and any signs of chronicity for instance small, echogenic kidneys. In patients with high-risk features for renovascular disease, evaluation for bilateral renal artery stenosis could be contemplated. Finally, given the increasing number of DT patients, who are generally older, age warrants extra caution since aging is usually accompanied by decreased physiological reserve. In addition, older age is associated with increased prevalence of co-morbidities, with worse pre- and post-surgical renal function as also as an increased risk of mortality.(39)

Intra-operative factors

Cardiopulmonary bypass (CPB) during cardiac surgery is a recognized contributor to renal failure.(40, 41) It may trigger the systemic inflammatory response syndrome (SIRS) through the blood to artificial CPB circuit surface contact, impairs vasomotor tone, cause temporary alterations in renal perfusion, and/or produce micro-emboli to renal capillaries.(26, 42, 43). Excessive bleeding (>1 liter) and the need for re-exploration are also associated with the development of AKI following LVAD implantation. On the other hand, transfusion of blood products is a known independent risk factor for postoperative AKI in the general cardiac surgery population, attributed to augmenting the pro-inflammatory state.(44-46) Post-LVAD acquired coagulations disorders, surgery related factors and the need for early institution of heparin results in high rates of postoperative bleedings and redo thoracotomy, which is an additional risk factor for AKI.(46-48)

The development of vasoplegia, either intra- or post-operatively, is a more frequently encountered problem after LVAD surgery than after other types of cardiac surgery. The incidences of vasoplegia, up to 50% have been reported in patients receiving continuous flow LVADS and was associated with postoperative AKI.(49, 50). Although norepinephrine is often considered the first line vasopressor, vasopressin was superior in preventing AKI in

post cardiac surgery vasoplegic shock in a randomized trial.(51) Refractory post-operative hypotension can be treated with methylene blue, which acts as an NO inhibitor, to prevent end-organ hypoperfusion and mortality.(52) Alternatively, hydroxocobalamin, an NO scavenger, has been used in vasoplegic shock post LVAD implantation as well.(53) Newer agents include the selective vasopressin 1a receptor agonist selepressin, and angiotensin II. However, further research is expedient to determine the optimal treatment strategy of vasoplegia in LVAD patients.

Device-related factors

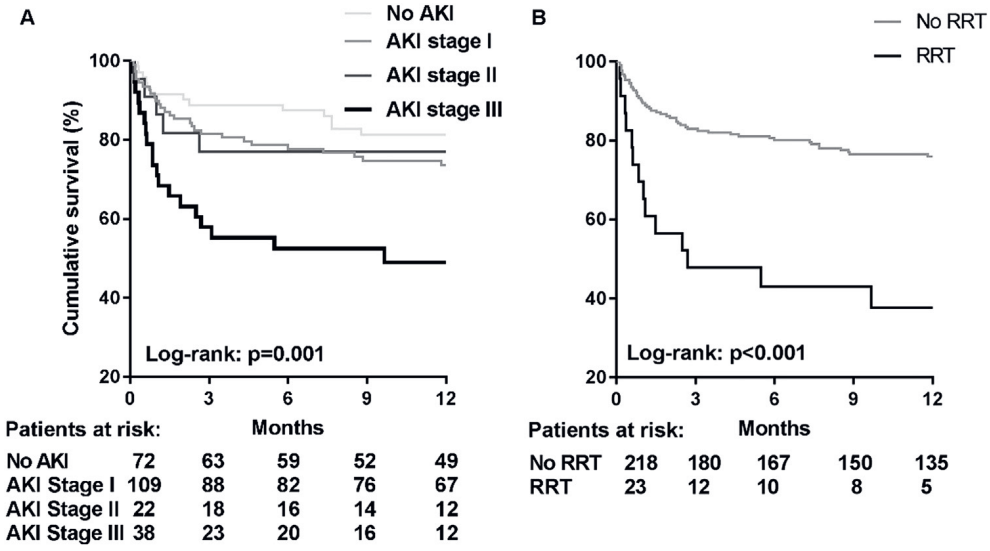
Although early LVAD iterations attempted to mimic the native pumping of the normal heart, providing enhanced arterial pulsatility, contemporary LVADs utilize a more continuous flow with low to no arterial pulsatility. This modality has proven to be superior in terms of survival, lower incidence of disabling strokes and overall device durability.(54) Initial research suggested that differences in blood flow physiology did not influence short-term renal function.(55-57) However, prolonged support with continuous flow has deleterious effects of on renal function.(58, 59) Supplemental research is needed to thoroughly distinguish the effect of continuous blood flow LVAD support in both short-term and at long-term periods. Another potential device related factor is the high shear stress generated within continuous-flow pumps. The high pump speed (up to 10,000 revolutions per minute) lyses erythrocytes and causes the release of free iron into the bloodstream with potential nephrotoxic effects.(60) In addition, high shear stress may reduce erythrocyte oxygen carrying capacity leading to tissue hypoxia within the kidneys and other vital organs. To date there is no optimal treatment or intervention to prevent hemolysis in these patients. Of note, since the introduction of recent device iterations, hemolysis has seen a noticeable decrease suggesting better hemocompatibility.(61)

Post-operative factors

RVF and low LVAD flow are the most important post-operative risk factors suggested to be associated with AKI. Although studies are lacking regarding the onset of AKI due to RVF after LVAD, venous congestion in heart failure and critically ill patients is strongly associated with AKI.(62, 63) Severe RVF occurs in up to 21.7% of patients after LVAD implantation. (14) End-stage HF patients often experience from pulmonary hypertension that causes progressive right ventricle (RV) dilation and deterioration in contractile function. Following LVAD implantation, a dysfunctional RV is unable to handle the increase in preload that improves after initiation of mechanical left ventricle (LV) support. In addition, LV unloading by the LVAD promotes a leftward shift of the septum, altering RV geometry and impairs normal ventricular interdependence, further worsening RV systolic function. Furthermore, the outflow graft of contemporary, LVADs devices may impinge on the RV free wall and deform RV geometry as it reaches the end-to-side anastomosis to the ascending aorta. All these factors may contribute to postoperative RVF, resulting in systemic venous congestion and, eventually, in decreased LVAD output, both affecting the kidneys.(64) . Thus, extra vigilance is warranted to preserve renal function when managing postoperative RVF in LVAD patients. This implies vigorous measures to prevent and treat RVF through early LVAD speed optimization, prolonged inotropic support, proactive pulmonary vasodilation, forced diuresis, early RRT, and/or temporary mechanical circulatory support (MCS).(65)

The impact of AKI on patient outcomes

The development of AKI following LVAD implantation has a detrimental effect on patient outcomes.(7) LVAD patients who experience AKI have a prolonged ICU and hospital admission, and are more likely to develop liver injury and sepsis.(14, 66-68) Patients who have encountered AKI may develop new-onset CKD, and occasionally end-stage disease. (69) Survival rates of AKI following LVAD implantation are far from favorable. Post LVAD implantation AKI is associated with a significantly increased 30 day (between 14% and 18%) and 1-year mortality (between 29% and 40%) in comparison to patients without AKI.(7, 38, 68, 70) Thus, it is inescapable that AKI post LVAD implantation be avoided. Figure 2 illustrates the impact of AKI on LVAD implantation. (6, 43)



Prevention of post LVAD AKI

Preoperative screening

Prevention of AKI commences during the screening of potential LVAD recipients. Selection criteria should include age, co-morbidities including baseline kidney function and proteinuria, INTERMACS profile and RV function. LVAD therapy that precedes the development of hemodynamic instability (i.e. INTERMACS profiles ≥2) should help prevent chronic hypoperfusion of vital organs, and thereby may positively impact post-operative renal function.

Once patients are selected for LVAD therapy, it is critical to proceed to surgery in an ameliorated hemodynamic state, after optimization of central venous pressures (CVP), as

well as RV, liver and renal function. Aiming for a CVP below 10mm Hg seems beneficial, however further research is needed to define the optimal range.(71) Inotropes and/or temporary MCS may be required to realize pre-operative hemodynamic and functional objectives.(72-74)

Intra-operative period

Careful intra-operative management could be important to prevent AKI. However, there is not much research focused specifically on intraoperative management of LVAD patients. Management strategies include targeting adequate mean arterial and perfusion pressure to the kidneys, limiting CBP time, reducing blood loss and preventing the need for re-exploration. As in all cardiac surgery, (episodes of) hypotension should be avoided, although increasing mean arterial pressure to values higher than 60 mm Hg (i.e. 75-85 mm Hg) will not prevent AKI after cardiac surgery.(75) Kidney perfusion on CPB should be sufficient, and lately there have been reports of a decreased incidence of AKI after cardiac surgery by implementing an array of measures, including aspiring to a delivery of above 300 ml O_2/min/m^2 BSA and avoiding mannitol.(76) Minimizing concomitant (valvular) surgery to limit the CPB time to <100 minutes, could prevent the postoperative risk of severe RV failure and subsequent AKI.(14) Moreover, in the case of imminent intraoperative RV failure, an aggressive approach with early temporary RVAD could be necessary.

Post-operative period

Postoperatively, protection of RV function and maintenance of hemodynamic stability and adequate renal perfusion are of paramount importance. Central venous pressure and pulmonary artery pressures should be monitored closely in the early postoperative phase when intravenous fluids are administered. Although specific cut-off values are to be defined, an increase in CVP > 10 to14 mm Hg strongly increases the incidence of AKI in general cardiac surgery, and the latter value may serve as an upper limit, where fluid loading will mostly be counterproductive.(77, 78) A recent report suggest that a chronically increased right arterial pressure (>11 mm Hg) independently predicts AKI after heart transplantation.(79) Inhaled nitric oxide (iNO) and inotropes can be used to prevent and/or treat RVF following LVAD implantation. However, it is important to accentuate that prolonged use of iNO has been associated with the development of AKI in acute respiratory distress syndrome (ARDS) patients.(80) Furthermore, research in ARDS patients indicate that mechanical ventilation should be "RV protective" by applying low positive end-expiratory pressure (PEEP) and avoiding high tidal volume.(81) However, when dealing with refractory RVF after LVAD implantation, utilization of early temporary RV mechanical support could be beneficial. (65, 82, 83)

Management of post LVAD AKI

In spite of preventative preventing measures should AKI occur, monitoring and optimization of hemodynamic status (i.e. CVP, pulmonary artery pressures and cardiac output) remains important to prevent progression of renal damage. Moreover, routine measurement of intra-abdominal pressure (IAP) should be considered, especially in case of abdominal distention, ascites, or discomfort, given the strong association of elevated IAP and impaired renal

function.(84) Nephrotoxic drugs should be discontinued or switched to less toxic alternative agents. If kidney function further declines, RRT (in the form of continuous/intermittent veno-venous hemofiltration) may become necessary to control volume status and metabolic derangement. Hemodialysis is applied for patients with LVADs who do not recover renal function, although peritoneal dialysis has also been utilized.(85) Peritoneal dialysis has several potential advantages when compared to hemodialysis. These include a lower risk for bloodstream infections, a reduced hemodynamic shift, and home-based logistics.(86) To facilitate this, a precise positioning of the driveline is imperative as it may not interrupt the peritoneum. However, patients receiving peritoneal dialysis are at risk for peritonitis and long-term protein loss.(87) Despite RRT, survival rates of dialysis patients on LVAD support are significantly worse, with mortality ranging between 40% and 70%.(6, 11, 12, 88) Early initiation of RRT to mitigate postoperative congestion, could, in theory, salvage renal function and prevent long-term CKD. Further studies are needed to determine the optimal timing of RRT initiation. Furthermore, in terms of fluid removal via RRT, RV function should frequently be assessed (by ultrasound imaging and/or invasive hemodynamic monitoring) and LVAD speed accordingly adjusted, to optimize RV performance and thereby renal perfusion with the goal of preventing additional kidney damage. **Table 2** shows a summary of all the important key point regarding the onset of acute kidney injury following the implantation of a left ventricular assist device.

Table 2. A summary of all the important key point regarding the onset of acute kidney injury following the implantation of a left ventricular assist device.

Key Points on AKI following LVAD implantation
• AKI following LVAD implantation is a frequent, severe complication with the incidence ranging between 11% and 45%. • AKI following LVAD implantation is multifactorial, and can be due to be pre-, intra-, and postoperative interactions. • AKI following LVAD has a detrimental effect on survival, with 30-day mortality ranging between 14% and 18% and 1-year mortality between 29% and 40% • Management of AKI is problematic, and not yet fully elucidated. • Preventing right ventricular failure seems paramount in the prevention of AKI, through LVAD speed optimization, prolonged inotropic support, pulmonary vasodilation, if need forced diuresis or early CVVH, and ultimately temporary MCS. • Prevention of AKI starts at stringent screening of LVAD candidates, especially in elderly patients, severe, irreversible renal dysfunction (i.e. eGFR of <30 ml/min) and INTERMACS profiles 1 or 2. • Novel imaging modalities and biomarkers could probably significantly aid in the accurate diagnosis of patients at risk for AKI.

AKI denotes acute kidney injury; LVAD, left ventricular assist device; RRT, renal replacement therapy; RVF, right ventricular failure; MCS, mechanical circulatory support; INTERMACS, interagency registry for mechanically assisted circulatory support.

Future perspectives

Prevention can be achieved using more stringent selection criteria for LVAD therapy. Especially, elderly patients (>65) with an INTERMACS profile of 1 or 2 and significant comorbidities, and persistent moderate to severe renal dysfunction (i.e. eGFR <30 ml/min) do not seem to be good candidates for the current main-stream continuous-flow LVAD devices. In addition, an early, preemptive implantation strategy in eligible patients, before

they progress to INTERMACS profile 1 to 2, is likely to improve outcomes. Preoperatively optimization of LVAD candidates deemed to be at high-renal risk, using right heart catheterization guidance and, when necessary, intravenous inotropes and/or temporary mechanical circulatory support, could be also beneficial. Intra-operatively, maintenance of adequate kidney perfusion, reduction of CPB time, minimization of blood loss and avoidance of nephrotoxic agents may also prevent AKI. Finally, postoperatively, hemodynamic stability, optimization of RV function, and timely initiation of RRT and RV mechanical support, when necessary, appear important to improve clinical outcomes.

In the future, novel biomarkers of early kidney damage may help to identify patients at risk of developing AKI before changes in serum creatinine occur, and, thereby, to guide timely interventions for kidney protection. Furthermore, engineering enhancements to the pumps may minimize shear stress and possibly restore physiologic pulsatility in the arterial circulation with potential beneficial effect to the kidneys. Lastly, the optimal strategy to support the RV pre- intra- and post-operatively (and thereby the kidneys) remains to be determined.

Conclusion

AKI is a frequent complication of LVAD therapy and carries a profound impact on short- and long-term survival. Several patient and procedure related factors play a major role in increasing the risk of AKI post LVAD implantation. Since an increasing number of older patients (with higher burden of co-morbidities) receive their LVAD as DT, the incidence of postoperative AKI is likely to rise. Therefore, it is of paramount importance to prevent acute kidney injury by early detection and aggressive perioperative management to address contributing causes.

Disclosure Statement

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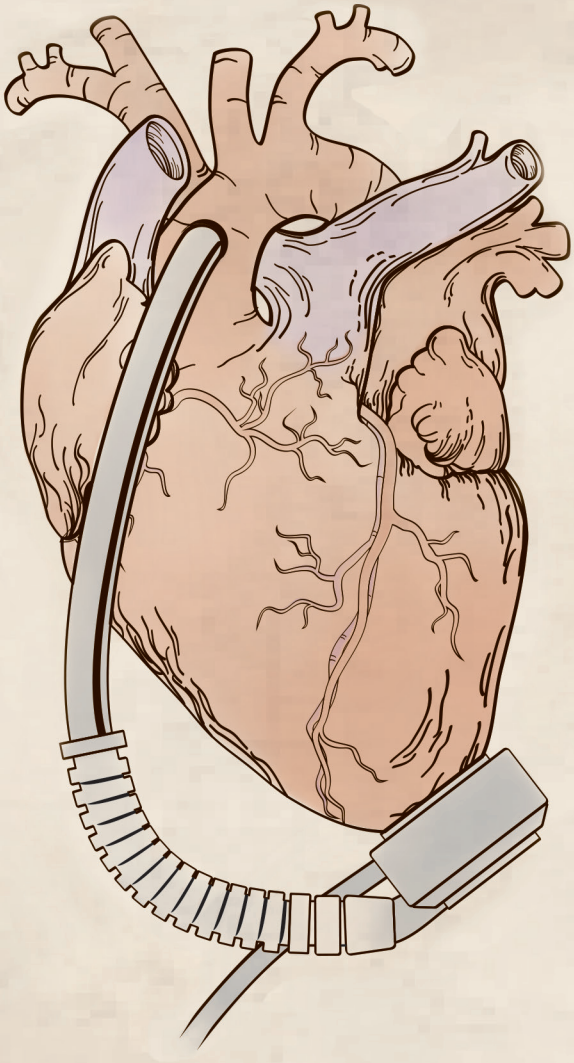

Chapter III

Impact of continuous flow left ventricular assist device therapy on chronic kidney disease: a longitudinal multicenter study

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Abstract

Background: Many patients undergoing durable left ventricular assist device (LVAD) implantation suffer from chronic kidney disease (CKD). Therefore, we investigated the effect of LVAD support on CKD.

Methods: A retrospective multi-center cohort study, including all patients undergoing LVAD (HeartMate II (n=330), HeartMate 3 (n=22) and HeartWare (n=48) implantation. In total, 227 (56.8%) patients were implanted as bridge-to-transplantation, 154 (38.5%) as destination therapy and 19 (4.7%) as bridge-to-decision. Serum creatinine measurements were collected over a 2-year follow-up period. Patients were stratified based on CKD stage.

Results: Overall, 400 patients (mean age 53±14 years, 75% male) were included: 186 (46.5%) patients had CKD stage 1 or 2, 93 (23.3%) CKD stage 3a, 82 (20.5%) CKD stage 3b, and 39 (9.8%) patients had CKD stage 4 or 5 prior to LVAD implantation. During a median follow-up of 179 days [IQR 28-627], 32629 creatinine measurements were available. Improvement of kidney function was noticed in every preoperative CKD stage group. Following this improvement, eGFR regressed to baseline values for all CKD stages. Patients showing early renal function improvement were younger and in worse pre-operative condition. Moreover, survival rates were higher in patients showing early improvement (69% vs 56%, log-rank p=0.013)

Conclusions: Renal function following LVAD implantation is characterized by improvement, steady state and subsequent deterioration. Patients who showed early renal function improvement were in worse pre-operative condition, however, had higher survival rates at 2-years of follow-up.

Introduction

Left ventricular assist devices (LVADs) have become an accepted treatment modality for end-stage heart failure (HF) patients.(1) End-stage HF patients often suffer from end-organ dysfunction, including chronic kidney disease (CKD), which is often attributed to the cardio-renal syndrome.(2) Cardio-renal syndrome type 2, renal dysfunction caused by a number of factors including high central venous pressures and insufficient cardiac output, frequently hampers the quality of life of these patients.(3) They are at risks for developing end-stage renal disease and have higher rates of mortality following LVAD implantation.(4-6)

Following LVAD implantation, several studies have reported that mean renal function improves within the first month.(2,7) However, this mean increase seems to be largely of transient nature, as mean renal function deteriorates subsequent to the improvement. This was largely confirmed by Brisco et al, when they analyzed the interagency registry for mechanically assisted circulatory support (INTERMACS).(2) They noticed a marked improvement of mean renal function following LVAD implantation, and a subsequent deterioration of renal function. The mechanisms as to why and how some patients renal function improves and why most patients subsequently deteriorate is yet to be elucidated. Subsequently, it was hypothesized that perhaps intrinsic renal injury, continuous flow physiology, hemolysis and neuro-hormonal activity could be the reason for this deterioration. Importantly, however, their utilized methodology to depict renal function is limited by the use of means at set points in time and their restricted follow-up period. This methodology favors the renal function of survivors and therefore may not accurately depict the evolution of renal function. There is a great demand for longitudinal assessment of renal function following LVAD implantation. Therefore, the aim of this study was to investigate the impact of prolonged LVAD support on changes in renal function and to identify patient related factors associated with renal function improvement following LVAD implantation.

Methods

Study Design

We retrospectively reviewed all patients who received a LVAD between October 2004 and April 2017 in the Erasmus MC, University Medical Center Rotterdam, Johns Hopkins Hospital, Baltimore, and the Medical University Hospital, South Carolina. Patients with missing data regarding pre-operative and/or post-operative serum creatinine were not included in the analysis (n = 34). The study was approved by the institutional review boards of all participating centers.

Patients were classified into 4 groups based on their preoperative CKD stages. Stages 1 & 2 and stages 4 & 5 were combined into one group (see supplement **Table S1** for the Kidney Disease Improving Global Outcomes (KDIGO) CKD stages).(8)

The primary study outcome was (1) quantification of the evolution of the kidney function and (2) the factors associated with (sustained) renal function improvement during the first 2-years following LVAD implantation using longitudinal data. The secondary outcomes

included all-cause mortality and the association between renal improvement and mortality. Patients were censored at the time of death, heart transplantation (HTx) or explantation of the LVAD.

Data collection

All data was obtained from the electronic patient records. Baseline laboratory values were collected pre-operatively for all patients. Devices included were HeartMate II, Heartmate 3 (Abbott, Chicago, IL) and HeartWare (HeartWare International, Inc). Kidney function was defined as the estimated glomerular filtration rate (eGFR), which was measured regularly during outpatient clinic visits. Samples of serum creatinine were collected over a two-year period to calculate eGFR. In order to validate the calculated eGFR the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used.(9) This formula is GFR = 141 * min(Scr/κ,1)α * max(Scr/κ, 1)-1.209 * 0.993Age * 1.018 (if female) * 1.159 (if black). Renal replacement therapy (RRT) after LVAD implantation was defined as the start of either continuous veno-venous hemofiltration (CVVH) or intermittent hemodialysis. Patients were not excluded if they had received CVVH or hemodialysis before or at the time of LVAD implantation. Early (≤70 days) renal function improvement was defined by either an increase of ≥10 ml/min/1.73m^2 of eGFR or as a ≥50% increase of baseline eGFR within 3 months following implantation. Sustained renal function was defined by maintaining the early improvement following LVAD implantation beyond 12 months.

Statistical Analysis

Continuous parameters are expressed as mean and standard deviation or median inter quartile range (IQR) according to distribution and compared with one-way ANOVA, Student's T-test, or Mann-Whitney U test. Continuous parameters were tested for normal distribution with the Shapiro-Wilk test. Categorical parameters are expressed as number and percentage and compared by Chi2 test or Fisher's exact test. Kaplan-Meier curves stratified by pre-operative CKD stage were constructed for the evaluation of mortality in the first two years post-implantation. Differences pooled over strata were compared by log-rank test

Continuous repeated measurement data were analyzed using mixed-models. Flexibility over time was established using natural splines. In total, 3 internal knots seemed sufficient upon graphical analyses (Supplementary Figure 1). Included random effects were intercepts for patients with random slopes for time. Two models were developed: the first only contained time since implant, the second contained time since implant and CKD stage, with their interaction term. T-tests were used to compare point estimates of CKD stage, derived from the model. The models were visualized by effect plots. Mixed modelling analyses were done in R (R Foundation for Statistical Computing, Vienna, Austria) version 3.3.3 with package "lme4" and "emmeans".(10)

Results

Baseline characteristics

In total, 400 patients were included (75% male, mean age 53±14 years); 84 (21%) patients from the Erasmus MC University Medical Center, 224 (56%) patients from Johns Hopkins Hospital and 92 (23%) patients from the Medical University of South Carolina. The Heartmate II device was most frequently implanted: 330 (82%), followed by the HeartWare device 48 (12%), and 22 (6%) patients received a HeartMate 3 device. The baseline characteristics of the 4 groups are presented in **Table 1**. Stratified according to preoperative CKD stages, 186 (46.5%) patients had CKD stages 1- 2, 93 (23.3%) patients CKD stage 3a, 82 (20.5%) patients CKD stage 3b and 39 (9.8%) patients CKD stage 4 or 5. Patients with a preoperative CKD stage of 1 or 2 were younger ($p < 0.001$), had more frequently a non-ischemic etiology of their cardiomyopathy ($p = 0.03$), and lower rates of implantable cardioverter-defibrillator (ICD) or pacemakers (PM) ($p = 0.02$).

Table 1. Baseline characteristics of patients with pre-operative CKD undergoing LVAD implantation

Variables	All Patients (n=400)	CKD Stage 1 & 2 (n=186)	CKD 3a (n=93)	CKD3b (n=82)	CKD 4 & 5 (n=39)	p-value
Age						<0.001
• <45	99 (25)	69 (37)	18 (19)	8 (10)	4 (10)	
• 45-54	84 (21)	44 (24)	17 (18)	19 (23)	4 (10)	
• 55-64	147 (37)	57 (30)	40 (43)	33 (40)	17 (44)	
• ≥65	70 (17)	16 (9)	18 (19)	22 (27)	14 (36)	
Male gender	298 (75)	125 (67)	74 (80)	68 (83)	31 (80)	0.02
BMI	26 [23-31]	26 [22-31]	26 [23-32]	26 (20-33)	28 [25-33]	0.51
Ischemic Cardiomyopathy	139 (35)	51 (27)	35 (38)	36 (44)	17 (44)	0.03
Diabetes mellitus	157 (39)	73 (39)	31 (33)	31 (39)	22 (56)	0.1
Hypertension	186 (47)	78 (42)	50 (54)	39 (48)	19 (47)	0.3
• ICD/PM	326 (82)	139 (75)	81 (87)	69 (84)	37 (95)	0.01
• TIA or CVA	66 (17)	32 (17)	14 (15)	13 (16)	7 (18)	0.97
• Destination therapy	154 (39)	58 (31)	35 (38)	39 (48)	22 (56)	0.14
• IABP	133 (33)	63 (34)	24 (26)	33 (40)	13 (33)	0.25
• ECMO	20 (5)	13 (7)	3 (3)	4 (5)	0	0.24
Inotropic support	323 (81)	156 (84)	71 (76)	67 (83)	29 (78)	0.45
INTERMACS (n=384)						0.67
• Profile 1	67 (17)	38 (20)	11 (13)	13 (17)	5 (14)	
• Profile 2	120 (30)	53 (29)	27 (30)	27 (36)	13 (37)	
• Profile 3	135 (34)	66 (36)	35 (39)	24 (32)	10 (29)	
• Profile ≥4	62 (16)	28 (15)	16 (18)	11 (15)	7 (20)	
Device type						0.02
• HM 2	330 (82)	162 (87)	74 (80)	61 (74)	33 (85)	
• HM 3	22 (6)	3 (2)	6 (6)	9 (11)	4 (10)	
• HW	48 (12)	21 (11)	13 (14)	12 (15)	2 (5)	
Laboratory values						

• eGFR, ml/ min/1.73m^2	57 [42-79]	81 [69-97]	52 [48-56]	39 [33-42]	24 [21-27]	<0.001
• Creatinine mg/dl	1.40 [1.09-1.79]	1.09 [0.9-1.19]	1.50 [1.40-1.65]	1.95 [1.70-2.10]	2.70 [2.39-3.09]	<0.001
• Blood Urea Nitrogen mg/dl	28 [19-42]	22 [16-30]	30 [24-42]	35 [28-50]	48 [36-63]	<0.001
• Sodium mmol/L	136 [132-139]	135 [131-138]	136 [132-139]	136 [133-140]	136 [132-138]	0.56
• Bilirubin mg/dl	1,1 [0,7-1,8]	1,1 [0,6-1,6]	1,1 [0,8-2,5]	1,1 [0,7-1,7]	1,2 [0,8-1,7]	0.12

HR denotes hazard ratio; CI, Confidence interval; CKD, chronic kidney disease; ICD, implantable cardioverter defibrillator; PM, pace maker; TIA, transient ischemic attack; CVA, cerebrovascular accident; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; INTERMACS, interagency registry for mechanically assisted circulatory support; HM II, Heart mate II; HM 3, Heartmate 3; HW, HeartWare; eGFR, estimated glomerular filtration rate

Evolution of eGFR

During the two years following LVAD implantation, 32,629 measurements of eGFR were collected (CKD stage 1 or 2 group: 15,760 (48.3%), CKD stage 3a group: 7,202 (22%), CKD stage 3b group: 6,854 (21%), CKD stage 4 or 5 group: 2,813 (8.6%)). The mean number of serum creatinine measurements per patient was 82 ± 43. The general evolution of eGFR for all patients is plotted in **Figure 1a**. Model summary is presented in Supplementary Table 2a. The greatest improvement of kidney function was noted at 90 days post LVAD implantation. In addition, kidney function did not differ from baseline at day 210, and the nadir was noted at day 455 after which kidney function plateaued.

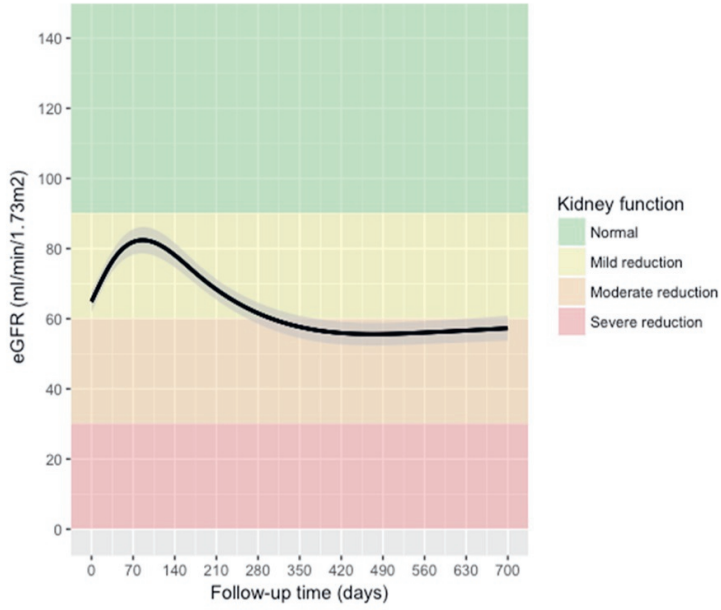
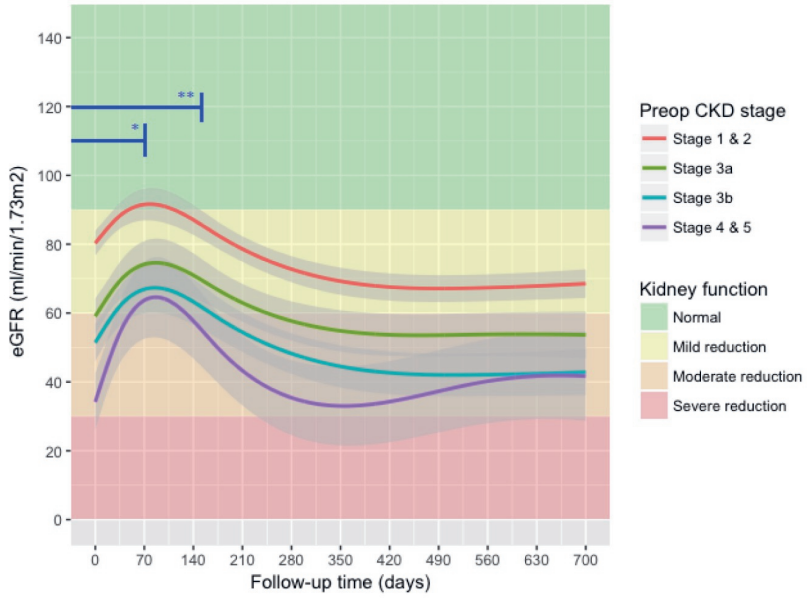


Figure 1a. Advanced mixed modeling illustrating the evolution of overall eGFR over 2 years of follow-up.

Figure 1b depicts the evolution of eGFR stratified by pre-operative CKD stage. Model summary is presented in Supplementary Table 2b. The mean improvement of eGFR at 70 days is 14% in the CKD stages 1 & 2, 25% in CKD stage 3a, 29% in CKD stage 3b and 83% in CKD stages 4 & 5. This improvement remained significant up to day 150 following LVAD implantation for CKD stages 3a, 3b and 4 & 5. Following the first 150 days, all CKD stages regressed towards their respective baseline. None of the preoperative CKD stages remained significantly improved compared to baseline. After 1-year follow-up, the kidney function reached a plateau comparable with the baseline kidney function. Following the 1-year follow-up mark, no significant changes (i.e. improvement or deterioration) were noticed compared to baseline.



Remaining number of patients and serum creatinine measurements in the model above

	Day 1	Day 150	Day 300	Day 450	Day 600	Day 730
CKD 1 & 2	182 pt & 20805 sCr	151 pt & 12313 sCr	130 pt & 9745 sCr	112 pt & 7798 sCr	93 pt & 6067 sCr	81 pt & 5045 sCr
CKD 3a	89 pt & 8642 sCr	Pt 66 & 4064 sCr	49 pt & 2826 sCr	42 pt & 2293 sCr	34 pt & 1902 sCr	30 pt & 1440 sCr
CKD 3b	81 pt & 8602 sCr	Pt 61 & 4257 sCr	57 pt & 3257 sCr	43 pt & 2636 sCr	38 pt & 2191 sCr	31 pt & 1748 sCr
CKD 4 & 5	36 pt & 3494 sCr	Pt 18 & 1515 sCr	14 pt & 1020 sCr	13 pt & 841 sCr	10 pt & 753 sCr	9 pt & 681 sCr

** significant improved mean eGFR for all CKD stages (p<0,001)*
*** significant improved mean eGFR for CKD stage 3a (p=0,002, CKD stage 3b (p=0,001) and CKD stage 4 & 5 (p=0,002)*
CKD denotes chronic kidney disease; pt, patients ; sCr, serum creatinine measurements; eGFR, estimated glomerular filtration rate

Figure 1b. Advanced mixed modeling illustrating the evolution of eGFR over 2 years of follow-up, stratified by preoperative CKD stage.

Early renal improvement

Early renal function improvement was experienced by 230 (57%) of the patients while 160 (40%) experienced no early renal improvement or early renal deterioration and 10 (3%) patients had missing follow-up until day 70. The patients showing early renal improvement were divided as follows: 96 (53.3%) patients had CKD stage 1 & 2, 56 (61.5%) patients were CKD stage 3a, 48 (58.5%) were CKD stage 3b and 30 (81.1%) were CKD stage 4 & 5 (p=0.018). Patients who experienced early renal function improvement were younger of age, had lower mean baseline eGFR and were more often implanted as BTT than DT. Additionally, patients showing early renal function improvement had a higher need of intra-aortic balloon pump (IABP) support and had overall lower INTERMACS scores (i.e. profile 1 or 2) prior to LVAD implantation. The need for ECMO and the need for inotropic support had no effect on renal function improvement. All baseline characteristics differences are noted in **Table 2.**

Sustained renal function improvement was observed in 53 (13.2%) patients. Differences in patients with sustained renal function improvement were younger age (47±14 vs 53±13, p=0.001), higher eGFR (65±27 vs 55±24, p=0.02) and less preoperative diabetes (22.6% vs 41.2%, p=0.01).

Table 2. Differences in baseline characteristics in patients who either experienced renal function improvement or not after LVAD implantation

Variables	Improvement (n=230)	No improvement (n=160)	p-value
Age			0.02
• <45	65 (28)	29 (18)	
• 45-54	43 (19)	41 (26)	
• 55-64	89 (39)	55 (34)	
• ≥65	33 (14)	35 (22)	
Male gender	166 (72)	123 (77)	0.3
BMI	26 [23-31]	27 [23-32]	0.23
Ischemic Cardiomyopathy	76 (33)	62 (39)	0.25
Diabetes mellitus	85 (37)	70 (44)	0.18
Hypertension	107 (47)	76 (48)	0.85
• ICD/PM	190 (83)	132 (83)	0.98
• TIA or CVA	39 (17)	27 (17)	0.99
Destination therapy	78 (34)	72 (45)	0.03
• IABP	89 (39)	40 (25)	0.005
• ECMO	8 (4)	10 (6)	0.2
Inotropic support	184 (80)	131 (82)	0.68
INTERMACS			0.003
• Profile 1	32 (15)	31 (20)	
• Profile 2	81 (37)	36 (23)	
• Profile 3	68 (31)	66 (42)	
• Profile ≥4	36 (17)	25 (15)	
Device type			0.08
• HM II	186 (81)	135 (84)	
• HM 3	26 (11)	21 (13)	

Variables	Improvement (n=230)	No improvement (n=160)	p-value
• HW	18 (8)	4 (3)	
Laboratory values			
• eGFR, ml/min/1.73m^2	53 [41-72]	65 [44-87]	<0.001
• Creatinine mg/dl	1,47 [1,19-1,94]	1,30 [0,99-1,67]	0.005
• Bilirubin mg/dl	1,2 [0,7-1,8]	1,1 [0,6-1,8]	0.73

HR denotes hazard ratio; CI, Confidence interval; CKD, chronic kidney disease; ICD, implantable cardioverter defibrillator; PM, pace maker; TIA, transient ischemic attack; CVA, cerebrovascular accident; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; INTERMACS, interagency registry for mechanically assisted circulatory support; HM II, Heart mate II; HM 3, Heartmate 3; HW, HeartWare; eGFR, estimated glomerular filtration rate

Thereafter, a subset of the cohort was analyzed with pre-operative (max. 30 days prior to implantation) right heart catheterization (RHC) measurements (n=300) (**Table 3a and 3b**). No significant difference in pre-operative RHC measurements between the pre-operative CKD stages was observed. Comparing patients who experienced early renal function improvement to those that did not experience improvement resulted in the following differences: patients who experienced early renal function improvement had lower pre-operative cardiac index, higher mean right arterial pressures, higher right ventricular diastolic pressures higher pulmonary artery diastolic pressures and higher pulmonary capillary wedge pressures.

Table 3a. Baseline right heart catheterization measurements (n=300) for each of the pre-operative CKD stages

Variables	All Patients (n=300)	CKD Stage 1 & 2 (n=141)	CKD 3a (n=68)	CKD3b (n=61)	CKD 4 & 5 (n=30)	p-value
Cardiac output (thermodilution L/min)	3.6 ± 1.1	3.6 ± 1.2	3.4 ± 1.1	3.6 ± 1	3.5 ± 1.2	0.71
Cardiac index (L/min/m^2)	2.7 ± 1.6	2.7 ± 1.5	2.7 ± 1.7	3 ± 1.9	2.1 ± 1.2	0.14
Right atrial pressure (mmHg)	13.1 ± 6.9	13.0 ± 7.0	12.8 ± 6.4	12.6 ± 6.0	15.6 ± 9	0.23
Right ventricular systolic pressure (mmHg)	53 ± 14.8	51.0 ± 14.5	52.5 ± 15.6	56.6 ± 13.8	56.3 ± 15.8	0.09
Right ventricular diastolic pressure (mmHg)	12.7 ± 6.8	12.8 ± 7.4	12.6 ± 6.3	12.3 ± 5.6	13.3 ± 7.4	0.93
Pulmonary artery pressure (mmHg)	37 ± 10.3	36.1 ± 11.1	37.7 ± 10.3	37.2 ± 8.5	39.0 ± 9.7	0.22
Pulmonary artery systolic pressure (mmHg)	53.8 ± 14.9	52.0 ± 15.4	54.2 ± 15.0	55.9 ± 13.7	56.7 ± 14.4	0.89
Pulmonary artery diastolic pressure (mmHg)	28.0 ± 8.8	27.7 ± 9.6	28.4 ± 8.4	27.7 ± 7.5	28.9 ± 8.5	0.48
Pulmonary capillary wedge pressure (mmHg)	25.9 ± 8.8	25.8 ± 9.9	26.4 ± 8.5	25.2 ± 6.4	26.7 ± 8.5	0.85

Table 3b. Differences in right heart catheterizations measurements (n=300) between patients who show early renal function improvement and those who do not improve.

Variables	Renal improvement at 70 days (n=160)	No renal improvement at 70 days (n=140)	p-value
Cardiac output (thermodilution L/min)	3.5 ± 1.2	3.6 ± 1.1	0.97
Cardiac index (L/min/m^2)	2.5 ± 1.5	3.0 ± 1.8	0.02
Right atrial pressure (mmHg)	14.0 ± 7.2	12.0 ± 6.6	0.01
Right ventricular systolic pressure (mmHg)	52.2 ± 14.5	52.0 ± 15.3	0.25
Right ventricular diastolic pressure (mmHg)	13.6 ± 7.3	11.7 ± 6.2	0.02
Pulmonary artery pressure (mmHg)	38.0 ± 9.8	35.8 ± 10.8	0.06
Pulmonary artery systolic pressure (mmHg)	55.0 ± 14.6	52.6 ± 15.3	0.17
Pulmonary artery diastolic pressure (mmHg)	29.1 ± 8.4	26.7 ± 9.0	0.02
Pulmonary capillary wedge pressure (mmHg)	27.0 ± 8.9	24.5 ± 8.7	0.02

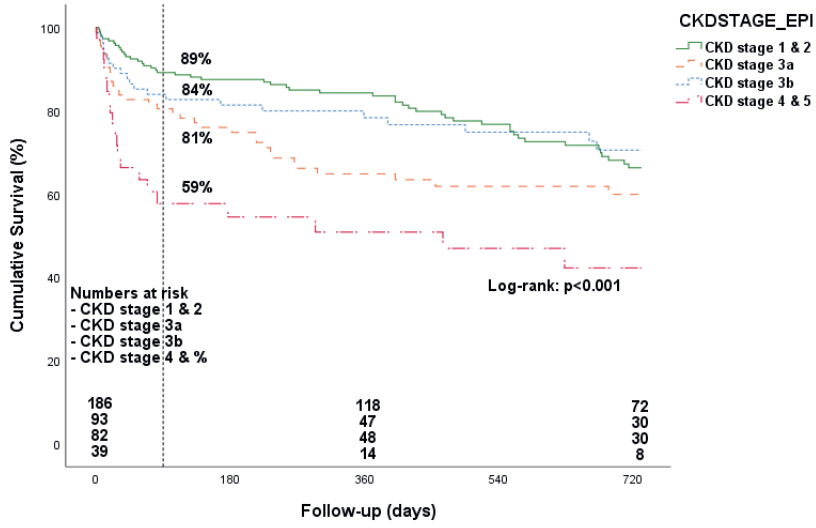


Figure 2. Kaplan Meyer survival curve based on pre-operative CKD stages, illustrating the differences in 2-year survival stratified by preoperative CKD stages.

Clinical course

Overall, 175 patients (44%) died during the first 2 years of follow-up. Stratified by CKD stage the median follow-up time was 244 [34-710] days for the CKD stage 1 & 2 group, 121 [24-481] days for the CKD stage 3a group, 141 [24-593] days for the CKD stage 3b group and 103 [24-409] days for CKD stage 4 & 5 group. The two-year overall survival rate (**Figure 2**) between these respective groups was 58.1% vs 54.8% vs 58.5% vs 46.2% (Log-rank: p<0.001). The 5-year survival Kaplan Meier curves is provided in the **Supplementary Figure 2**. Furthermore, patients with higher CKD stages required more frequently RRT following LVAD implantation, 12% in the CKD stage 1 & 2, 22%, 22%, and 39% in the CKD stage 3a,

stage 3b, and stage 4 & 5 groups (Log-Rank: p<0.001), respectively. **Figure 3** compares the 2-year survival rates for patients who did (69,5%) and did not (56,2%) experience early renal function improvement (Log-rank: p=0.013) respectively. Finally, patients with sustained renal function improvement were identified (n=53). Patients with sustained renal function improvement were younger of age (p=0.01), had lower rates of diabetes mellitus (p=0.01), had higher baseline eGFR (p=0.01) and higher mean diastolic pulmonary pressures (p=0.02).

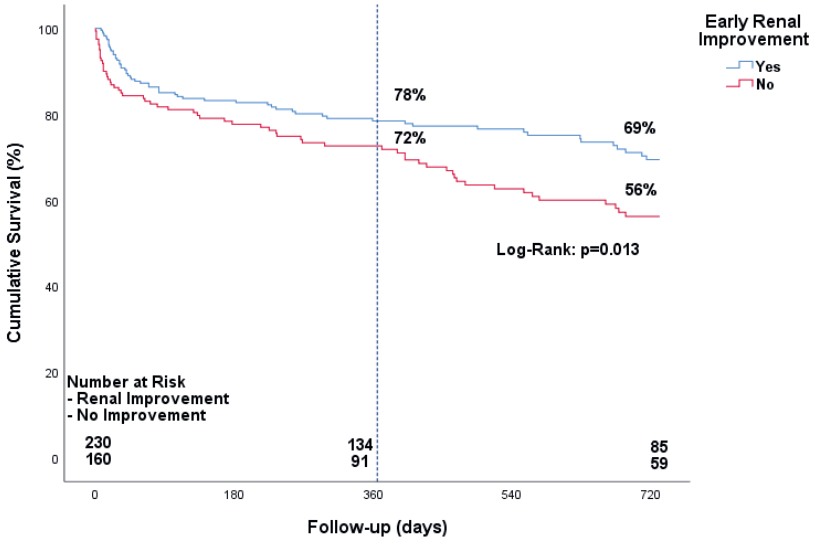


Figure 3. Kaplan Meyer survival curve based on post-operative early renal function improvement, illustrating the differences in survival.

Discussion

The current study evaluated the impact of prolonged LVAD therapy on kidney function. Our principal findings are as follows: (1) Following LVAD therapy, all patient groups (in all pre-operative CKD stages) experienced a significant early mean renal function improvement and subsequent regression to baseline. At 1-year of follow-up, all patient groups have mean renal functions similar to their respective mean baseline eGFR's. (2) Patients who experience early renal function improvement are younger, have higher pre-operative CKD stages, lower INTERMACS scores and worse hemodynamic profiles. (3) Patients who experience early renal function improvement have higher 2-year survival rates than patients who do not experience improvement. These results underline the transient nature of renal function improvement in all pre-operative CKD stages. However, despite the observed transient nature, early renal function improvement is associated with higher survival rates at 2-years of follow-up.

The next step in personalized medicine is considering and examining all available data. The appropriate methodology to accurately depict changes takes all individual measurements into consideration. This allows for the use of mixed modelling analyses, depicting more accurate evolutions. This novel approach adjusts both the correlation between patients, and the correlation between measurements of the same patient. Moreover, it adjusts, to a certain degree, for missing data and mortality. This methodology yields the most accurate depiction of renal function evolution following LVAD implantation.

The different phases of renal function

We confirm that the evolution of renal function can be divided into 3 phases. The first phase is characterized by a marked improvement in renal function, which is proportionally greater in patients with higher CKD stages. This phase transpires in the first 70 days following LVAD implantation. Improvement of renal function is most likely driven by improved cardiac output and relief of venous congestion. In HF patients, venous congestion is one of the major factor that drives worsening renal function.(11) Indeed our results show that patients with higher pre-operative right atrial pressures, which is closely linked to central venous pressure, were more likely to show early renal function improvement.

The second phase marks the renal recovery phase. This phase initiates following the renal improvement phase and concludes at approximately 150-day of follow-up. This phase represents an opportunity to maintain the regained function from the first phase for as long as possible, perhaps by adjusting the LVAD parameters to provide optimal output, closely monitoring the fluid status and by monitoring/optimizing right ventricle (RV) function.

Lastly, the deterioration phase sets in. This phase is noticed in all baseline CKD stages, suggesting a multifactorial determinant, and could be inherent to contemporary LVAD therapy. Being the most poorly understood phase, various hypotheses have been proposed. One postulated mechanism for renal function deterioration is worsening of RV function. Longitudinal studies have yield mixed conclusions on this phenomenon, with some showing improvement in RV function over time and others the opposite.(12,13) Unfortunately, the effects of post-operative RV dysfunction/failure on kidney function in LVAD patients remain poorly understood.(14) Other postulated mechanisms include dysregulation of the baroreceptors, a local up-regulation of the renin-angiotensin system and possible hyper filtration.(15-17) Additionally, shear stress caused by the mechanical suction (inducing hemolysis) could cause chronic renal ischemia, nephrotoxity and pro-apoptosis of renal tubular epithelial cells.(18) Lastly, the prolonged use of anticoagulation, in the form of warfarin, may be associated with the onset anticoagulant related nephropathy.(19) Future prospective studies are necessary to elucidate the delicate mechanisms behind renal function deterioration.

Survival

Unfortunately, not all individuals experience renal function improvement following LVAD implantation. We found early improvement present in 59% of patients. These patients were younger, were implanted under worse conditions (i.e. needing IABP support, overall lower INTERMACS scores and worse hemodynamic profiles), and had worse pre-operative renal function. The findings are consistent with a group of patients suffering from type 2

cardio-renal syndrome.(3) Interestingly, subsequent survival rates were higher in patients experiencing early renal function improvement, despite its transient nature. Renal function improvement was linked with superior outcomes compared to those with no improvement, regardless of LVAD implantation indication. (Supplementary material 5). This distinction is of paramount importance due to the increasing number of LVAD candidates who are implanted with acute renal dysfunction, cardiogenic shock, and seemingly worse renal function. Lastly, sustained renal function improvement was observed in 13% of all implanted patients. Older diabetic patients with worse pre-operative renal functions were more frequently associated with non-sustained renal function improvement. Evidently, earlier studies reported that pre-operative proteinuria (often seen in diabetic patients) is independently associated with an increase in RRT and worse survival rates.(5,6) This finding alludes to intrinsic pre-operative renal damage, most likely caused by diabetic nephropathy. More research is needed to further elucidate factors associated with sustained renal function following LVAD implantation.

Clinical perspectives

The trend of eGFR after LVAD implantation displays an initial improvement of overall mean eGFR. However, subsequent to this improvement, a regression in overall mean eGFR to the baseline is noticed in all patient groups, regardless of eGFR function prior to LVAD implantation. Nonetheless, early renal function improvement is associated with better survival rates following LVAD implantation. Therefore, sole severe renal dysfunction (eGFR <45), should not exclude candidacy for LVAD implantation. Selection criteria should include age, the primary presentation, the setting of LVAD implantation (emergent or elective), the baseline renal function and concomitant hemodynamic profile (renal venous congestion and/or forward failure). Those with the most severe hemodynamic derangements are most likely to benefit. Additional research is warranted to identify which factors predict, and what the underlying mechanisms are for sustained renal function improvement post LVAD implantation.

Strengths & limitations

There are a number of limitations that should be taken into consideration when interpreting our findings. First, due to the retrospective study design, causality cannot be established. Second, the CKD stages 4 or 5 group consisted of a relatively small number of patients, possibly affecting the outcome of the analysis by overestimating their survival. Third, this cohort consisted mostly of INTERMACS class 1 & 2 patients, which has resulted in a rather higher 2-year mortality rate. This may have affected the evolution of renal function. Forth, not all patients had RHC data 30 days prior to LVAD implantation. In order to uphold the predictive value of the measurements, the only 300 patients, with prior 30-day RHC data, could be analyzed. This should be taken into consideration when reading the results. Fifth, clinicians are not blinded to changes in renal function and treat patients accordingly, therefore possibly altering the clinical outcomes. Fourth, the lack of postoperative hemodynamic measurements hinders our ability to associate late hemodynamic profile changes to renal function deterioration. Lastly, using serum creatinine based GFR estimations in a population suffering from muscle wasting, and subsequent gain of muscle after LVAD implantation, can over- and/or underestimate the impact of changes in serum creatinine. Unfortunately, no other renal function estimation biomarkers like cystatin C or 24-hour urine creatinine

clearance, were available. However, due to the longitudinal approach, instead of using means over set points in time, a more accurate evolution of renal function, was possible. In addition, inclusion of all available contemporary types of CF-LVADs and multicenter, transatlantic patients, strengthens in our opinion the conclusions and generalizability of this study.

Conclusion

Renal function following LVAD implantation shows a triphasic pattern characterized by significant early improvement, a period of steady state function and subsequent deterioration to baseline. Patients with early renal function improvement were younger, had worse pre-operative condition and CKD stages, but with better survival rates at long-term FU.

Disclosure Statement

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Legend

Supplement 1 (Table.) Stages of CKD according to the Kidney Disease Improving Global Outcomes criteria

Supplement 2 (Figure 1.) Visualization of subject-specific prediction of 9 randomly chosen patients of a model containing time with a spline function using 4 knots (red line) and a model containing 3 knots (blue line). The blue and red line overlap considerably. It seems that 3 knots are sufficient to make adequate predictions.

Supplement 3 (Table 2a & 2b.) Model summary depicting the individual time points used to determine the p-values (compared to time = 0, and in table 2b, compared to CKD stages 1 & 2) of the of the mixed model figures 1 and 2.

Supplement 4 (Figure 2) Kaplan Meier Curve based on pre-operative CKD stage, illustrating the differences in 5-year survival stratified by preoperative CKD stages.

Supplement 5 (Figure 3) Competing outcomes (mortality, explantation or alive) for patients with either a bridge-to-transplantation indication, with (A) and without (B) renal function improvement, or destination therapy indication, with (C) and without (D) renal function improvement.

Supplement 1

Table 1

GFR	CKD stage	Kidney function
≥90	1	Normal
60-89	2	Mild reduction
45-59	3a	Mild-moderate reduction
30-44	3b	Moderate-severe reduction
15-29	4	Severe reduction
<15	5	Kidney failure

GFR denotes glomerular filtration rate; CKD, chronic kidney disease.

Supplement 2

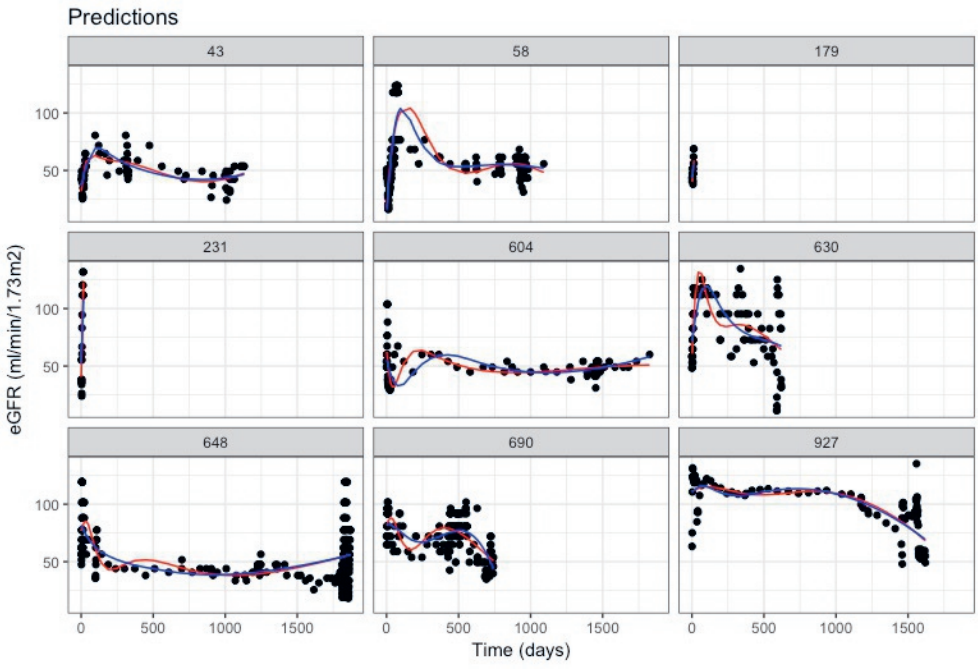


Figure 1

Supplement 3.

Table 2a

Summary model for figure 1	Value	Standard Error	p-value
Intercept	66,47	1,56	<0,001
Time 1*	-11,42	1,9	<0,001
Time 2*	-17,91	2,39	<0,001
Time 3*	17,16	5,6	0,002
Time 4*	-9,38	6,52	0,15

*Flexibility over time was estimated using a spline function which splits the dataset a certain points (knots). Therefore, there are multiple line segments for time, which each have their own coefficient. In this case three knots are used, resulting in 4 line segments and thus 4 coefficients for time.

Table 2b

Summary model for figure 2	Value	Standard Error	p-value
Intecept	81,28	1,8	<0,001
Time 1 *	-14,18	2,71	<0,001
Time 2 *	-21,5	3,15	<0,001
Time 3 *	11,69	6,61	0,077
Time 4 *	-0,2	8,73	0,981
Preoperative CKD Stage 3A	-20,95	3,15	<0,001
Preoperative CKD Stage 3B	-28,57	3,23	<0,001
Preoperative CKD Stage 4 & 5	-44,6	4,42	<0,001
Time 1:Preoperative CKD Stage 3A **	5,1	4,93	0,301
Time 2:Preoperative CKD Stage 3A **	11,49	6,82	0,092
Time 3:Preoperative CKD Stage 3A **	-8,14	13,55	0,547
Time 4:Preoperative CKD Stage 3A **	-32,83	20,92	0,116
Time 1:Preoperative CKD Stage 3B **	3,82	4,97	0,442
Time 2:Preoperative CKD Stage 3B **	1,48	6,31	0,814
Time 3:Preoperative CKD Stage 3B **	4,02	12,92	0,755
Time 4:Preoperative CKD Stage 3B **	-5,74	18,74	0,759
Time 1:Preoperative CKD Stage 4 & 5 **	-4,23	8,29	0,609
Time 2:Preoperative CKD Stage 4 & 5 **	40,62	13,01	0,001
Time 3:Preoperative CKD Stage 4 & 5 **	-11,91	24,01	0,619
Time 4:Preoperative CKD Stage 4 & 5 **	-105,66	40,91	0,009

*Flexibility over time was estimated using a spline function which splits the dataset a certain points (i.e. knots). Therefore, there are multiple line segments for time, which each have their own coefficient. In this case three knots are used, resulting in 4 line segments and thus 4 coefficients for time.
** Each time segment was allowed to have a different slope in the three groups of preoperative CKD stage, estimated with the interaction term of time*preoperative CKD stage

Supplement 4

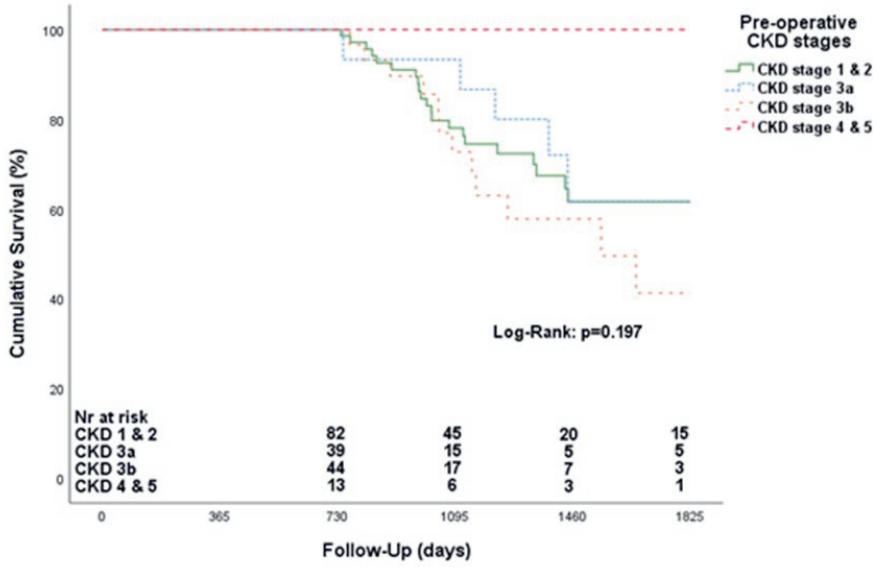
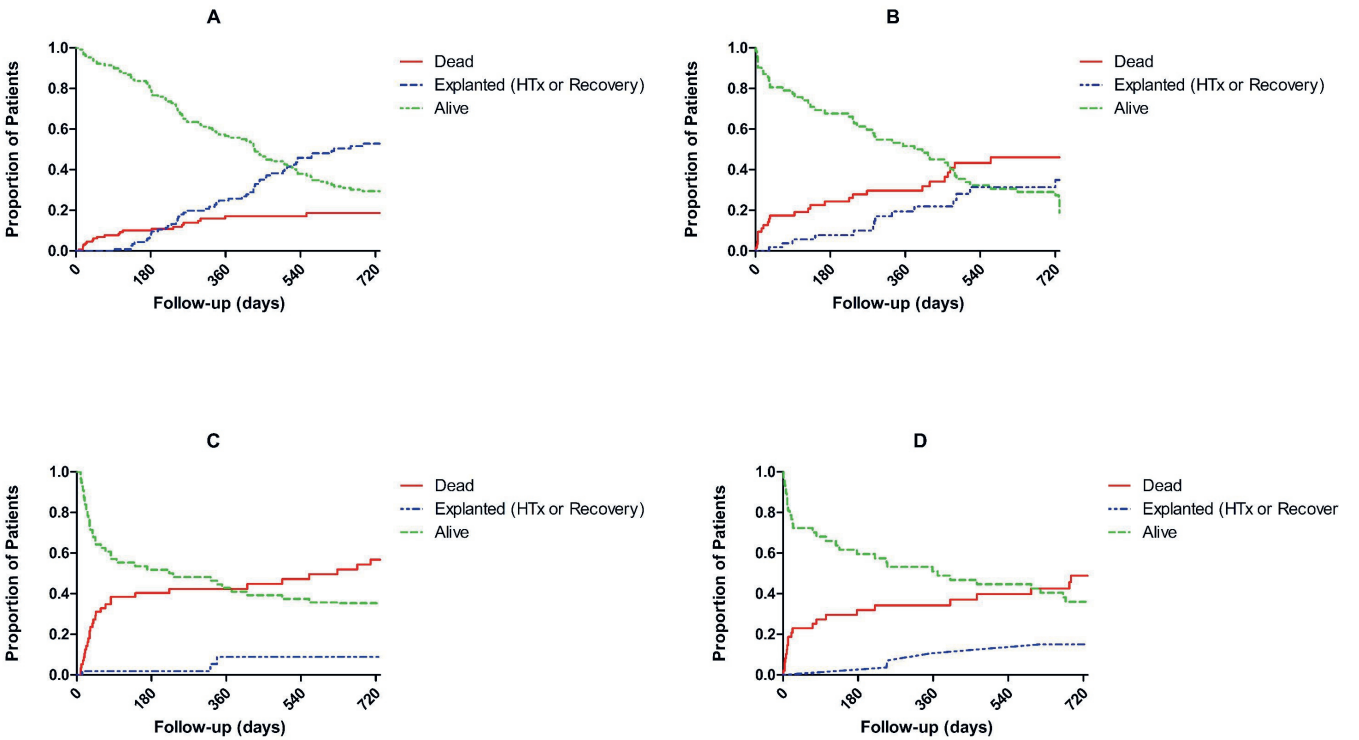
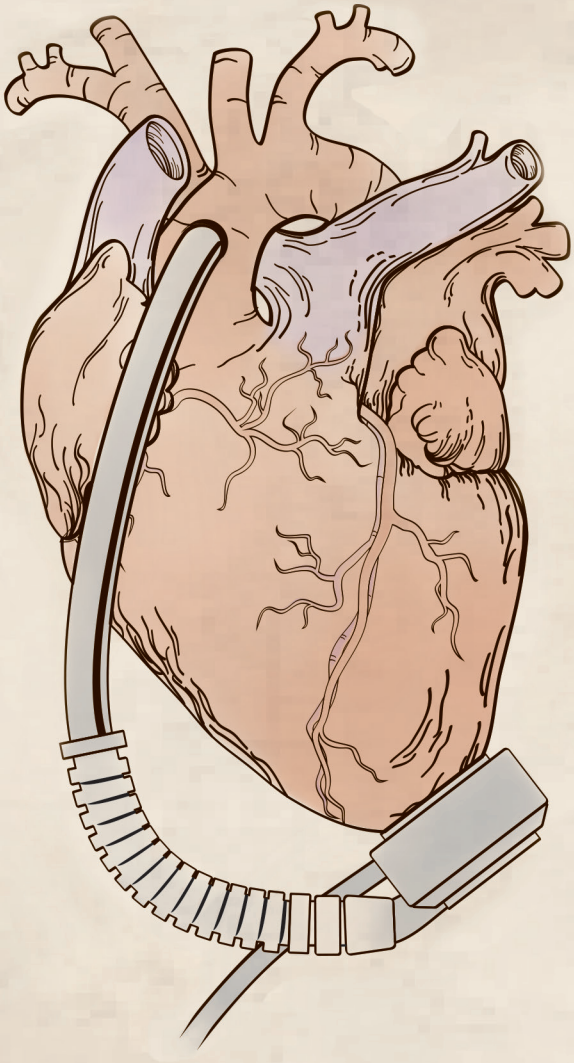


Figure 2

Supplement 5

Figure 3A, B, C, D





Chapter IV

Impact of pre-operative liver dysfunction on outcomes in patients with left ventricular assist devices

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Abstract

Objectives: In the current study, we evaluated the impact of pre-operative liver function on early and 1-year postoperative outcomes in patients supported with a left ventricular assist device (LVAD), and subsequent evolution of liver function markers.

Methods: A retrospective multicenter cohort study was conducted, including all patients undergoing continuous flow LVAD implantation. The definition of model for end-stage liver disease (MELD) score was used to define liver dysfunction.

Results: Overall, 290 LVAD patients (78% HeartMate II, 15% HVAD, and 7% HeartMate 3, mean age 55 [18], 76% male) were included. Over 40000 measurements of liver function markers were collected over a 1-year period. A receiver operating characteristics curve analysis for 1-year mortality rate identified the optimal cutoff value of 12.6 for the MELD-score. Therefore, the cohort was dichotomized into patients with a MELD-score of below or higher than 12.6. Early (90-days) survival rate in patients with and without liver dysfunction was 76% and 91% ($p=0.002$), and at 1-year 65% and 90%, respectively ($p<0.001$). Furthermore, pre-operative liver dysfunction in patients was associated with more embolic events and more re-explorations. At 1-year follow-up, liver function markers showed overall improvement in the majority of patients, with or without pre-LVAD liver dysfunction.

Conclusions: Pre-operative liver dysfunction is associated with higher early 90-days and 1-year mortality rates after LVAD implantation. Furthermore, liver function ameliorated in both patient groups. It has become imperative to optimize the selection criteria for possible LVAD candidates, since those who survive the first year show excellent recovery of their liver markers.

Introduction

In end-stage heart failure patients (HF), continuous flow left ventricular assist devices (CF-LVAD's) are increasingly used as bridge-to-transplantation or as destination therapy.[1] Although the overall clinical outcomes of the second and third generation LVAD's are favorable, patient selection for LVAD therapy is still sub-optimal given the considerable morbidity and mortality.[2] Many of these end-stage HF patients have signs of hepatopathy due to the systemic hypoperfusion and passive congestion of the liver, most likely due to increased systemic venous pressure.[3,4] Prior studies showed that pre-operative liver dysfunction in LVAD patients is associated with worse survival and adverse events including the onset of right ventricle failure, acute kidney injury and bleedings. [5,6]

The Model for End-Stage Liver Disease (MELD), a score to assess liver function, was developed to predict mortality in patients undergoing trans-jugular intrahepatic portosystemic shunt procedure. The score includes 3 parameters: serum creatinine, total bilirubin, and international normalized ratio.[7] Following its introduction, the MELD-score has been utilized in the cardiac population, predicting mortality in patients undergoing cardiac surgery and heart transplantation. [8,9] This has led to the utilization of the MELD-score in LVAD patients, in order to asses liver function and to predict mortality.[5,10] However, the question whether liver function changes following the initial pre-operative MELD-score assessment is unknown.

Therefore, the aim of this study was to determine the association of pre-operative liver dysfunction with early (90-days) and 1-year mortality in LVAD patients. Subsequently, we aimed to depict the evolution of several liver function markers following the initial MELD-score assessment.

Materials and Methods

Study design

We conducted a retrospective multicenter cohort study including all patients with available baseline laboratory data implanted with a Heartmate II, Heartmate 3 (Abbott, Chicago, IL), and HVAD (Medtronic HeartWare, Framingham, USA) CF-LVAD between October 2004 and April 2017 in two participating tertiary referral centers. Clinical and laboratory data was obtained from a computerized database and electronic patient files. Pre-operative laboratory values were defined as the last available set of results prior to LVAD implantation. This study was approved by the institutional review board of the Erasmus MC, University Medical Centre, Rotterdam, the Netherlands and the Johns Hopkins Hospital, Baltimore, Maryland.

Endpoints

The primary endpoint was all-cause mortality, early (90-days) and 1-year post LVAD implantation. Secondary outcomes were neurologic events, re-explorations and the evolution of liver function markers in patients with and without pre-LVAD liver dysfunctions.

Liver function assessment was based on pre-implantation values of total bilirubin, albumin as well as the MELD-score modification used by the United Network for Organ Sharing: 3.78 × ln(bilirubin) + 11.2 × ln(INR) + 9.57 × ln(Creatinine) + 6.43.[11] Evaluation for possible liver cirrhosis was done at the discretion of the treating physician. A receiver operating characteristic (ROC) curve analysis was performed for the 1-year mortality rates for the MELD scoring system. The Youden Index was calculated from the MELD-score ROC curve analysis to establish the optimized cohort cutoff point.

Statistical analysis

Continuous parameters are expressed as median and interquartile range or mean and standard deviation, depending on the distribution, and were compared by Student's t-test or Mann-Whitney U test. The normality of data was assessed by performing the Shapiro-Wilk test. Categorical parameters were expressed as number and percentage and compared by Chi2 test or Fisher's exact test (if any of the expected cell sizes was ≤5) for association. Kaplan-Meier curves stratified by liver function were constructed for the evaluation of mortality in the first year after CF-LVAD implantation. Differences were compared by log-rank test. A ROC curve analysis was conducted to determine the optimal cutoff MELD-score value for predicting mortality. A multivariable Cox proportional hazards analysis was performed for the identification of parameters associated with mortality. Variables were included in the multivariable models if $p \leq 0.20$ in the univariate analysis. All multivariable models were constructed by using the enter method. Two-tailed $p < 0.05$ was considered statistically significant. Analyses were performed using the SPSS statistical software package, version 24.0 for Mac (SPSS Inc., IBM company, Chicago, IL) and GraphPad Prism version 5.0a for Mac (GraphPad Software, La Jolla, CA).

Mixed modelling

Continuous repeated measurement data were analyzed using mixed-models with the maximum likelihood estimator. Flexibility over time was established by using natural splines. Included random effects were intercepts for patients with random slopes for time. A backwards selection procedure was applied using Akaike information criterion and Bayesian information criterion to select the number of splines for time in the random effect. Likelihood ratio tests were used to compare nested models. The model was visualized by effect plots. Statistical analyzes were done in R (R Foundation for Statistical Computing, Vienna, Austria) version 3.3.3 with package "lme4". [12]

Results

In total, 290 patients received a LVAD (77% male, mean age 55 [IQR 18]): 225 (78%) patients received a Heartmate II device, 43 (15%) patients received a HVAD, and 22 (7%) patients received a Heartmate 3 device. The baseline characteristics of the patients are presented in **table 1**. None of the implanted patients had preoperative signs or symptoms of liver cirrhosis. Postoperatively, 15 (6%) patients required a temporary right ventricular assist device, 110 (38%) patients needed re-exploration due to early bleedings and 38 (13%) experienced a neurologic event. After one year of LVAD support, 216 (75%) patients were still alive. In total, 41 (14%) patients were successfully transplanted after LVAD implantation.

In a univariable cox regression analysis, age, gender, body mass index, a pervious coronary artery bypass graft, pre-implantation need for intra-aortic balloon pump (IABP), interagency registry for mechanically assisted circulatory support (INTERMACS) profile 1 and 2, destination therapy and the HeartMate II were all predictors of mortality within one year after LVAD implantation (**Table 2**). Laboratory data, significantly associated with mortality at one year, included total bilirubin, creatinine, albumin, international normalized ratio, and the MELD-score.

Table 1. Baseline characteristics of the study population

Table 1	
Baseline characteristics	**All patients (n=290)**
Age	55 [18]
Male	221 (76%)
Body mass index	25 [8]
Non-ischemic cardiomyopathy	188 (65%)
Hypertension	131 (45%)
CABG	33 (11%)
ICD/PM	237 (82%)
TIA/CVA	53 (18%)
Atrial fibrillation	114 (39%)
IABP	114 (39%)
ECMO	17 (6%)
INTERMACS	
• Profile 1	60 (21%)
• Profile 2	104 (35%)
• Profile 3	63 (22%)
• Profile 4 and up	63 (22%)
Indication	
• Bridge-to-transplant	182 (63%)
• Destination therapy	108 (37%)
Device	
• HeartMate II	225 (78%)
• HVAD	43 (15%)
• HeartMate 3	22 (7%)
Lab values (mg/dl)	
• Total bilirubin	1.3 [1.4]
• INR	1.3 [0.5]
• Creatinine	1.4 [0.8]
• AST	30 [31]
• ALT	32 [31]
• Albumin	3.6 [0.8]
• MELD-Score	15.1 [7.7]

Continuous variables are presented as median [interquartile range], Categorical variables are presented as numbers (percentage). ALT denotes Alanine transaminase; AST, Aspartate transaminase; CABG, Coronary artery bypass graft; CVA, Cerebrovascular accident; ECMO, Extracorporeal membrane oxygenation; IABP, Intra-aortic balloon pump; ICD, Implantable cardioverter defibrillator; INR, International normalized ratio; INTERMACS, Interagency registry for mechanically assisted circulatory support; MELD, model for end-stage liver disease; PM, Pacemaker; TIA, Transient ischemic attack

Table 2. Univariable cox hazard analysis of variables predicting mortality within 1-year post-implantation

Table 2			
Variable	**HR**	**CI**	**P-Value**
Age	1.02	1.00 – 1.04	**0.024**
Gender (male)	1.99	1.04 – 3.77	0.035
Body Mass Index	1.02	1.00 – 1.04	**0.051**
Etiology (Non-Ischemic)	0.97	0.60 – 1.57	0.919
Hypertension	1.21	0.77 – 1.91	0.404
CABG	1.68	0.90 – 3.12	**0.098**
TIA/CVA	1.04	058 – 1.61	0.89
Atrial fibrillation	1.26	0.80 – 2.00	0.331
IABP	1.94	1.23 – 3.07	**0.004**
ECMO	1.08	0.39 – 2.97	0.870
INTERMACS			
• Profile 1	5.87	2.57 – 13.3	**<0.001**
• Profile 2	2.53	1.10 – 5.82	**0.028**
• Profile 3	1.56	0.59 – 4.10	0.367
• Profile 4 and up	1.00	-	-
Indication			
• Bridge-to-transplant	1.00	-	-
• Destination therapy	2.92	1.81 – 4.70	<0.001
Device type			
• HeartMate II	2.93	0.71 – 11.99	**0.134**
• HVAD	2.45	0.53 – 11.99	0.247
• HeartMate 3	1.00		
Laboratory data (mg/dl)			
• Creatinine (Per unit increase)	1.40	1.07 – 1.82	**0.012**
• Total bilirubin (Per unit increase)	1.15	1.06 – 1.26	**0.001**
• Albumin (Per unit decrease)	1.64	1.16 – 2.30	**0.004**
• INR (Per unit increase)	1.13	0.99 – 1.30	**0.061**
• AST (Per unit increase)	0.99	0.99 – 1.00	0.661
• ALT (Per unit increase)	1.00	0.99 – 1.00	0.957
• MELD (Per unit increase)	1.06	1.02 – 1.10	**0.001**
• MELD <12.6	1	-	-
• MELD ≥12.6	3.76	1.93-7.34	**<0.001**

ALT denotes Alanine transaminase; AST, Aspartate transaminase; CABG, Coronary artery bypass graft; CI, Confidence interval; CVA, Cerebrovascular accident; ECMO, Extracorporeal membrane oxygenation; HR, Hazard Ratio; IABP, Intra-aortic balloon pump; ICD, Implantable cardioverter defibrillator; INR, International normalized ratio; INTERMACS, Interagency registry for mechanically assisted circulatory support; MELD, model for end-stage liver disease; PM, Pacemaker; TIA, Transient ischemic attack

A receiver operating characteristics curve analysis was performed for both the 90-day and 1-year mortality rates for the MELD scoring system to determine the optimal cutoff value. The 90-day mortality rate gave a cut-off value of MELD 15.0 with a sensitivity of 70% and specificity of 54% with an area under the curve of 0.62. The 1-year mortality rate gave a cutoff value for the MELD-score was established at 12.6, with a sensitivity of 87% and a specificity of 40% with an area under the curve of 0.63. Therefore, the cohort was dichotomized,

dividing patients with a MELD-score of <12.6 or ≥ 12.6 (**Figure 1**). Subsequently, the MELD-score <12.6 and ≥12.6 were added to the univariate analysis. The MELD-score of ≥12.6 was a significant predictor in the univariable analysis and therefore added to the multivariable analysis.

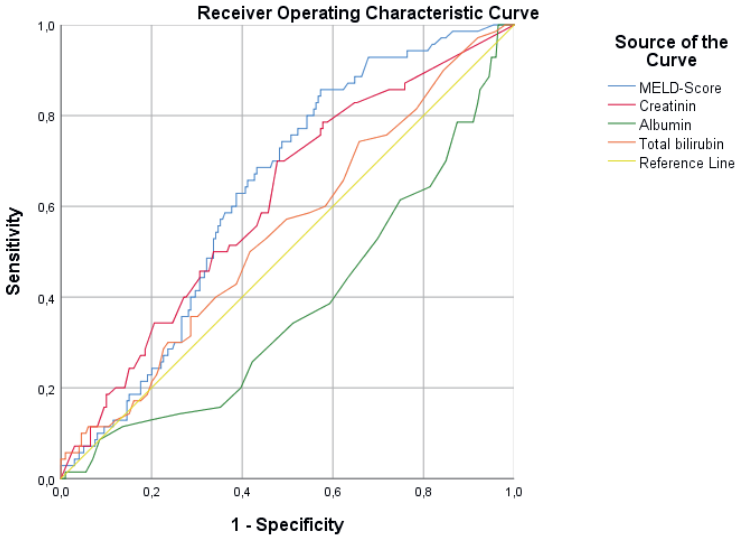


Figure 1. Receiver operating characteristics curve analysis performed for 1-year survival for the MELD-score system and accompanying area under the curve

In multivariable cox regression analyses, age, body mass index, INTERMACS profile 1, destination therapy, a decrease in albumin and a MELD-score of ≥12.6 were all independent predictors of mortality within 1-year after LVAD implantation (**Table 3**).

Patients with a MELD-score ≥ 12.6 were more often male, had higher percentage of implanted cardioverter-defibrillators or pacemakers and were more often in need of pre-operative IABP support. Accordingly, the patients with a MELD-score ≥ 12.6 had worse INTERMACS profiles, higher total bilirubin, international normalized ratio (INR), serum creatinine and alanine aminotransferase (ALT) prior to implantation. (**Table S1**) Patients with a MELD-score ≥12.6 had a significant worse early 90 days and 1-year survival compared to patients with a MELD-score <12.6 following LVAD implantation (**Figure 2**). Additionally, patients with a MELD-score ≥12.6 had a significantly higher neurological event rate and higher rate of re-explorations (**Table 4**).

Table 3. Multivariable cox hazard analysis of variables predicting mortality within 1-year post-implantation

Table 3				
Variable	**HR**	**CI lower 95%**	**CI Upper 95%**	**P-Value**
Age	1.031	1.007	1.054	0.01
Gender (male)	1.541	0.77	3.084	0.222
Body Mass Index	1.033	1.013	1.053	0.001
CABG	0.899	0.443	1.826	0.769
IABP	0.83	0.431	1.602	0.579
INTERMACS				
• Profile 1	4.698	1.452	15.205	0.01
• Profile 2	2.809	1.002	7.877	0.05
• Profile 3	1.941	0.644	5.853	0.239
• Profile 4 and up	1	-	-	-
Indication				
• Bridge-to-transplant	1	-	-	-
• Destination therapy	2.673	1.563	4.57	<0.001
Device type				
HeartMate II	4.33	0.965	19.433	0.056
HVAD	2.453	0.451	13.343	0.299
HeartMate 3	1.00	-	-	-
Laboratory data (mg/dl)				
• Creatinine (Per unit increase)	1.13	0.753	1.695	0.556
• Total bilirubin (Per unit increase)	1.066	0.945	1.203	0.297
• Albumin (Per unit decrease)	0.601	0.383	0.944	0.027
• INR (Per unit increase)	1.201	0.917	1.573	0.183
• MELD (Per unit increase)	0.988	0.891	1.096	0.826
• MELD <12.6	1	-	-	-
• MELD ≥12.6	3.211	1.25	8.25	0.015

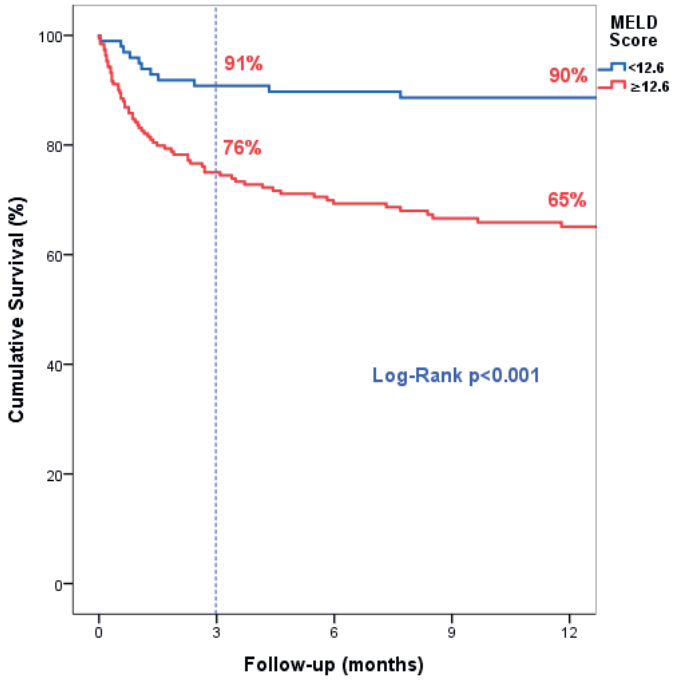
CABG denotes Coronary artery bypass graft; CI, Confidence interval; HR, Hazard Ratio; IABP, Intra-aortic balloon pump; INR, International normalized ratio; INTERMACS, Interagency registry for mechanically assisted circulatory support; MELD, model for end-stage liver disease

Additionally, a sub-group analysis of patients with available pre-operative right heart catheterization measurements, was performed (n= 200; 77 patients with MELD-score <12.6 and 113 with MELD-score ≥12.6). The patients with a MELD-score ≥12.6 had higher preoperative right atrial pressures (RAP; 11.4 ± 6.7 vs 15±7.1, p<0.001), higher pulmonary artery pressures (PAP; 34.6±11 vs 38.6±10.3, p=0.01), higher pulmonary capillary wedge pressures (PCWP; 24.9±9 vs 28.2±9.3, p=0.02), RA/PCWP (0.45 ± 0.18 vs 0.56 ± 0.22, p<0.001) and lower pulmonary artery pulsatility index (PAPi; 0.29 ± 0.33 vs 0.19 ± 0.19 p=0.01). In univariable cox regression analysis, all the measurements except for RA/PCWP and PAPi, were predictors of 1-year mortality. However, none of the measurements reached significance in multivariate analysis.

Table 4				
	All patients	**MELD <12.6**	**MELD ≥12.6**	**P-Value**
Follow-up time (days)	401 [695]	533 [755]	264 [661]	0.001
RVAD after LVAD	15 (6%)	4 (4%)	11 (6%)	0.453
Neurologic event*	38 (13%)	7 (7%)	31 (16%)	0.035
Confirmed pump thrombosis	2 (1%)	0	2 (1%)	0.538
Re-explorations post LVAD	110 (38%)	31 (32%)	79 (47%)	0.024
Transplantation	41 (14%)	13 (13%)	28 (15%)	0.799

*Ischemic or hemorrhagic
Follow-up depicted as median [interquartile range]
LVAD denotes Left ventricular assist device; MELD, model for end-stage liver disease; RVAD, Right ventricular assist device

Table 4. Clinical outcomes within 1-year following LVAD implantation, for the entire cohort and the dichotomized cohort based on their preoperative MELD-score.



Nr at Risk	0 months	3 months	6 months	9 months	12 months
MELD <12.6	99	87	82	74	70
MELD ≥12.6	191	136	115	94	81

Figure 2. Kaplan- Meier survival curve following LVAD implantation with 1-year follow-up. Comparing patients with a pre-implantation MELD-score of <12.6 with patient with a MELD-score of ≥12.6

In addition, we evaluated the impact of liver dysfunction in patients who did not receive any extracorporeal life support (ECLS) prior to LVAD implantation. In total, 170 (59%) patients were free of ECLS; 69 patients had a MELD-score <12.6 and 101 patients had a MELD-score ≥12.6. The 1-year survival rates for patients with and without live dysfunction in this subset of patients was 72% vs 91%, respectively (Log Rank, p=0.005).

Evolution of liver function

In total, 23333 repeated measurements of serum total bilirubin (mg/dl) were collected during follow-up: MELD-score ≥12.6: 14858, MELD-score <12.6: 8475. The mean follow-up time was 228±147 days for the MELD-score ≥12.6 group and 305±118 days for the MELD-score <12.6 group, respectively. Initially, patients with pre-operative liver dysfunction have higher mean levels of total bilirubin. The evolution of total bilirubin for all patients dichotomized based on pre-operative MELD-score is plotted in **figure 3**. At one year of follow-up, patients with and without pre-operative liver dysfunction have similar mean total bilirubin levels. Moreover, both groups have a mean total bilirubin within the acceptable range at one year of follow-up.

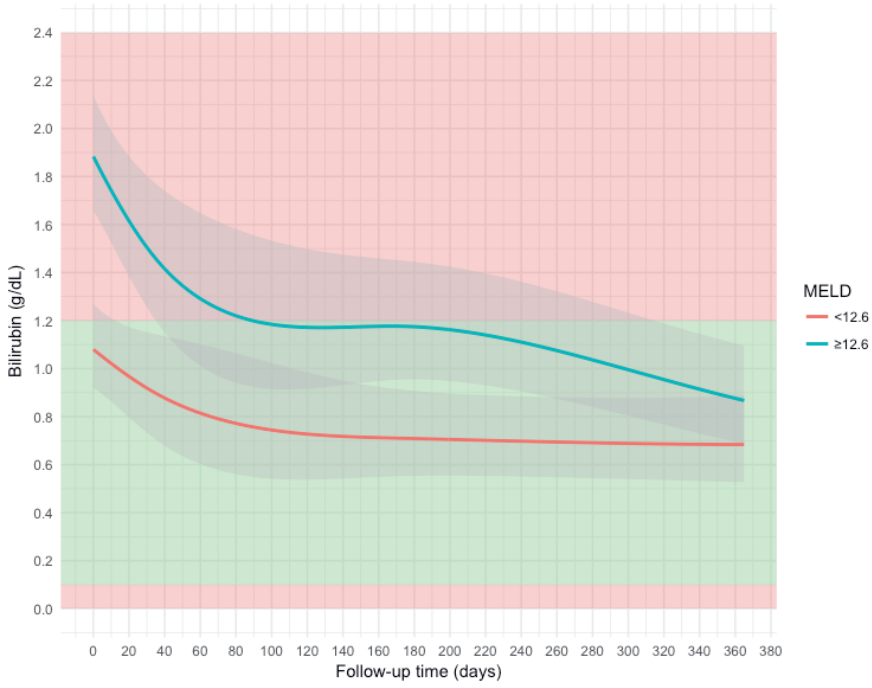


Figure 3. An advanced mixed-modelling analysis depicting the evolution of total bilirubin within 1-year during LVAD support. The two different evolutions represent the patients with (MELD ≥ 12.6) and without (MELD <12.6) pre-operative liver dysfunction.

Overall, 21069 repeated measurements of serum albumin (g/dl) were collected during follow-up: MELD-score ≥12.6: 14747, and MELD-score <12.6: 8322. The evolution of albumin, dichotomized based on pre-operative MELD-score, is plotted in **figure 4**. Although mean albumin levels start at an acceptable range pre-operatively, directly post-operative mean albumin levels are substantially lower in both groups. Following implantation, mean albumin levels incrementally increase in both groups, with recovery in the low MELD-score patients after 140 days vs 1-year in the high MELD-score group. At the 1-year follow-up mark, both patients with and without pre-operative liver dysfunction have regained their initially lost serum albumin levels.

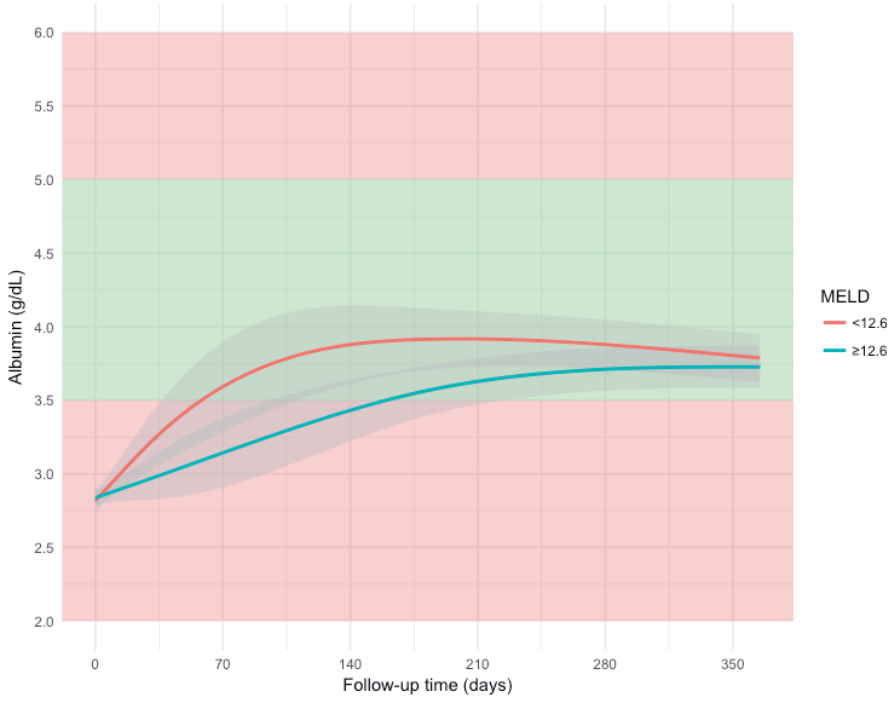


Figure 4. An advanced mixed-modelling analysis depicting the evolution of albumin within 1-year during LVAD support. The two different evolutions represent the patients with (MELD ≥ 12.6) and without (MELD <12.6) pre-operative liver dysfunction.

The evolution of ALT in both patient groups shows a similar decrease of mean levels of ALT until 2-3 months after LVAD implantation. Subsequently, both patient groups experience a plateau phase with no significant changes in mean ALT levels. Mean serum levels of ALT, for both groups, remain within the acceptable range during the first year following LVAD implantation. Mean serum levels of aspartate aminotransferase (AST) levels, however, are at less-than-optimal levels early after LVAD implantation (52 U/L in MELD <12.6 and 66 U/L in MELD ≥12.6). Following the initial elevation, mean levels of serum AST decrease as the

early post-operative period progresses. At the 3 months of follow-up, a substantial decrease of mean AST is noticed: 38% in low MELD vs 45% in high MELD-score patients. Following this decrease, a plateau phase follows until the end of the first year of follow-up. (See Supplements 2, 3, 4-7).

Discussion

The current study evaluated the impact of pre-operative liver function on 90 day and 1-year postoperative outcomes in patients with a LVAD implantation and subsequent evolution of liver function evolution over time. The principal findings of this study were: patients with significant liver dysfunction (MELD-score ≥12.6) have worse 90 day and 1-year postoperative survival. Moreover, patients with liver dysfunction have higher rates of adverse events, including higher rates of neurologic events and higher need of re-exploration due to early bleeding/tamponade following LVAD implantation. Regardless of baseline liver dysfunction, all liver function markers improve post LVAD implantation, and at 1-year of follow-up, no significant differences were observed between the separate MELD groups.

In order to determine the effect of liver dysfunction on LVAD recipients, similar studies have investigated the predictive value of the MELD-score for early and late mortality and adverse events.[10,13] Although the exact value of MELD-score used to differentiate liver dysfunction varies between studies, it evidently demonstrates that liver dysfunction has a detrimental impact on outcomes. The optimal cut-off value for MELD-score was calculated for both 90-day mortality and 1-year mortality. Though the AUC was similar, the cut-off value for 1-year mortality had a substantially higher sensitivity. Therefore, the cut-off value for MELD-score at 1-year was used to define liver dysfunction. Other studies have used the MELD-XI (by excluding INR) instead of the MELD-score, given the frequent use of oral anticoagulation. Their results demonstrate that the MELD-XI can similarly be used to predict worse outcomes in LVAD patients.[5,14,15] To account for this, we conducted a ROC curve analysis to determine the predictive value of the MELD, MELD-XI and the MELD-NA (which adds sodium to the MELD equation) in our cohort: 0.63 (CI 0.56-0.70), 0.63 (CI 0.56-0.70) and 0.62 (0.55-0.69) respectively. Given minimal to no difference in the predictive value, we used the classic MELD-score without any modifications. Of note, the use of MELD XI is warranted if patients have received anti-coagulants shortly before LVAD surgery. In this cohort, only 13 (4.5%) patients received Warfarin, and 3 patients Dabigatran 7 days prior to LVAD surgery. This constituted a small portion of the cohort and, therefore, the classic MELD-score was used.

Thereafter, a mixed model analysis was performed to illustrate the evolution of several liver function markers. This analysis adjusts for the correlation between multiple measurements of one patient and for the correlation between patients. The analysis notes improvement of liver function markers in both patient groups. Although both groups show different time frame of improvement, this finding underlines the benefits of LVAD therapy for the failing secondary organ systems in end-stage HF patients.

The differences between outcomes in patients with and without liver dysfunction is probably multifactorial. However, the main factor causing liver dysfunction most likely is chronic right-

sided congestion due chronic primary or secondary right ventricular failure.[16] Pre-operative liver dysfunction is a predictor of postoperative right-sided heart failure (RHF) in LVAD patients.[17] Subsequently, the onset of RHF in LVAD recipients has been associated with worse outcomes including worse survival.[18] To evaluate the severity of pre-operative right ventricle dysfunction we analyzed the available 200 right heart catheterization measurements. We sought for possible impact of higher preoperative mean RAP, PAP, PCWP, RA/PCWP and PAPi on mortality. However, higher preoperative pressures were not predictors of mortality following LVAD transplantation in our cohort., The analysis in patients who received no ECLS prior to LVAD surgery showed that a pre-operative MELD-score of ≥12.6 is still an accurate predictor of mortality in this population. Previous work from Maxhera et al. showed that in the patients receiving ECLS, higher pre-operative MELD-score was associated with an increased mortality following LVAD implantation.[19] This remains true for the patient population without an ECLS prior to LVAD implantation.

Clinical implications

Our study emphasizes the impact of liver dysfunction on outcomes following LVAD implantation. Despite worse outcomes in patients with liver dysfunction, our study shows that LVAD therapy can facilitate the recovery of liver dysfunction in end-stage HF patients. Furthermore, our results suggest that pre-operative MELD-score can aid in the selection process of high-risk potential LVAD candidates, who are older (>65), suffer from advanced renal failure and have additional co-morbidities. In addition, the MELD-score can probably identify patients at risk for bleeding complications following LVAD implantation. It has become imperative to optimize the selection criteria for possible LVAD candidates, since those who survive the first year show excellent recovery of their liver markers. The liver status is essential for an optimal decision making; however, the current study only gave a glimpse of what the possible impact of liver dysfunction could be. More, prospective, research is needed.

Limitations

The study knows several limitations that should be taken into consideration while interpreting the results. Firstly, due to the retrospective nature of our study it could not establish causality. Furthermore, an AUC of 0.63 is less than optimal. Moreover, despite standardized treatment plans for all patients, individual changes in medication and therapy could potentially have influenced the findings. The strengths of the study are the relatively large sample size and the multicenter design incorporating both European and American patients. The use of advanced mixed modelling enables a more accurate depiction of liver function markers.

Conclusion

Preoperative liver dysfunction is associated with higher early and 1-year mortality rates after LVAD implantation. However, improvement of liver function markers is noticed at 1-year follow-up, regardless of preoperative MELD-score. The increasing age and number of co-morbidities of potential LVAD candidates, especially in DT candidates, warrants continuous validation and improvement of selection criteria. By considering patients' pre-implantation

MELD-score in addition to other co-morbidities, could improve the shared-decision making process, preoperative optimization, and probably the postoperative management in this yet high-risk surgery.

Disclosure Statement: No financial relations to disclose

Conflict of interest (all authors): none

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Legend

Supplement 1. The baseline characteristics and the significant differences between the cohort dichotomized based on their pre-operative MELD-score.

Supplement 2. An advanced mixed-modelling analysis depicting the evolution of alanine-aminotransferase within 1-year during LVAD support. The two different evolutions represent the patients with (MELD ≥ 12.6) and without (MELD <12.6) pre-operative liver dysfunction.

Supplement 3. An advanced mixed-modelling analysis depicting the evolution of aspartate-aminotransferase within 1-year during LVAD support. The two different evolutions represent the patients with (MELD ≥ 12.6) and without (MELD <12.6) pre-operative liver dysfunction.

Supplement 4. An advanced mixed-modelling analysis depicting the overall mean total bilirubin evolution for the combined cohort.

Supplement 5. An advanced mixed-modelling analysis depicting the overall mean albumin evolution for the combined cohort.

Supplement 6. An advanced mixed-modelling analysis depicting the overall mean alanine-aminotransferase evolution for the combined cohort.

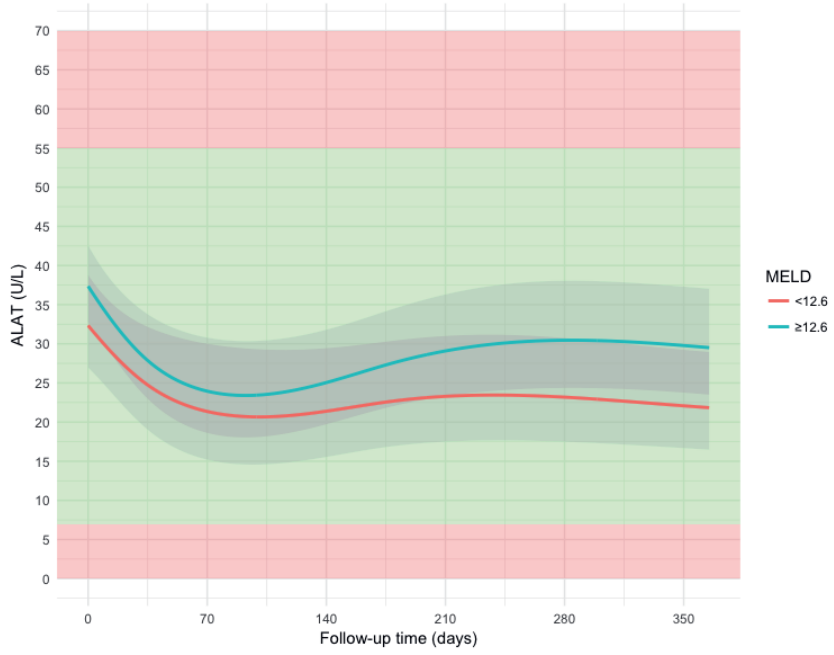
Supplement 7. An advanced mixed-modelling analysis depicting the overall mean aspartate-aminotransferase evolution for the combined cohort.

Supplement 1. The baseline characteristics and the significant differences between the cohort dichotomized based on their pre-operative MELD-score.

Supplementary table 1			
Baseline characteristics	**MELD < 12.6 (n=99)**	**MELD ≥12.6 (n=191)**	**P-value**
Age	54 [19]	56 [19]	0.87
Male	62 (64%)	159 (82%)	<0.001
Body mass index	25 [9]	26 [7]	0.99
Non-ischemic cardiomyopathy	59 (61%)	129 (67%)	0.31
Hypertension	47 (49%)	84 (44%)	0.43
CABG	10 (10%)	23 (12%)	0.68
ICD/PM	72 (74%)	165 (86%)	0.019
TIA/CVA	12 (12%)	41 (21%)	0.07
Atrial fibrillation	33 (33%)	81 (42%)	0.13
IABP	26 (27%)	88 (46%)	0.002
ECMO	6 (6%)	11 (6%)	0.87
INTERMACS			0.01
• Profile 1	11 (11%)	49 (26%)	
• Profile 2	33 (34%)	71 (37%)	
• Profile 3	27 (28%)	36 (19%)	
• Profile 4 and up	26 (27%)	36 (19%)	
Indication			0.85
• Bridge-to-transplant	63 (65%)	119 (62%)	
• Destination therapy	34 (35%)	74 (38%)	
Device			0.008
• HeartMate II	83 (86%)	142 (78%)	
• HVAD	1 (1%)	30 (16%)	
• HeartMate 3	13 (13%)	21 (11%)	
Lab values (mg/dl)			
• Total bilirubin	1.1 [0.2]	1.7 [1.8]	<0.001
• INR	1.1 [0.1]	1.4 [0.6]	<0.001
• Creatinine	1.1 [0.3]	1.6 [0.9]	<0.001
• AST	34 [69]	43 [58]	0.09
• ALT	37 [26]	48 [154]	0.002
• Albumin	3.7 [0.7]	3.5 [0.8]	0.82

Continuous variables are presented as median [interquartile range], Categorical variables are presented as numbers (percentage). ALT denotes Alanine transaminase; AST, Aspartate transaminase; CABG, Coronary artery bypass graft; CVA, Cerebrovascular accident; ECMO, Extracorporeal membrane oxygenation; IABP, Intra-aortic balloon pump; ICD, Implantable cardioverter defibrillator; INR, International normalized ratio; INTERMACS, Interagency registry for mechanically assisted circulatory support; MELD, model for end-stage liver disease; PM, Pacemaker; TIA, Transient ischemic attack

Supplement 2



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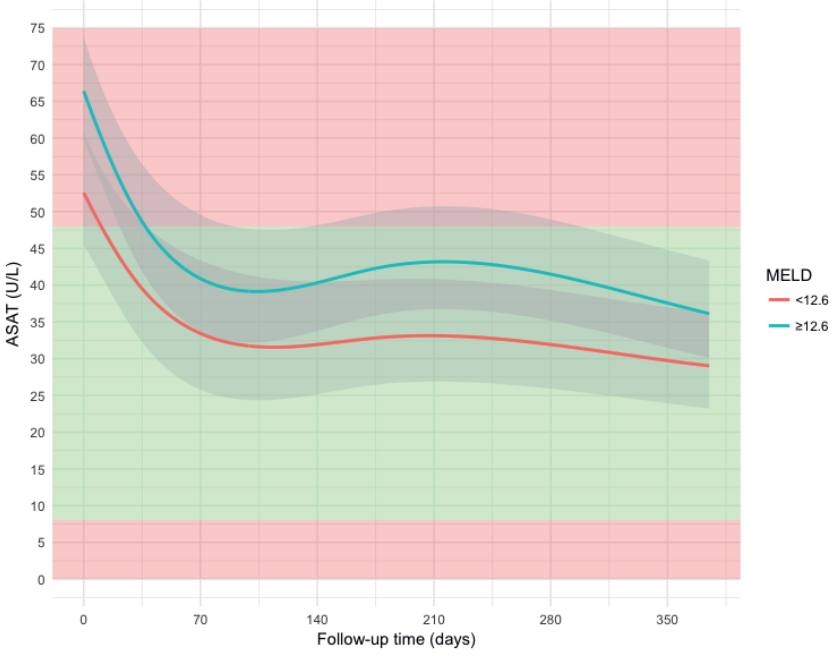

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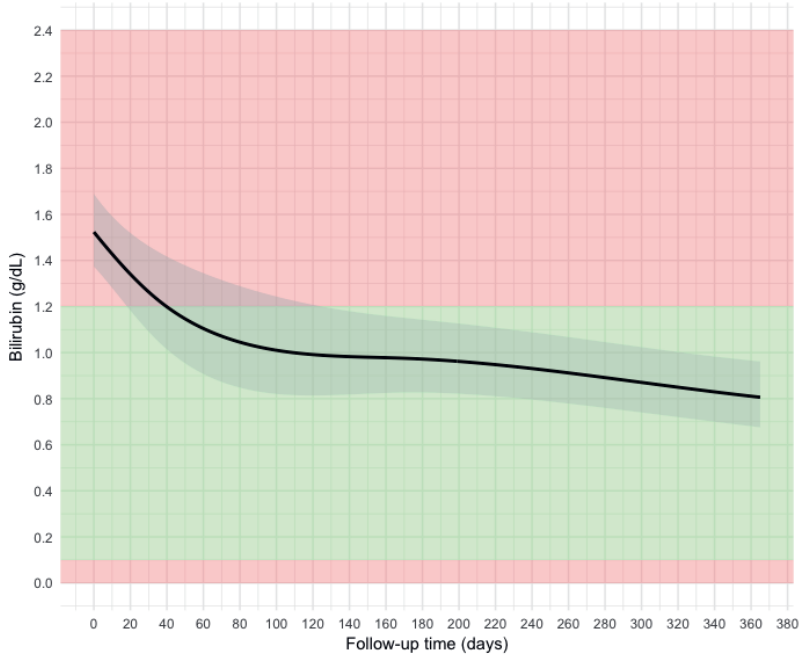

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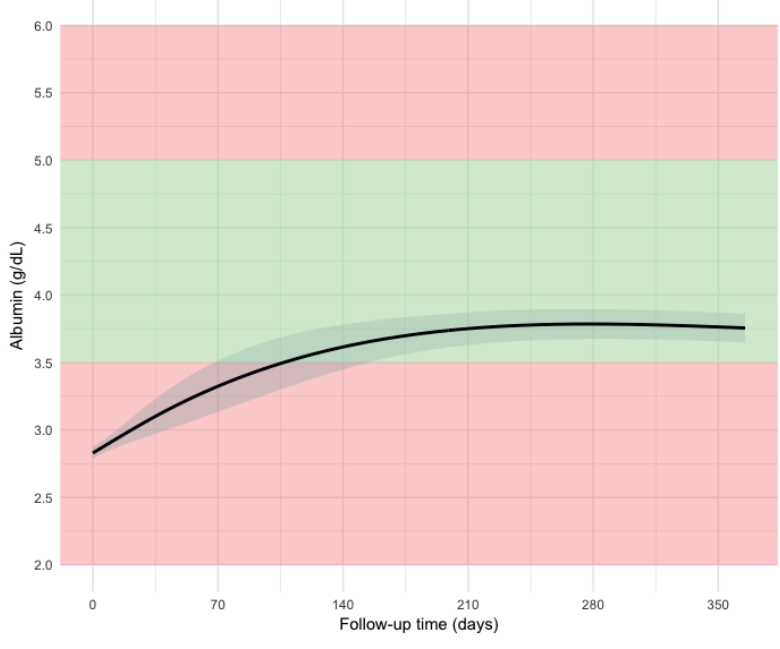

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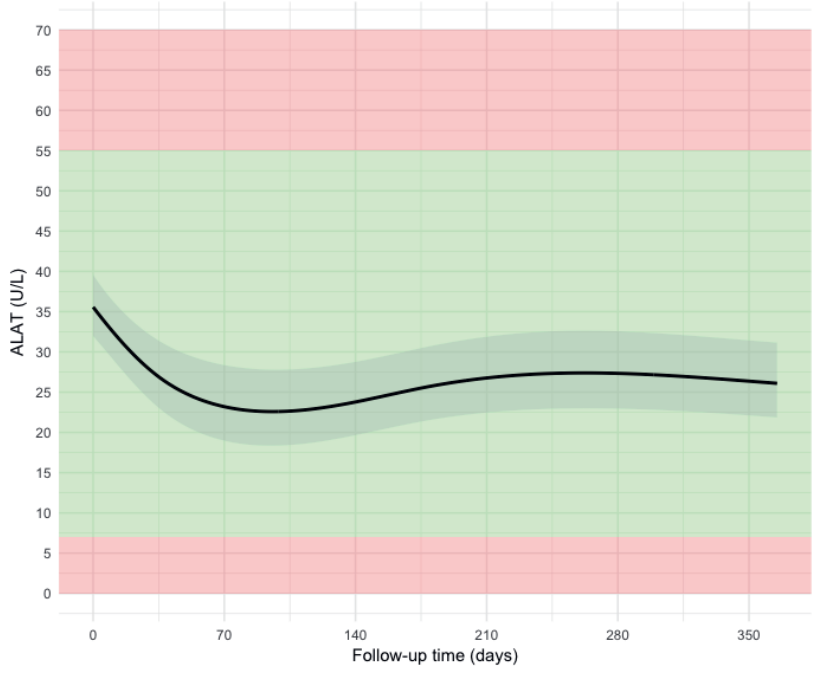

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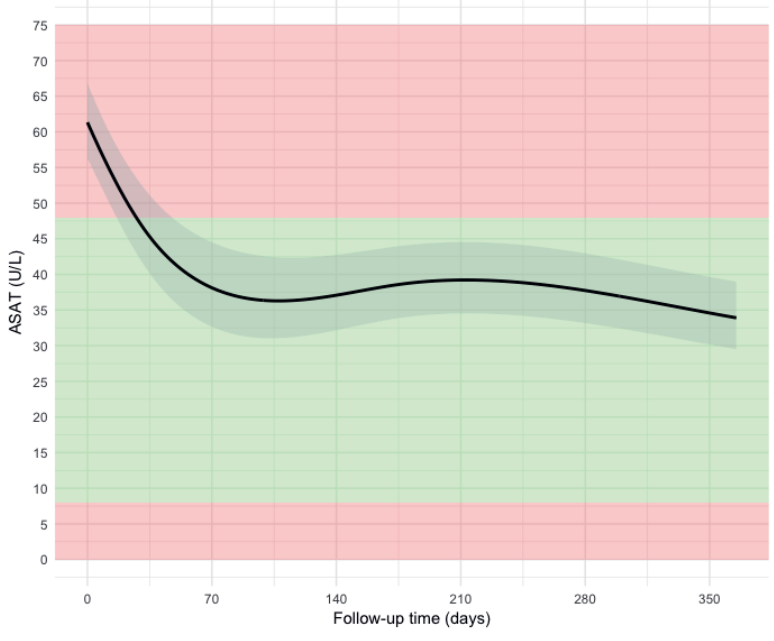

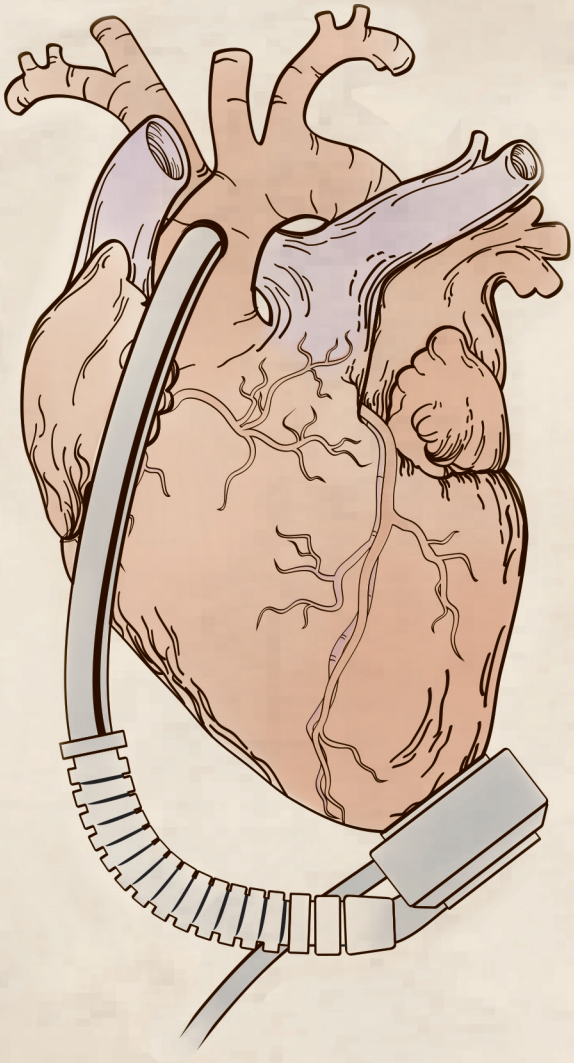

Chapter V

Emerging electromagnetic interference between implantable cardioverter defibrillators and left ventricular assist devices

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Abstract

Aims: To investigate the prevalence of electromagnetic interference (EMI) between left ventricular assist devices (LVADs) and implantable cardioverter defibrillators (ICDs)/ pacemakers (PMs).

Methods: A retrospective single center study was conducted, including all patients undergoing HeartMate II (HMII) and HeartMate 3 (HM3) LVAD implantation (n=106). EMI was determined by the inability to interrogate the ICD/PM.

Results: Overall, 85 (mean age 59 ± 8, 79% male) patients had an ICD/PM at the time of LVAD implantation; 46 patients with HMII and 40 with HM3. Among the 85 LVAD patients with an ICD's/PM's, 11 patients (13%) experienced EMI; 6 patients (15%) with a HMII and 5 patients (11%) with a HM3 (p=0.59). EMI from the HM II LVADs was only present in patients with a St Jude/Abbott device; 6 of the 23 St Jude/Abbott devices However, in the HM3 patients, EMI was mainly present in patients with Biotronik devices: 4 of the 18 with only one (1/25) patient with a Medtronic device. While initial interrogation of these devices was not successful, none of the 11 cases experienced pacing inhibition or inappropriate shocks.

Conclusion: In summary, the prevalence of EMI between ICD/PM's in the older and newer type of LVAD's remains rather high. While HM 2 patients experienced EMI with a St Jude/ Abbott device (which was already known), HM 3 LVAD patients experience EMI Abstract and Keywords mainly with Biotronik devices. Prospective flow-up, preferably in large registries, is warranted to investigate the overall prevalence and impact of EMI in LVAD patients.

Introduction

Left ventricular assist device therapy is increasingly utilized to treat end-stage heart failure patients who are in dire need of circulatory support.[1] Most patients who are eligible for continuous-flow left ventricular assist device (LVAD) therapy, already have an implantable cardioverter defibrillator (ICD) and/or pacemaker (PM) implanted.[2] However, following LVAD implantation, electromagnetic interference (EMI) can occur between the LVAD and the ICD/PM. Recently, multiple cases of EMI between LVADs and ICD's/PM's have been reported.[3-5] The EMI hinders the interrogation of the ICD/PM's and leave clinicians in the dark. Therefore, the aim of the present study was to investigate the prevalence of EMI between different types of ICD/PM in patients implanted with HeartMate II (HM II) and the recently introduced HeartMate 3 (HM 3).

Methods

Study design

We reviewed all patients who received a LVAD between December 2006 to February 2019 in our tertiary referral center with a prior ICD/PM implantation or device replacement due to end-of-life. The study was approved by the institutional review board of the ErasmusMC medical center Rotterdam.

Endpoints

The primary outcome was the occurrence of EMI, defined as ICD/PM telemetry interference (i.e. the inability to interrogate ICD/PM).

Data collection

All data was obtained from the electronic patient records. Baseline characteristics were collected pre-operatively for all patients. Devices included were the HeartMate II (HMII), Heartmate 3 (HM3) (Abbott, Illinois).

Statistical analysis

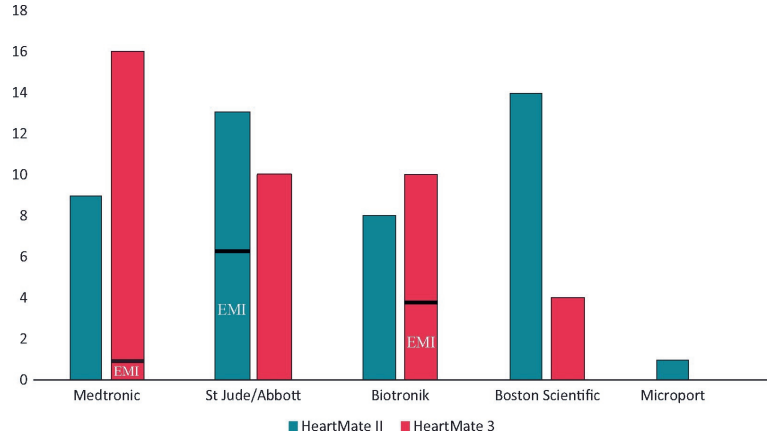
Continuous parameters are expressed as median and interquartile range or mean and standard deviation, depending on the distribution. Categorical parameters were expressed as number and percentage and compared by Chi2 test. Analyses were performed using the SPSS statistical software package, version 24.0 for Mac (SPSS Inc., IBM company, Chicago, IL).

Results

In total, 109 patients received a LVAD (mean age at implantation 52 ± 12, 83% male). Overall, 86 (mean age 59 ± 8, 79% male) patients had an ICD (n=85) or PM (n=1) at the time of LVAD implantation; 46 patients with HMII and 40 with HM3. One patient with an ICD was excluded from further analysis because of missing follow-up data. None of the ICDs/PMs showed any abnormalities prior to the LVAD implantation. The implanted ICD/PM devices were from Medtronic (Dublin, Ireland) (n=25), St Jude/Abbott (Chicago, Illinois) (n=23),

Biotronik (Berlin, Germany) (n=18), Boston Scientific (Marlborough, Massachusetts) (n=18), and Microport (Shanghai, China) (n=1) (see **Figure 1**). Among the 85 LVAD patients with an ICD's/PM's, 11 patients (13%) experienced EMI; 6 ICD patients (15%) with a HMII and 5 ICD patients (11%) with a HM3 (p=0.59).

Figure 1 Cardiac implantable electronic device manufacturer distribution among the HeartMate II and HeartMate 3 left ventricular assist devices



Electromagnetic interference from the HM II LVADs was only present in patients with a St Jude/Abbott device; 6 of the 23 St Jude/Abbott devices (1 Atlas, 1 Unify, 1 Fortify, 1 Elipse and 2 Promote). However, in the HM3 patients, EMI was mainly present in patients with Biotronik devices: 4 of the 18 (device types: Lumax, Ilivia, Ilesto, and Iperia) with only one (1/25) patient with a Medtronic (Claria) device (see **Table** for complete overview). None of the PM patients showed any signs of EMI.

Clinical outcomes

In 4 out of 11 patients, interrogation could not be performed in any form. For the other 7 patients, with some minor adjustments, interrogation was made possible. While initial interrogation of these devices was not successful, none of the 11 cases experienced pacing inhibition or inappropriate shocks.

Table. Electromagnetic interferences between implantable cardioverter-defibrillators and left ventricular assist devices observed in study population.

Patient	ICD manufacturer	Type	LVAD type	Indication	Support duration	Type of EMI	Intervention
1	ST Jude Medical	Unify (CRT-D)	HM II	Bridge-to-transplantation	25 days	Interference with telemetry function	RF use
2	ST Jude Medical	Elipse (ICD)	HM II	Bridge-to-transplantation	203 days	Interference with telemetry function	No interrogation possible
3	ST Jude Medical	Atlas (ICD)	HM II	Bridge-to-transplantation	287 days	Interference with telemetry function	No interrogation possible
4	ST Jude Medical	Fortify (ICD)	HM II	Bridge-to-transplantation	970 days	Dysfunction ICD system*	Device replacement
5	ST Jude Medical	Promote (CRT-D)	HM II	Bridge-to-transplantation	1061 days	Interference with telemetry function	RF use
6	ST Jude Medical	Promote (CRT-D)	HM II	Bridge-to-transplantation	1886 days	Interference with telemetry function	RF use
7	Biotronik	Ilesto (CRT-D)	HM 3	Bridge-to-decision	199 days	Interference with telemetry function	Patient in lying position
8	Medtronic	Viva (CRT-D)	HM 3	Bridge-to-transplantation	275 days	Interference with telemetry function	No interrogation possible
9	Biotronik	Iperia (CRT-D)	HM 3	Destination therapy	348 days	Interference with telemetry function	Uplift device
10	Biotronik	Ilivia (CRT-D)	HM 3	Bridge-to-transplantation	724 days	Interference with telemetry function	No interrogation possible
11	Biotronik	Lumax (ICD)	HM 3	Bridge-to-transplantation	997 days	Interference with telemetry function	Patient in lying position

ICD denotes implantable cardioverter defibrillator; LVAD, left ventricular assist device; EMI, electromagnetic interference; CRT-D, cardiac resynchronization therapy defibrillator; HM, Heart Mate; RF, radiofrequency

* After implantation of the LVAD, the ICD device appeared to be in back-up mode (VVI 65bpm) and shock therapy was disabled. After a multidisciplinary consultation (together with Abbott), it was decided to replace the ICD device. The cause of this problem was attributed to the EMI generated by the implanted HeartMate II. Following the replacement with an device from an different manufacturer, no further issues were observed.

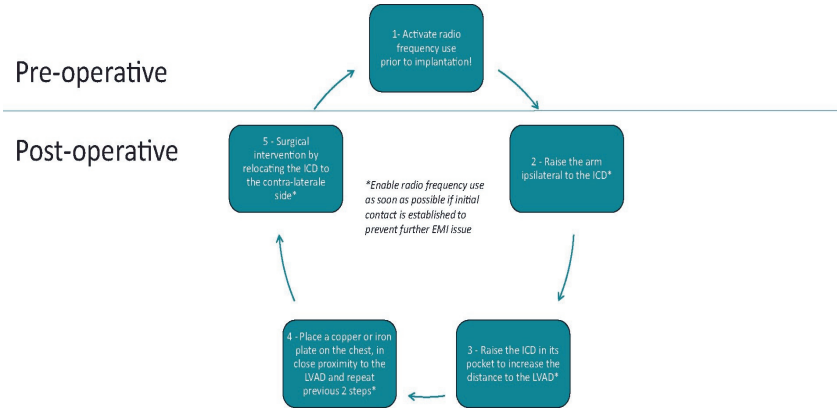
Discussion

The current study was aimed to gain insight on the prevalence of EMI between the HMII and HM3 LVAD's and several ICD/Pm device types. The principal findings are as follows: (1) EMI is present in 13% of LVAD patients with ICD's in situ. (2) In patients with a HMII, EMI is present only when they had an ICD from St Jude/Abbott implanted. However, in HM3 LVAD patients, EMI was mainly present in patients with ICD's from Biotronik. (3) While 11 patients presented with difficulties regarding interrogation of their ICD, none of the patients experienced pacing inhibition or inappropriate shocks.

Currently, the LVAD literature mainly describes EMI in patients with a St Jude / Abbott device. Yet in the more recent HM 3 type LVADs, it almost exclusively occurred in patients who had received a Biotronik device. Recently, several reported cases noticed the occurrence EMI between a Biotronik ICD and a HM 3 LVAD.[3-5] This emerging phenomenon warrants increased vigilance as an increasing number of patients receive HM3 LVAD therapy. Of note, since in our single cohort, no pacing inhibition or inappropriate shock have been administered, the clinical implication of the phenomenon appears limited. However, in larger cohorts with longer follow-up and/or emergency settings, the recognition of this phenomenon, the possible following complications and subsequent appropriate approach of EMI between ICD and LVAD could be of paramount importance.

The occurrence of EMI in most likely occurs due to the magnetic components of the HMII and HM3 LVAD's, which hinder the interrogation of the ICD. The use of radio frequency (RF), which is not affected by EMI, could be used to bypass this issue. Therefore, activating the RF use prior to LVAD implantation (if possible) should be considered. In patient with an LVAD in situ this is no longer is an option. Nonetheless, RF use can be beneficial. However, to activate the RF use, initial contact with the ICD is required. To achieve this, it seems that the distance between the ICD and the LVAD must be increased. Raising the ipsilateral arm and/or raising the ICD in its pocket can create enough distance to enable RF use. Alternatively, a Faraday cage (using coper or iron plates) can be put over the area with the LVAD to minimize EMI and enable RF use. Unfortunately, in some cases, these methods were insufficient, and the ICD could not be interrogated. These situations could benefit from surgical intervention to increase the distance between both devices. This could be done by implanting the ICD in the contra-lateral side (see **Figure 2** for complete overview). While no pacing inhibition took place or inappropriate shocks were administered, the EMI between the LVAD and the ICD hampers optimal ICD therapy. As this is a retrospective study, to further elucidate the effect of EMI between the contemporary HM 3 LVAD and ICDs, prospective registries like the interagency registry for mechanically assisted circulatory support (INTERMACS) and the European registry for patients with mechanical circulatory support (EUROMACS) should incorporate these findings.

Figure 2 A stepwise approach to reduce the occurrence and impact of electromagnetic interference in left ventricular assist devices



Conclusion

In summary, the prevalence of EMI between ICDs in the older and newer type of LVAD's remains rather high. While HM 2 patients experienced EMI with a St Jude/Abbott device (which was already known), in our single center cohort, the HM 3 LVAD patients experience EMI mainly with Biotronik devices. Ensuring enough distance between the ICD and the LVAD seems to be beneficial. The provided methods can aid clinicians who experience similar problems with the interrogation of the ICD of their LVAD patients. While the aforementioned options to bypass this issue exist, they are sometimes inadequate. We therefore recommend further research, preferably conducted prospective multicenter registries, to elucidate the full extent of the currently observed issue.

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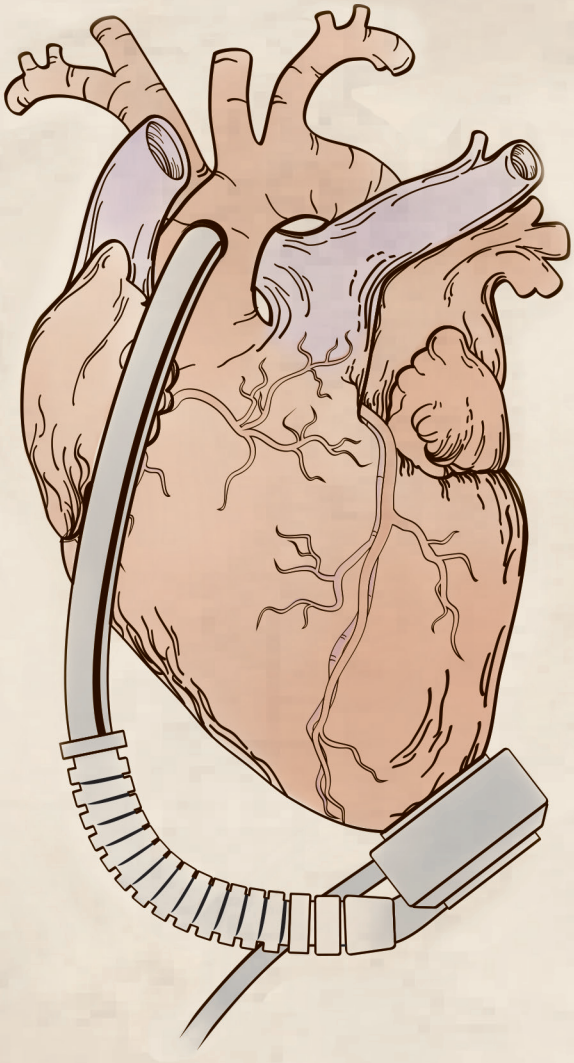

Chapter VI

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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ABSTRACT

Objectives: Atrial fibrillation (AF) is a risk factor for mortality and cerebrovascular accidents (CVA) 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 (EUROMACS).

Methods: Patients with a continuous-flow LVAD, AF or SR and a follow-up were included. Kaplan-Meier analyses for survival (including a propensity scored matched analysis), freedom from CVA, pump thrombosis (PT), bleeding and a composite of PT/CVA were performed. To correct for covariate imbalance a KM-analysis was performed after propensity score matching (PSM) 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 (IQR:4.3–27.7). Pre-operative 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 PSM 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 PSM-analysis, AF was no longer significant, indicating a worser pre-operative condition in these patients. Concerning thrombo-embolic events, only patients with pre-LVAD AF alive beyond 24 months have a higher risk of CVAs.

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 approximately 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 pre-operative AF compared to patients without AF, with conflicting results[8-12]. Multiple studies report a lower survival in patients with pre-operative 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 a left ventricular assist device (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 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, Lake Bluff, IL, USA) and HeartWare VAD (Medtronic, Minneapolis, MN, USA) (n= 582) and patients without a captured pre-operative 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 **Figure 1** for the overview of patient selection.

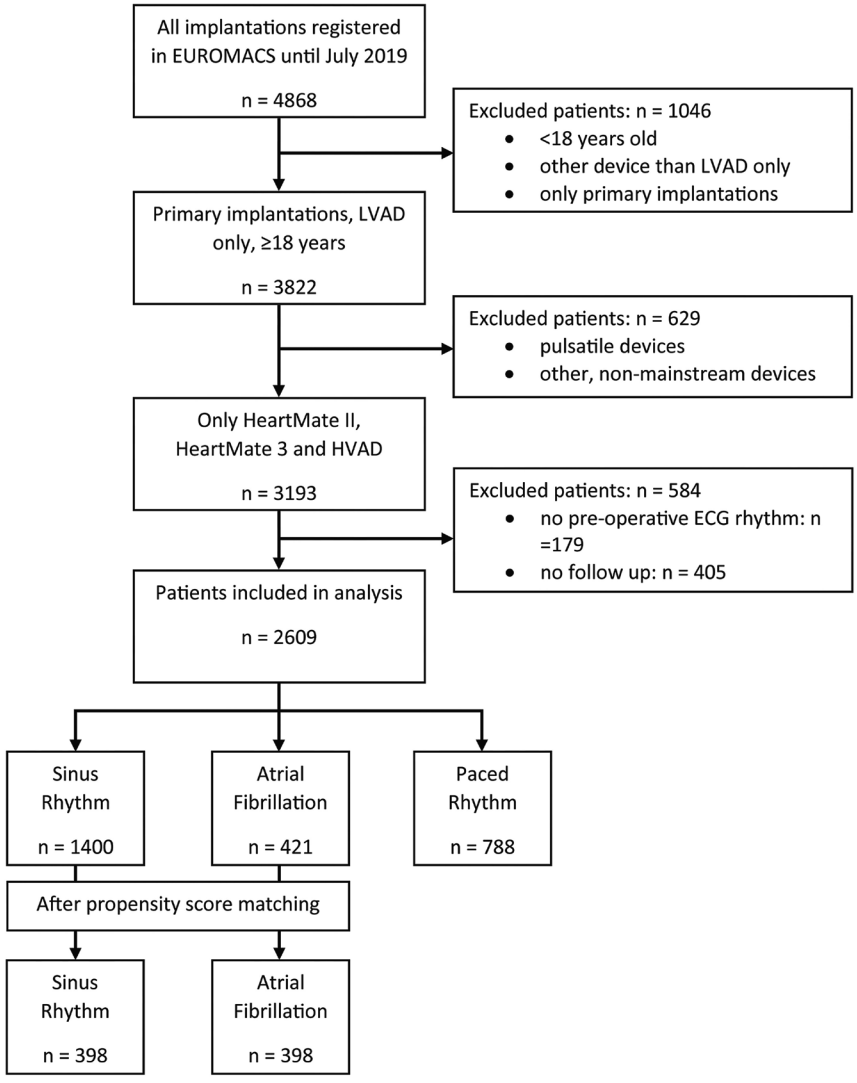

Figure 1. Flowchart of patient selection

EUROMACS: European Registry for Patients with Mechanical Circulatory Support; LVAD: Left ventricular assist device; HVAD: HeartWare Ventricular Assist Device.

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

Endpoints
The primary endpoint were early (≤90 days) and late (4-year) survival estimates following LVAD implantation for patients with pre-LVAD AF and SR. Secondary endpoints were suspected or confirmed pump thrombosis, cerebrovascular accident, and bleeding. Finally, the freedom of a composite endpoint of thromboembolic events (including CVA and pump thrombosis) was analysed.

Statistical analysis
Continuous parameters are expressed as median and interquartile range (IQR) or as mean and 95% confidence interval (95% 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 Chi2 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 two groups (AF vs 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 (SDM). A SMD 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.

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 analysis. If variables had too much missing data (more than 50%), they were excluded from the analysis (see **Supplementary table 1** for percentages missing for each baseline variables). However, the majority of the used variables had less than 10% missing values. A total of five rounds of imputations were performed and the data were pooled according to Rubin's rules. Variables were included in the multivariable models if p 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) 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'.

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 heart failure was dilated cardiomyopathy (46%). The most prevalent LVAD strategy was bridge-to-transplantation/bridge-to-candidacy (74%), with HeartWare LVAD (Medtronic, Minneapolis, MN, USA) as the most frequently implanted device in 1378 (52.8%) patients, followed by 780 (29.9%) HeartMate II (Abbott, Lake Bluff, IL, USA) patients and 451 (17.3%) HeartMate 3 (Abbott, Lake Bluff, IL, USA) patients.

Baseline characteristics

Overall, 3 groups of cardiac rhythm were identified within the registry: sinus rhythm (SR) (n=1400), paced rhythm (n=788) and atrial fibrillation (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 Table 2**). 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**).

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
Ischemic	469 (35)	146 (36)	
Dilated	601 (45)	200 (49)	
Other	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

Baseline characteristic	Sinus rhythm (n=1400)	Atrial fibrillation (n=421)	p-value
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
Pre-operative 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
Pre-operative 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
• ALAT (U/L)	31 [19-71]	26 [17-54]	0,197
• ASAT (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 ($x10^9$/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 ($x10^9$/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			

Baseline characteristic	Sinus rhythm (n=1400)	Atrial fibrillation (n=421)	p-value
• 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)	
• RV dysfunction			0,834
• Trivial - Mild	244 (25)	78 (26)	
• Moderate - severe	530 (54)	154 (52)	
Haemodynamic parameters			
• Heart rate (b.p.m.)	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). NYHA: New York health association; INTERMACS, interagency registry for mechanically assisted circulatory support; COPD, chronic obstructive pulmonary disease; VAD, ventricular assist device; MELD, model for end-stage liver disease; ALT alanine aminotransferase; AST, Aspartate aminotransferase; LDH, lactate dehydrogenase; WBC, white blood cell; INR, international normalized ratio; PTT, partial thromboplastin time; CRP, c-reactive protein; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle

Peri-operative and post-operative outcomes

Overall, peri-operative results between the groups were comparable, with similar rates of concomitant cardiac procedures, implantation of temporary right ventricular assist device (RVAD) 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 (IQR: 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) (**Figure 2**). Causes of death were predominantly multi-organ failure (18,1%), CVAs (14,4%), sepsis (11.8%) and infection (9,5%) (**Supplementary table 3).** An exploratory univariable Cox regression analysis (**Supplementary table 4**) 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, ischemic 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 (95%CI: 1.01-1.03)), primary diagnosis of ischemic 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)), extra corporeal 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)).

Table 2. Peri-operative and post-operative 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; RVAD: right ventricular assist device; PFO: patent foramen ovale

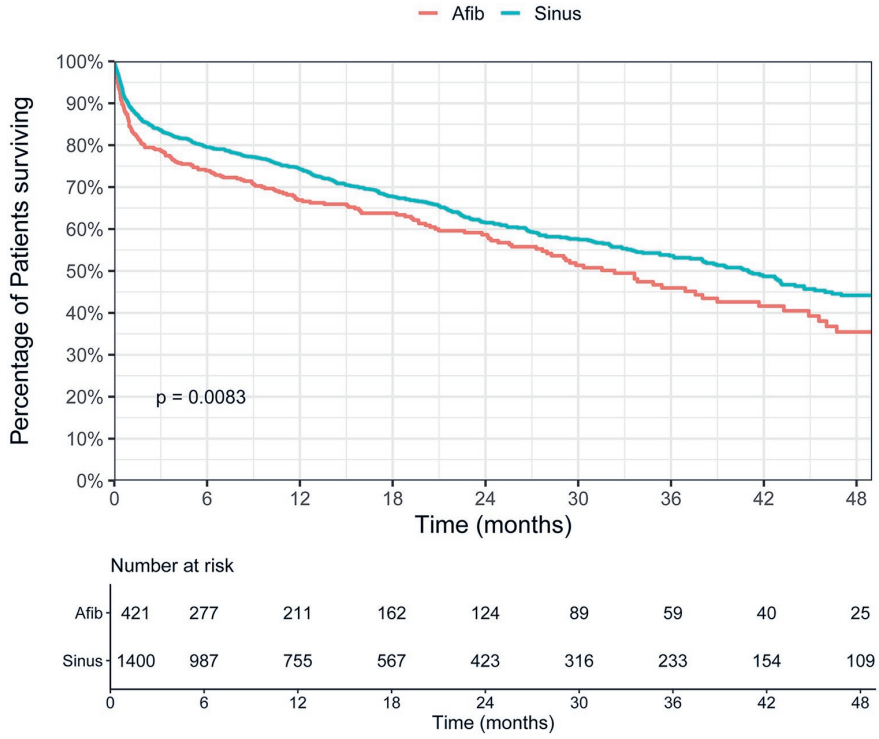

Figure 2. Survival according to pre-implantation rhythm: atrial fibrillation versus sinus rhythm

Afib: atrial fibrillation

Table 3. Univariable and multivariable cox regression analysis of predictors of inferior survival

	Univariable Analysis		Multivariable Analysis	
Baseline characteristics	**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				
• Ischemic	1,41 (1,21-1,63)	<0,001	1,23 (1,04-1,45)	0,017
• Non-ischemic	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
Pre-operative 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 ($x10^9$/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 (b.p.m.)	0,997 (0,99-1,00)	0,162	1,000 (0,995-1,004)	0,996

NYHA: New York health association; INTERMACS, interagency registry for mechanically assisted circulatory support; COPD, chronic obstructive pulmonary disease; MELD, model for end-stage liver disease; AST, Aspartate aminotransferase; LDH, lactate dehydrogenase; WBC, white blood cell; INR, international normalized ratio; PTT, partial thromboplastin time; ref, reference

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 are shown in **Figure 3** and **Supplementary Table 5.** 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) (**Figure 4**)

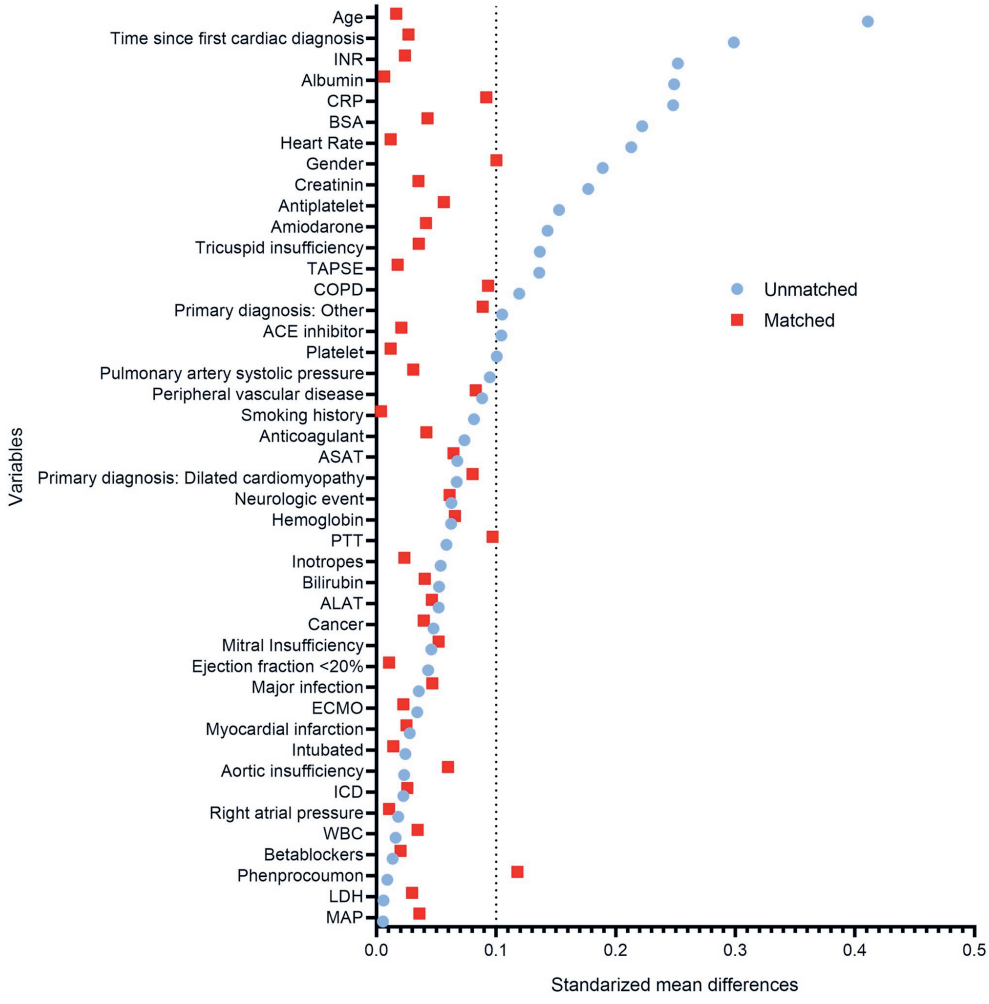

Figure 3. Standardized mean difference between patients with pre-LVAD atrial fibrillation and sinus rhythm, before and after propensity score matching

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

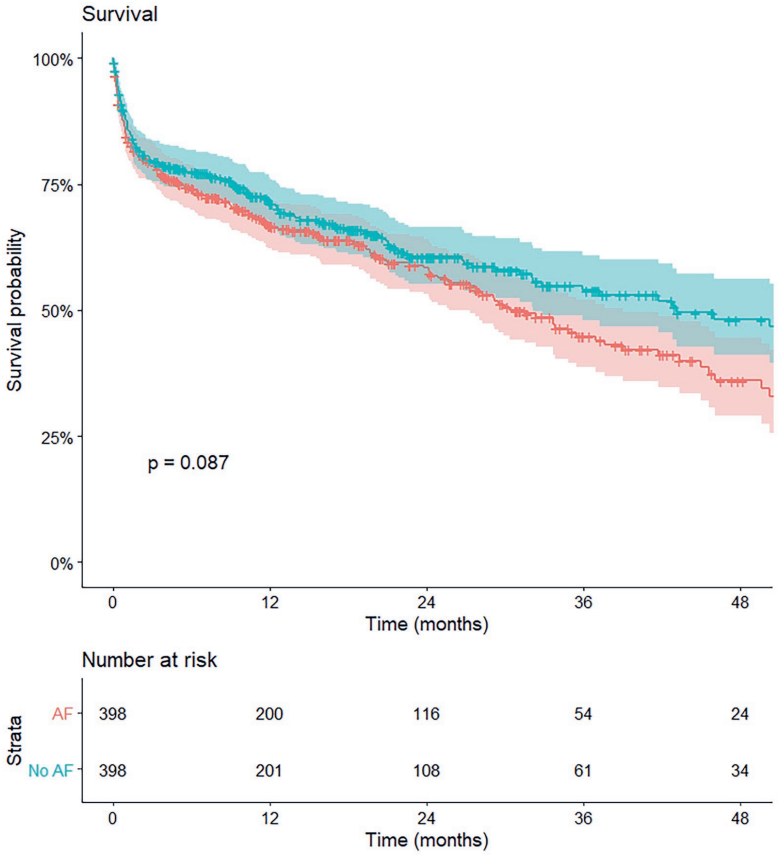

Figure 4. Survival according to pre-implantation rhythm atrial fibrillation versus sinus rhythm with propensity scoring matched groups

AF: atrial fibrillation

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) (**Figure 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 (**Figure 5B**). A cox proportional hazards model confirmed this finding with a HR of 0.99 (95%CI: 0.70 to 1.41) for the first two years and a HR of 4.01 (2.05 to 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 group as the complete baseline (**Supplementary Table 6**). 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 Figure 1**).

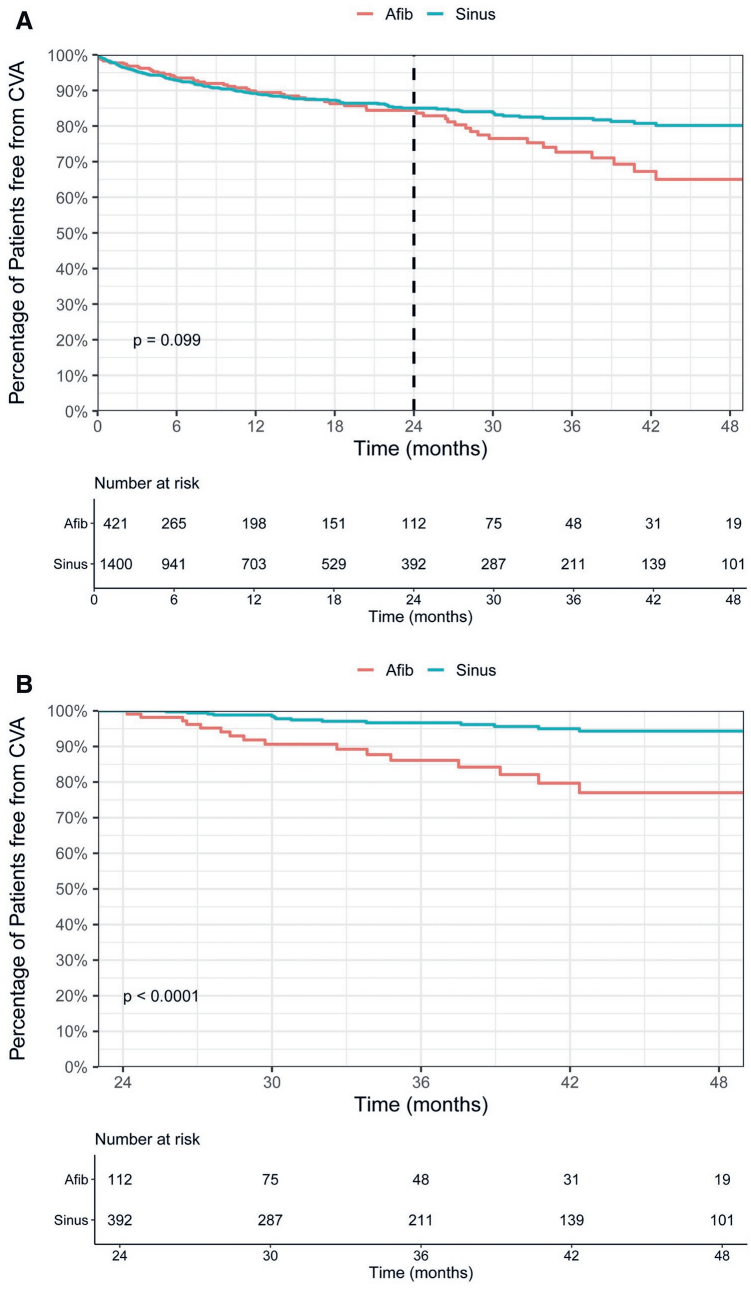

Figure 5. Freedom from CVA according to pre-implantation atrial fibrillation versus sinus rhythm. **Panel A:** 0 to 48 months freedom from CVA. **Panel B:** Conditional analysis after 24 months for freedom from CVA according to pre-implantation atrial fibrillation and sinus rhythm

Afib: atrial fibrillation; CVA: cerebrovascular accident

The rate of other coagulation related events was also compared between the pre-LVAD AF and SR groups. Firstly, 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 Figure 2**). Freedom from bleeding showed a trend towards more events in the AF group (69.9%) compared to the SR group (79.4%) (p = 0.077) (**Supplementary Figure 3**). Finally, the freedom from the composite endpoint 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 versus 61.0% for SR, p = 0.71) (**Supplementary Figure 4**).

Discussion

In this study we reviewed if pre-operative 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, pre-operative AF was not independently significantly associated with a lower survival in the multivariable model of this study. A propensity score 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 group, no overall significant differences for freedom from CVA, PT, bleeding and the composite endpoint 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 multicenter, "real world" registry data, set out to elucidate the consequence of pre-operative AF for outcomes during LVAD support. Deshmukh *et al.* 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[9]. 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 one 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. Pre-operative 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 3,909 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 group 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 group. 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 (LAA), although the current paper does not provide direct evidence for this. Finally, all patients on vitamin K antagonists will inevitably have multiple periods of sub-therapeutical INR (reported to be higher dan 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 pre-operative baseline characteristics and all patients have at least a score of 1, due to the fact that one of the criteria is congestive heart failure[15]. Moreover, due to the lack of data, pre-operative 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 pre-operative AF, it is unclear whether these patients had pre-existent or new onset AF, and if they had paroxysmal or persistent AF. Additionally, 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 which 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.

Study limitations

Some limitations should be taken into consideration. Firstly, this study is based on the data of a large international multi-centre 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 was imputed, although the percentage of data missing of the variables used was limited (max <50%) (**Supplementary table 1)**. Finally, a substantial fraction of the patients had no data on pre-operative cardiac rhythm (n = 179) or had the designation paced (n = 788). For both groups it is unclear what the pre-operative 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, multi-centre registry study, patients with pre-operative 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 PSM. 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 group, 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.

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Conflict of interest

F.G declares the following conflicts of interest: paid advisor: Carmat, Abbott, Pfizer, Bayer; speakers fee: Novartis, Orion pharma, Astra Zeneca, Boehringer Ingelheim; Unpaid advisor: Corvia medical. All other authors have declared no conflict of interest.

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Supplementary materials

Supplementary Table 1. Percentage of baseline variables missing

Baseline characteristic	Percentage missing data (%)
Demographics	
Age (years)	0
Sex	0
Body surface area (m^2)	0.33
Body mass index (kg/m^2)	0.33
Device strategy	0.33
Primary diagnosis	4.94
Time since first cardiac diagnosis	8.42
NYHA Class	28.83
INTERMACS patient profile	0.55
Comorbidities	
• Diabetes mellitus	1.38
• ICD therapy	8.68
• Major myocardial infarction	2.42
• Major infections	2.69
• COPD	4.34
• Symptomatic peripheral vascular disease	17.24
• Neurologic event	3.29
• Cancer, other than skin cancer	9.77
• Smoking history	31.8
Pre-operative condition	
Intra-aortic balloon pump	2.75
Intubation	2.3
Other surgical procedures	2.91
Other VAD	2.42
Extra corporeal membrane oxygenation	2.69
Need for inotropes	6.21
Medication	
• Amiodarone	10.38
• Ace inhibitors	8.84
• Beta blockers	9.77
• Phenprocoumon	24.44
• Anticoagulant therapy	10.05
• Antiplatelet therapy	10.05
Blood chemistry	
• MELD-Score	25.04
• Creatinine (µmol/L)	9.72
• ALAT (U/L)	31.36
• ASAT (U/L)	12.03
• LDH (U/L)	33.55
• Total bilirubin (mg/dL)	15.82
• WBC ($x10^9/L$)	1.92

Baseline characteristic	Percentage missing data (%)
• Haemoglobin (g/dL)	5.27
• Platelets (x10^9/L)	7.41
• INR	3.73
• PTT (s)	10.65
• CRP (mg/L)	12.96
Echocardiography	
• TAPSE	49.42
• Mitral regurgitation	11.37
• Tricuspid regurgitation	11.31
• Aortic regurgitation	16.91
• Ejection fraction grade <20%	15.71
• RV dysfunction	29.65
Haemodynamic parameters	
• Heart rate	4.17
• Systolic blood pressure	5.49
• Diastolic blood pressure	5.88
• Mean blood pressure	5.88
• Pulmonary artery systolic pressure	44.92
• Pulmonary artery diastolic pressure	45.03
• Mean pulmonary artery pressure	45.03
• Right atrial pressure	44.87
• Pulmonary artery wedge pressure	48.54

Supplementary Table 2. Baseline characteristics for patients with pre-operative atrial fibrillation, and paced rhythm

Baseline characteristic	Sinus rhythm (n=1400)	Paced (n=788)	p-value
Demographics			
Age (years)	54 [44-61]	59 [53-65]	<0,001
Male	1148 (82)	691 (88)	<0,001
Body surface area (m^2)	1,94 [1,79-2,1]	1,99 [1,85-2,17]	<0,001
Body mass index (kg/m^2)	22,2 [19,7-25,3]	23,1 [20,2-26,3]	<0,001
Device strategy			
Possible bridge-to-transplantation	1056 (75)	584 (74)	0,668
Primary diagnosis			<0,001
• Ischemic	469 (35)	298 (39)	
• Dilated	601 (45)	391 (51)	
• Other	254 (19)	78 (10)	
Time since first cardiac diagnosis >2 years ago	848 (66)	687 (86)	<0,001
CHA_2DS_2-VASc score >3	191 (14)	136 (17)	0,023
NYHA Class 4	607 (61)	388 (60)	0,771
INTERMACS			<0,001
• Profile 1	212 (15)	97 (12)	
• Profile 2	416 (30)	296 (38)	
• Profile 3	369 (27)	253 (32)	
• Profile ≥4	395 (28)	141 (18)	
Comorbidities			
• Diabetes mellitus	316 (23)	277 (35)	<0,001
• ICD therapy	799 (63)	380 (70)	0,002
• Major myocardial infarction	262 (19)	60 (8)	<0,001
• Major infections	140 (10)	48 (6)	0,001
• COPD	108 (8)	79 (10)	0,065
• Symptomatic peripheral vascular disease	71 (6)	34 (8)	0,229
• Neurologic event	135 (10)	99 (13)	0,029
• Cancer, other than skin cancer	53 (4)	11 (2)	0,087
• Smoking history	628 (46)	312 (40)	<0,001
Pre-operative condition			
• Intra-aortic balloon pump	138 (10)	75 (10)	0,762
• Intubation	219 (16)	60 (8)	<0,001
• Other surgical procedures	144 (11)	113 (15)	0,098
• Other VAD	67 (5)	18 (2)	0,003
• Extra corporeal membrane oxygenation	167 (12)	64 (8)	0,005
• Need for ≥3 inotropes	138 (11)	176 (23)	<0,001
Medication			
• Amiodarone	395 (32)	385 (51)	<0,001
• Ace inhibitors	530 (42)	259 (35)	0,002
• Beta blockers	671 (54)	435 (57)	0,105
• Phenprocoumon	76 (7)	18 (4)	0,034
• Anticoagulant therapy	757 (60)	571 (74)	<0,001
Antiplatelet therapy			<0,001
• Single therapy	354 (28)	138 (19)	

Baseline characteristic	Sinus rhythm (n=1400)	Paced (n=788)	p-value
• Dual Therapy	105 (8)	22 (3)	
Blood chemistry			
• MELD-Score	12,1 [7,8-16,4]	7,5 [3,6-12,1]	<0,001
• Creatinine (µmol/L)	107 [85-141]	120 [92-161]	0,002
• ALAT (U/L)	31 [19-71]	28 [16-64]	0,452
• ASAT (U/L)	32 [22-68]	33 [23-56]	0,261
• LDH (U/L)	308 [235-473]	300 [238-388]	0,028
• Total bilirubin (mg/dL)	1,2 [0,8-2]	1,4 [0,9-2,2]	0,899
• WBC ($x10^9$/L)	8,5 [6,7-11]	8,4 [6,6-10,7]	0,045
• Haemoglobin (g/dL)	11,9 [10,3-13,6]	11,3 [9,9-13,1]	0,012
• Platelets ($x10^9$/L)	207 [155-265]	179 [127-231]	<0,001
• INR	1,25 [1,1-1,5]	1,3 [1,1-1,7]	0,036
• PTT (s)	36 [28-45]	39 [33-49]	0,001
• CRP (mg/L)	3 [1-9]	3 [1-6]	0,017
Echocardiography			
TAPSE	14 [12-17]	15 [12-18]	0,05
Mitral regurgitation			<0,001
Trivial - Mild	498 (39)	239 (32)	
Moderate - severe	368 (50)	374 (51)	
Tricuspid regurgitation			<0,001
Trivial - Mild	652 (51)	318 (43)	
Moderate - severe	461 (36)	305 (42)	
Aortic regurgitation			<0,001
Trivial - Mild	402 (32)	212 (29)	
Moderate - severe	51 (4)	22 (3)	
Ejection fraction grade <20%	743 (64)	358 (56,4)	0,002
RV dysfunction			<0,001
Trivial - Mild	244 (25)	93 (24)	
Moderate - severe	530 (54)	250 (65)	
Haemodynamic parameters			
• Heart rate	84 [72-97]	83 [72-95]	0,213
• Systolic blood pressure	100 [90-110]	100 [90-110]	0,019
• Diastolic blood pressure	65 [30-71]	63 [55-70]	<0,001
• Mean blood pressure	81 [74-90]	80 [72-89]	0,727
• Pulmonary artery systolic pressure	53 [40-65]	49 [39-62]	0,008
• Pulmonary artery diastolic pressure	27 [33-20]	25 [19-32]	0,103
• Mean pulmonary artery pressure	19 [2-37]	23 [7-36]	0,032
• Right atrial pressure	11 [7-15]	11 [7-15]	0,301
• Pulmonary artery wedge pressure	25 [19-31]	23 [17-29]	0,002

Continuous variables are depicted as median [interquartile range] and categorical variables as count (percentage). NYHA denotes New York health association; INTERMACS, interagency registry for mechanically assisted circulatory support; COPD, chronic obstructive pulmonary disease; VAD, ventricular assist device; MELD, model for end-stage liver disease; ALT alanine aminotransferase; AST, Aspartate aminotransferase; LDH, lactate dehydrogenase; WBC, white blood cell; INR, international normalized ratio; PTT, partial thromboplastin time; CRP, c-reactive protein; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle

Supplementary table 3: Causes of death according to year of follow up from year 1 until year 4, comparing patients with pre-LVAD implantation sinus rhythm to patients with atrial fibrillation

	Sinus Rhythm					Atrial Fibrillation					Overall
Year	**1**	**2**	**3**	**4**	**Total**	**1**	**2**	**3**	**4**	**Total**	**Total**
Causes of death	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Bleeding	23 (6.8)	5 (4,6)	2 (4,5)	1 (3,2)	31 (5,9)	6 (4,5)	0 (0)	1 (4,5)	0 (0)	7 (3,7)	38 (5,4)
Cancer	0 (0)	4 (3,7)	0 (0)	1 (3,2)	5 (0,9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (0,7)
Cardio-pulmonary failure	24 (7,1)	3 (2,7)	0 (0)	0 (0)	27 (5,1)	7 (5,3)	1 (4,7)	0 (0)	0 (0)	8 (4,3)	35 (5,0)
Cerebrovascular accident	48 (14,2)	22 (20,3)	10 (22,7)	4 (12,9)	84 (16,1)	8 (6)	1 (4,7)	5 (22,7)	3 (30)	17 (9,1)	101 (14,4)
Device failure	7 (2)	7 (6,4)	3 (6,8)	0 (0)	17 (3,2)	3 (2,2)	1 (4,7)	0 (0)	0 (0)	4 (2,1)	21 (3,0)
Infection	30 (8,8)	14 (12,9)	1 (2,2)	4 (12,9)	49 (9,4)	11 (8,3)	4 (19)	0 (0)	3 (30)	18 (9,7)	67 (9,5)
Left heart failure	1 (0,2)	0 (0)	2 (4,5)	1 (3,2)	4 (0,7)	1 (0,7)	1 (4,7)	0 (0)	0 (0)	2 (1)	6 (0,9)
Lung failure	1 (0,2)	0 (0)	1 (2,2)	2 (6,4)	4 (0,7)	4 (3)	1 (4,7)	0 (0)	0 (0)	5 (2,7)	9 (1,3)
Multi-organ failure	73 (21,5)	4 (3,7)	3 (6,8)	4 (12,9)	84 (16,1)	35 (26,5)	4 (19)	4 (18,1)	0 (0)	43 (23,2)	127 (18,1)
Myocardial infarction	1 (0,2)	1 (0,9)	0 (0)	0 (0)	2 (0,3)	1 (0,7)	0 (0)	0 (0)	0 (0)	1 (0,5)	3 (0,4)
Other cause of death	19 (5,6)	4 (3,7)	0 (0)	2 (6,4)	25 (4,7)	11 (8,3)	0 (0)	0 (0)	1 (10)	12 (6,4)	37 (5,3)
Pulmonary artery embolization	3 (0,8)	0 (0)	0 (0)	0 (0)	3 (0,5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0,4)
Right heart failure	17 (5)	3 (2,7)	1 (2,2)	1 (3,2)	22 (4,2)	6 (4,5)	1 (4,7)	1 (4,5)	0 (0)	8 (4,3)	30 (4,3)
Sepsis	44 (13)	7 (6,4)	3 (6,8)	2 (6,4)	56 (10,7)	21 (15,9)	3 (14,2)	3 (13,6)	0 (0)	27 (14,5)	83 (11,8)
Suicide	2 (0,5)	1 (0,9)	0 (0)	0 (0)	3 (0,5)	1 (0,7)	0 (0)	0 (0)	0 (0)	1 (0,5)	4 (0,6)
Technical problems	1 (0,2)	0 (0)	0 (0)	0 (0)	1 (0,1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0,1)
Trauma	1 (0,2)	0 (0)	0 (0)	0 (0)	1 (0,1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0,1)
Unknown cause of death	43 (12,7)	33 (30,5)	18 (40,9)	9 (29)	103 (19,7)	17 (12,8)	4 (19)	8 (36,3)	3 (30)	32 (17,2)	135 (19,2)
Total	338 (100)	108 (100)	44 (100)	31 (100)	521 (100)	132 (100)	21 (100)	22 (100)	10 (100)	185 (100)	702 (100)

Supplementary table 4. Complete list of baseline characteristics included in univariable cox regression analysis for inferior survival

Baseline characteristics	HR (95% CI)	p-value
Demographics		
Age	1,023 (1,017 - 1,029)	<0,001
Male	1,03 (0,85 - 1,26)	0,744
AF at baseline	1,25 (1,06 - 1,47)	0,008
Body surface area	0,98 (0,73 - 1,34)	0,938
Body mass index	1,013 (0,997 - 1,029)	0,105
Device strategy		
• Possible bridge-to-transplantation	ref	
• Destination therapy	1,06 (0,88 - 1,29)	0,525
• Bridge-to-recovery	0,95 (0,65 - 1,62)	0,859
• Rescue therapy	0,95 (0,69 - 1,97)	0,735
• Other	0,99 (0,30 - 3,29)	0,995
Primary diagnosis		
• Ischemic	1,41 (1,21 - 1,63)	<0.001
• Non-ischemic	ref	
Time since first cardiac diagnosis >2 years ago	1.05 (0.89 - 1.24)	0.210
NYHA Class 4	1,12 (0,94 - 1,33)	0,217
INTERMACS		
• Profile 1	1,73 (1,40 - 2,15)	<0,001
• Profile 2	1,21 (0,99 - 1,46)	0,053
• Profile 3	0,93 (0,76 - 1,15)	0,512
• Profile ≥4	ref	
Comorbidities		
• Diabetes mellitus	1,30 (1,11 - 1,53)	0,001
• ICD therapy	1,04 (0,89 - 1,21)	0,618
• Major myocardial infarction	1,25 (1,05 - 1,50)	0,013
• Major infections	1,02 (0,80 - 1,30)	0,866
• COPD	1,42 (1,14 - 1,78)	0,002
• Symptomatic peripheral vascular disease	1,50 (1,10 - 2,06)	0,012
• Neurologic event	1,15 (0,91 - 1,46)	0,226
• Cancer, other than skin cancer	0,95 (0,63 - 1,43)	0,798
• Smoking history	1,15 (0,95 - 1,40)	0,154
Pre-operative condition		
• Intra-aortic balloon pump	1,19 (0,95 - 1,50)	0,122
• Intubation	1,62 (1,35 - 1,94)	<0,001
• Other Surgical procedures	1,59 (1,29 - 1,96)	<0,001
• Other VAD	1,02 (0,70 - 1,47)	0,934
• Extra corporeal membrane oxygenation	1,79 (1,47 - 2,20)	<0,001
• Need for ≥3 inotropes	1,03 (0,8 - 1,33)	0,807
Medication		
• Amiodarone	1,03 (0,88 - 1,20)	0,749
• Ace inhibitors	0,94 (0,81 - 1,10)	0,445
• Beta blockers	0,88 (0,76 - 1,02)	0,082
• Phenprocoumon	0,83 (0,53 - 1,29)	0,388
• Anticoagulant therapy	1,04 (0,89 - 1,21)	0,663

Baseline characteristics	HR (95% CI)	p-value
Antiplatelet therapy		
• Single therapy	1,15 (0,97 - 1,37)	0,086
• Dual Therapy	0,89 (0,67 - 1,19)	0,436
Blood chemistry		
• Creatinine (µmol/L)	1,003 (1,002 - 1,004)	<0,001
• ALAT (U/L)	1,000 (0,999 - 1,000)	0,599
• ASAT (U/L)	1,000 (1,000 - 1,000)	0,165
• LDH (U/L)	1,000 (1,000 - 1,001)	0,023
• Total bilirubin (mg/dL)	1,030 (1,010 - 1,049)	0,003
• WBC (x109/L)	1,013 (0,997 - 1,029)	0,104
• Haemoglobin (g/dL)	0,98 (0,95 - 1,01)	0,189
• Platelets (x109/L)	0,998 (0,997 - 0,999)	<0,001
• INR	1,08 (0,99 - 1,17)	0,097
• PTT (s)	1,006 (1,002 - 1,009)	<0,001
• CRP (mg/L)	0,998 (0,996 - 1,000)	0,042
Echocardiography		
TAPSE	0,990 (0,964 - 1,015)	0,401
Mitral regurgitation		
Trivial - Mild	0,79 (0,60 - 1,03)	0,078
Moderate - severe	0,54 (0,42 - 0,69)	<0,001
Tricuspid regurgitation		
Trivial - Mild	0,76 (0,60 - 0,96)	0,022
Moderate - severe	0,90 (0,71 - 1,14)	0,383
Aortic regurgitation		
• Trivial - Mild	0,94 (0,80 - 1,11)	0,482
• Moderate - severe	1,12 (0,76 - 1,64)	0,574
• Ejection fraction grade <20%	0,97 (0,83 - 1,13)	0,678
• RV dysfunction		
• Trivial - Mild	1,09 (0,85 - 1,40)	0,497
• Moderate - severe	1,08 (0,89 - 1,31)	0,407
Haemodynamic parameters		
• Heart rate (b.p.m.)	0,997 (0,993 - 1,001)	0,162
• Systolic blood pressure (mmHg)	1,002 (1,000 - 1,004)	0,086
• Diastolic blood pressure (mmHg)	0,997 (0,992 - 1,003)	0,381
• Mean blood pressure (mmHg)	1,002 (0,999 - 1,005)	0,239
• Pulmonary artery systolic pressure (mmHg)	1 (0,995 - 1,005)	0,918
• Pulmonary artery diastolic pressure (mmHg)	0,989 (0,980 - 0,998)	0,017
• Mean pulmonary artery pressure (mmHg)	0,994 (0,986 - 1,002)	0,135
• Right atrial pressure (mmHg)	1,007 (0,994 - 1,021)	0,259
• Pulmonary artery wedge pressure (mmHg)	0,986 (0,976 - 0,996)	0,008

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

Supplementary Table 5. Overview of characteristics included in the propensity scored matching model with standardized mean difference before and after matching

Characteristic	Standardized mean difference before matching	Standardized mean difference after matching
Age	41.09	1.64
Time since first cardiac diagnosis	29.88	2.69
INR	25.2	2.38
Albumin	24.88	0.64
CRP	24.81	9.17
BSA	22.21	4.27
Heart Rate	21.30	1.18
Gender	18.91	10.02
Creatinin	17.70	3.51
Antiplatelet	15.28	5.63
Amiodarone	14.31	4.14
Tricuspid insufficiency	13.65	3.54
TAPSE	13.60	1.76
COPD	11.94	9.33
Primary diagnosis (other)	10.50	8.88
ACE inhibitor	10.44	2.08
Platelets	10.06	1.19
Pulmonary artery systolic pressure	9.48	3.07
Peripheral vascular disease	8.83	8.31
Smoking history	8.16	0.38
Anticoagulant	7.36	4.18
ASAT	6.76	6.45
Dilated cardiomyopathy	6.71	8.03
Neurologic event	6.25	6.11
Haemoglobin	6.24	6.56
PTT	5.84	9.70
Inotropes	5.36	2.32
Bilirubin	5.24	4.04
ALAT	5.20	4.64
Cancer	4.77	3.95
Mitral insufficiency	4.58	5.20
Ejection fraction <20%	4.33	1.06
Major infection	3.55	4.67
ECMO	3.41	2.25
Myocardial infarction	2.78	2.52
Intubated	2.42	1.40
Aortic insufficiency	2.32	5.79
ICD	2.25	2.59
Right atrial pressure	1.82	1.06

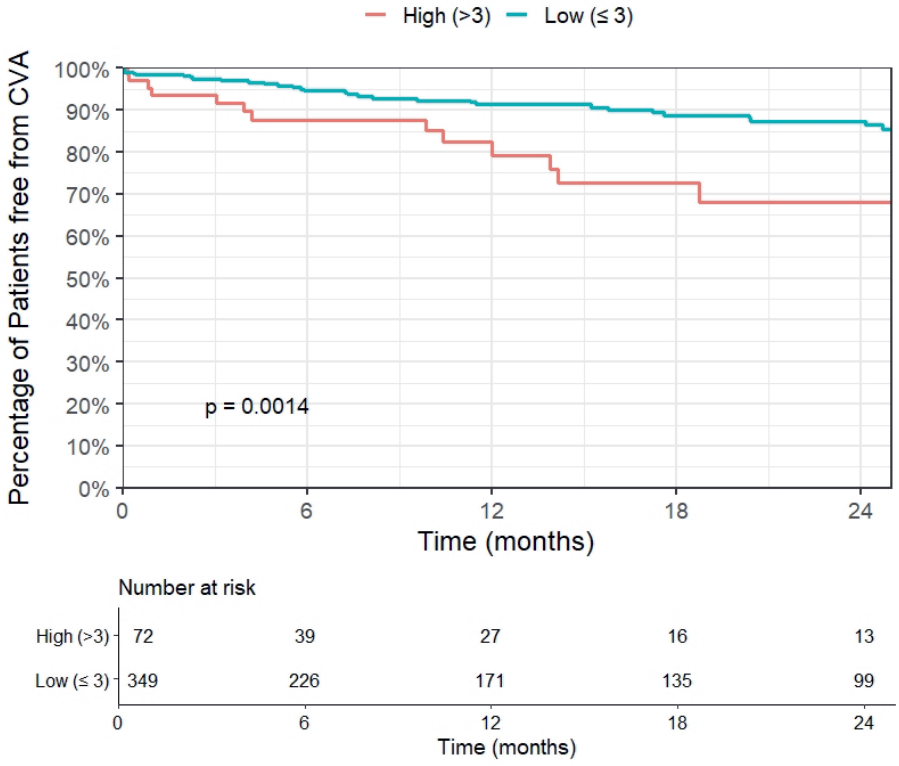
Characteristic	Standardized mean difference before matching	Standardized mean difference after matching
WBC	1.60	3.44
Beta blockers	1.34	2.01
Phenprocoumon	0.90	11.77
LDH	0.58	2.97
MAP	0.54	3.59

BSA: body surface area; COPD: chronic obstructive pulmonary disease; CRP; C-reactive protein; ECMO: extracorporeal membrane oxygenation; ICD: implantable cardioverter-defibrilator; INR: international normalized ratio; PTT: Partial thromboplastin time; TAPSE; Tricuspid annular plane systolic excursion; WBC: white blood cell count

Supplementary Table 6. Baseline characteristics for patients with pre-operative atrial fibrillation or sinus rhythm still at risk at 24 months.

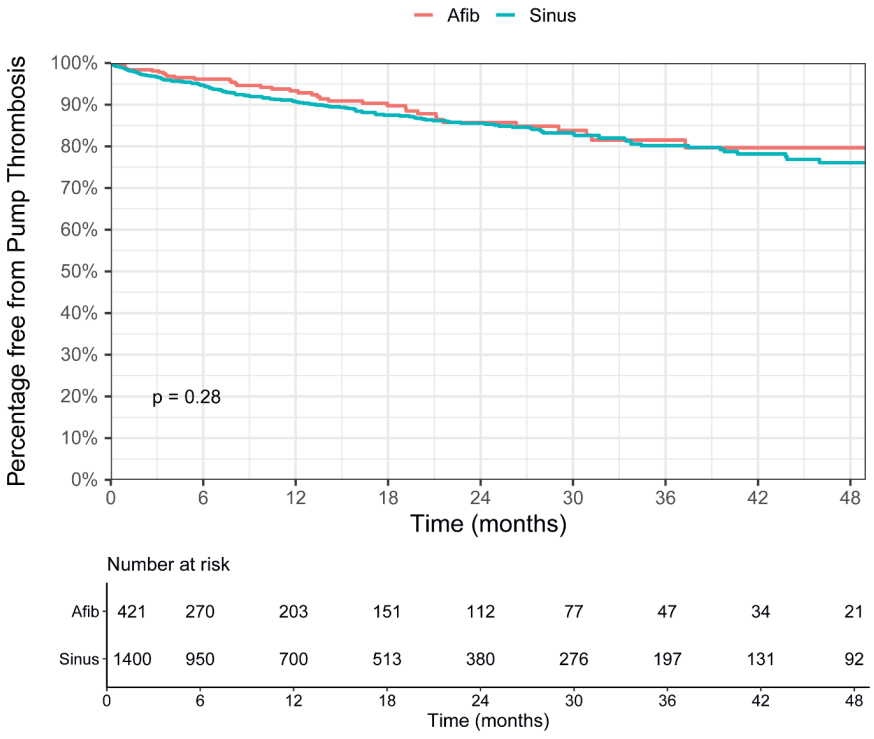
Baseline characteristic	Sinus rhythm (n=392)	Atrial fibrillation (n=112)	p-value
Age	53 [41 – 59]	57.5 [49.5 – 63]	0.001
Male	362 (83.2%)	104 (92.9%)	0.011
Body surface area	1.94 [1.79 – 2.11]	2.05 [1.90 – 2.19]	0.001
Body mass index	22.2 [19.6 – 25.2]	23.6 [21.2 – 26.6]	0.001
Primary diagnosis			0.238
• Ischemic	129 (33.9%)	36 (33.3%)	
• Dilated	177 (46.6%)	58 (53.7%)	
• Other	74 (19.5%)	14 (13%))	
Time since first cardiac diagnosis			0.008
• < 1 month	57 (14.6%)	7 (6.4%)	
• 1 month to a 1 year	64 (16.4%)	10 (9.1%)	
• One to 2 years	37 (9.5%)	7 (6.4%)	
• > 2 years	204 (52.3%)	78 (70.9%)	
• unknown	28 (7.2%)	8 (7.3%)	
INTERMACS Patient Profile			0.277
• INTERMACS 1 – 2	168 (43%)	45 (40.2%)	
• INTERMACS ≥3	223 (57%)	67 (59.8%)	
ECMO support pre-implant	28 (7.3%)	11 (10.1%)	0.335
IABP pre-implant	39 (10.2%)	13 (11.8%)	0.226
Mechanical ventilation	40 (10.5%)	8 (7.3%)	0.992
Comorbidities			
• Carotid artery disease	9 (2.7%)	1 (1.0%)	0.321
• History of Neurological event	32 (8.4%)	12 (10.9%)	0.417
• Cancer	10 (3.0%)	3 (3.0%)	0.994
• Dialysis	10 (2.6%)	5 (5.5%)	0.134
• Major myocardial infarction	53 (13.8%)	19 (17.3%)	0.363

Continuous variables are depicted as median [interquartile range] and categorical variables as count (percentage). ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; INTERMACS, interagency registry for mechanically assisted circulatory support



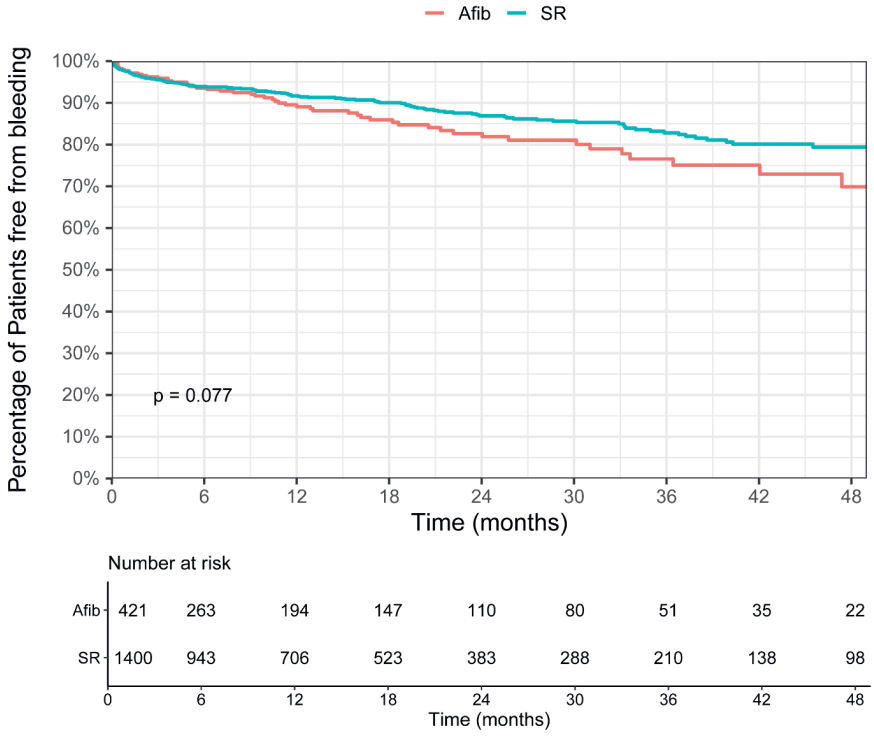
Supplementary Figure 1. Freedom from CVA according for patients with atrial fibrillation and patients with CHA_2DS_2-VASC score >3 or <4.

Kaplan Meier analysis for freedom from cerebrovascular accidents (CVA) for patients with atrial fibrillation according to a low (≤3) or high (>3) CHA_2DS_2-VASC score.



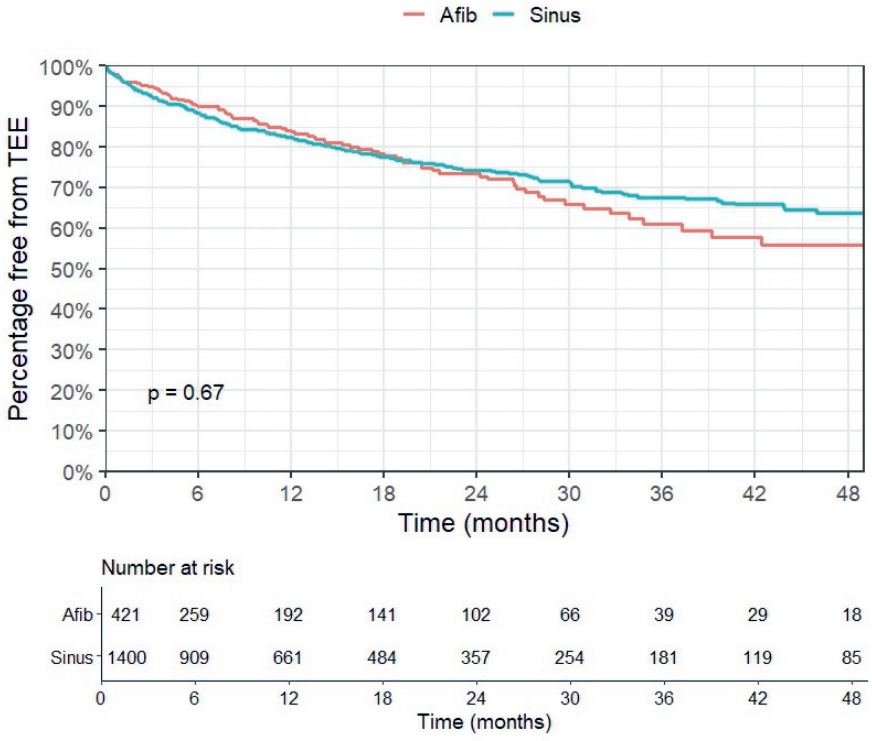
Supplementary Figure 2. Freedom from pump thrombosis according to pre-implantation atrial fibrillation and sinus rhythm

Afib: atrial fibrillation



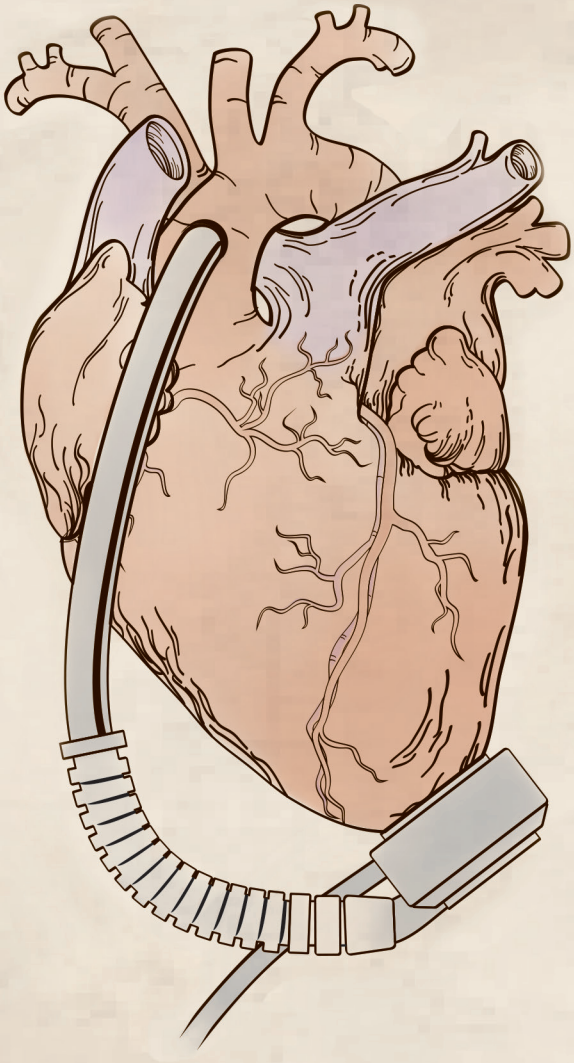
Supplementary Figure 3. Freedom from bleeding according to pre-implantation atrial fibrillation and sinus rhythm

Afib: atrial fibrillation



Supplementary Figure 4. Freedom from thromboembolic events according to pre-implantation atrial fibrillation and sinus rhythm

Afib: atrial fibrillation; TEE: thromboembolic events



Chapter VII

Driveline Exit-Site Wound Care Protocols in Left Ventricular Assist Device Patients: A Systematic Review

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ABSTRACT

Objectives: Driveline infections continue to be a significant complication following left ventricular assist device (LVAD) implantation. Driveline exit-site care is crucial for the prevention of infections, however there are no uniform guidelines. This study aimed to provide an overview of the currently published driveline exit-site care protocols in patients with LVAD.

Methods: A systematic literature review was performed. Studies before 15 December 2020 were included if the number of driveline infections were a primary outcome and the driveline exit-site care protocol was explained.

Results: Eleven articles were included in the systematic review, including 1602 LVAD patients. The median of driveline infection frequency in the articles was 13.8% with a range of 0% to 52.6%. There was a marked variability in the care methods of driveline exit-site, without a standardized driveline dressing technique in LVAD patients. Driveline infection frequencies were found between 6%-7.5% in studies using a dressing kit including chlorhexidine, silver-based dressing and an anchoring device. Furthermore, there was a variability in the anchoring devices and the dressing change frequency, varying from daily to weekly. No specific anchoring device or change frequency was found to be superior.

Conclusion: Based on this systematic review, driveline exit care protocols including chlorhexidine, silver-based dressing, the use of an anchoring device, and dressing kits might be best in reducing driveline infection rates. However, prospective studies with larger cohorts are needed to establish the optimal protocol for driveline exit-site care.

INTRODUCTION

Driveline infections continue to be a significant complication following left ventricular assist device implantation (LVAD) and are a limiting factor to successful long-term LVAD support [1, 2]. The International Society for Heart and Lung Transplantation (ISHLT) Mechanically Assisted Circulatory Support (IMACS) reported driveline infection rates as high as 29% after 3 months LVAD implantation [2]. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) reported that driveline infections occur in approximately 19% LVAD recipients by 12 months after implant [3].

The driveline exit-site is frequently the entry site of pathogens that may cause local infection and these infections could track to the pocket and the pump. Therefore, driveline infections increase the risk for pump-/cannula-, pocket-, and bloodstream infections [2]. We know that driveline exit-site care is paramount for the prevention and treatment of driveline infections [4, 5]. Despite the importance of care, there are few specific recommendations for the management of the LVAD driveline exit-site [4, 6-8]. Research on driveline exit-site care has shown that driveline exit-site management is not standardized, resulting in a wide variety of management protocols among LVAD centres [9]. The aim of this systematic review was to provide an overview of the currently published driveline exit-site care protocols in patients with an LVAD.

MATERIALS AND METHODS

Search strategy

This systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. Search strategy was developed with a librarian for inclusion sensitivity. A literature search was performed using Embase, Medline Ovid, Cinahl Ebscohost, Web of Science Core Collection, Cochrane Central register of trials, Google scholar databases using the following search terms: 'left ventricular assist device', 'ventricular assist device', 'heart assist device', 'driveline', 'wound care', 'infection prevention', 'driveline infection', 'device infection', 'exit site', 'wound infection', 'wound care', 'care', 'wound management', 'dressing', 'protocol'.

Study selection

Two reviewers (Z.O.K. and Y.C.Y.) independently reviewed potentially eligible studies for evaluation. Titles and abstracts were examined for possible inclusion, before the full-text version of the remaining articles were obtained. All authors were involved in the final selection and data extraction of included articles. Any discrepancies regarding inclusion between the authors were resolved by consensus between all authors. Full-text clinical research articles written in English and published before 15 December 2020 were included in the systematic review. Studies were included if driveline exit-site care protocol was explained, and if driveline-related and specific infections was a primary outcome. Case reports, review articles, animal studies and conference abstracts were excluded. In addition, studies were excluded if they only discussed surgical interventions for care management, examined pulsatile flow devices, or less than 30 patients included.

Table 1. Summary of baseline characteristics of the articles in the systematic literature review

Article / Country	Study design	Study period	Sample size	LVAD characteristics	Patients characteristics	Definition of LVAD infection	Perioperative antibiotic prophylaxis	STROBE score
Schlöglhofer et al. 2020 Austria [12]	Retrospective analysis, single center	January 2013 -July 2017	Cohort n=183	Device: HM II™, HM 3™, HW™ HVAD Device strategy: BTC:35.5%, BTT:32.8%, DT:27.9%, BTR: 0.5%	Mean age: 58.0 BMI: 26.6 DM: 32.7% Length of support: N/R	ISHLT	N/R	19
Lander et al. 2018 USA [8]	Retrospective cohort study, single center	January 2010 - October 2015	Intervention n= 92 Control n=61	Device: HM II™, HW™ Device strategy: BTC:59%, DT:41%	Mean age: 58.1 BMI: 29.7 DM: 43.8% Length of support: N/R	INTERMACS ISHLT	N/R	20
Aburjania et al. 2017 USA [16]	Retrospective cohort study, single center	November 2006-September 2015	Intervention n=120 Control n=163	Device: HM II™ Device strategy: N/R	Mean age: 59 BMI: 29.1 DM: N/R Length of support: 713 days	Institution's standard definition	Yes	20
Durand et al. 2017 USA [17]	Retrospective cohort study, single center	August 2005-December 2014	Intervention n=65 Control n=19	Device: N/R Device strategy: BTT:82%, DT:18%	Mean age: 55 BMI: 25.8 DM: 22% Length of support: 370 days	ISHLT	Yes	20
Cagliostro et al. 2016 USA [15]	Prospective cohort study, single center	January 2009-December 2013	Intervention n=159 Control n=107	Device: HM II™, HW™ Device strategy: BTT: 67%, DT:33%	Mean age: 58.2 BMI: N/R DM: 34.2% Length of support: N/R	INTERMACS	N/R	18
Son et al. 2016 USA [14]	Retrospective analysis, single center	January 2009-December 2013	CHG group n=37 PVP-I group n=7	Device: HM II™ Device strategy: N/R	Mean age: 60 BMI: 25.0 DM: 36.4% Length of support: 521 days	INTERMACS	Yes	19
Stahovich et al. 2016 USA [7]	Prospective study, multicenter	N/R	Cohort n=50	Device: HM II™ Device strategy: N/R	Mean age: 62 BMI: N/R DM: 25% Length of support: 496 days	N/R	N/R	18
Menon et al. 2015 Germany [18]	Retrospective cohort study, single center	January 2008-April 2011	Intervention n=31 Control n=17	Device: HM II™ Device strategy: BTT/BTC/BTR=77.5%, DT=22.5%	Mean age: 58.1 BMI: 27.2 DM: 29% Length of support: 198 days	The Cleveland Clinic Classification	Yes	20

Article / Country	Study design	Study period	Sample size	LVAD characteristics	Patients characteristics	Definition of LVAD infection	Perioperative antibiotic prophylaxis	STROBE score
Stulak et al. 2013 USA [13]	Retrospective cohort study, single center	February 2007- September 2011	Intervention n=144 Control n=141	Device: HM II™ Device strategy: BTT 59%, DT 41%	Mean age: 54 BMI: N/R DM: N/R Length of support: N/R	N/R	Yes	18
Sharma et al. 2012 USA [4]	Retrospective analysis, single center	January 2007- January 2011	Cohort n=143	Device: HM II™ Device strategy: BTT 39%, DT 61%	Mean age: 61.3 BMI: 30.8 DM: 33.6% Length of support: N/R	ISHLT	Yes	18
Hozayen et al. 2012 USA [19]	Retrospective cohort study, single center	N/R	Utah protocol n=16 Minnesota protocol n=47	Device: HM II™, HW™, VentrAssist™ Device strategy: N/R	Mean age: 57.1 BMI: 29.7 DM: 39.6% Length of support: 483 days	ISHLT	N/R	15

Categorical values are mentioned as n (%). LVAD: Left ventricular assist device infection, N/R: Not reported, CHG: Chlorhexidine gluconate, PVP-I: Povidone-iodine, INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support, ISHLT: International Society for Heart and Lung Transplantation, BTT: Bridge to transplant DT: Destination therapy, BTC: Bridge to candidacy, HM: HeartMate™, HW: HeartWare™, BMI: Body mass index (kg/m^2), DM: Diabetes Mellitus, STROBE: Strengthening the Reporting of Observational Studies in Epidemiology Statement

Data Extraction
Data that were extracted included study and LVAD characteristics, sample size, follow up time, device type and strategy, definition criteria of driveline infections, perioperative antibiotic prophylaxis. The primary outcomes expected to report in the studies were driveline care protocols and driveline infections. We also evaluated time to first infection, infection relapse rates and microorganisms causing driveline infections.

Quality assessment
Quality of each article was appraised using the Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE) checklist (Table 1). A higher score from the checklist indicates higher quality [11].

Statistical analysis
Data from the articles were analyzed with SPSS 22.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were presented in numbers and percentages. Continuous variables were presented as median and mean. A meta-analysis could not be performed due to the substantial heterogeneity in the exit-site care methods of the studies.

RESULTS

A total of 846 articles were identified through the literature search after duplicates had been removed and were assessed by title and abstract for the review. Forty-seven articles were reviewed by full texts based on the selection criteria, and thirty-six were excluded based on full manuscript assessment. Eleven articles fulfilled the inclusion criteria, underwent quality assessment and were included in the final review (Figure 1).

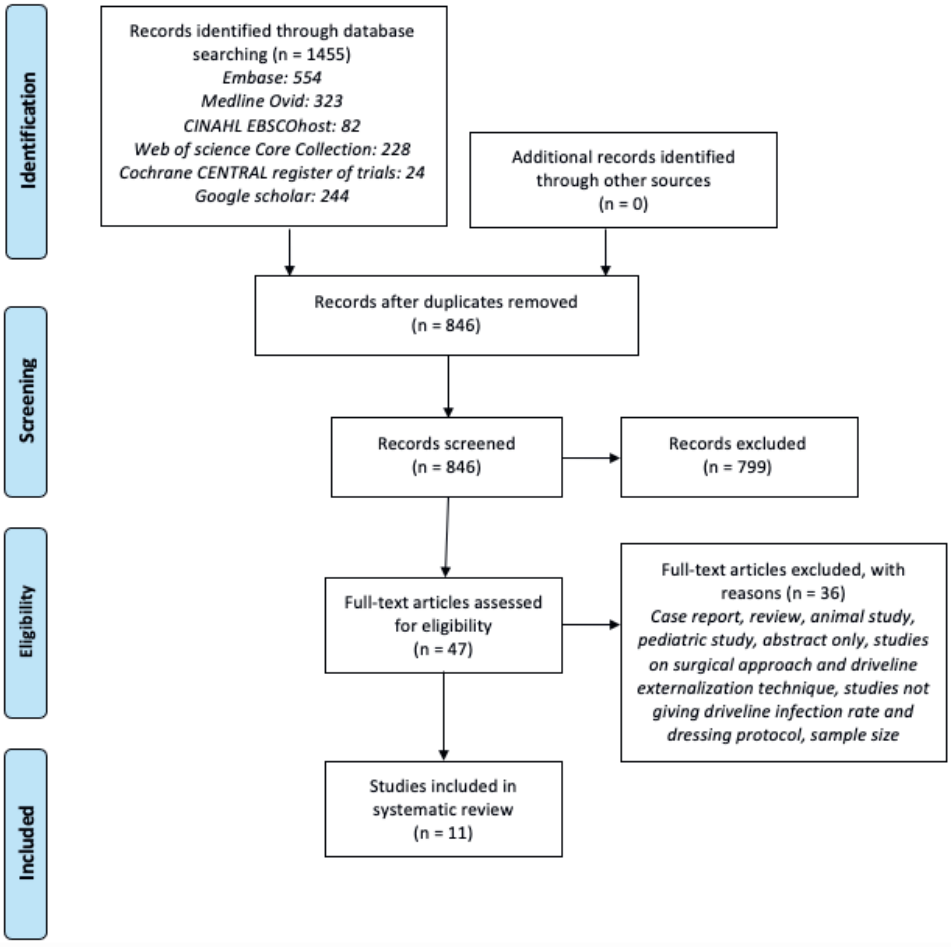

Figure 1. Flow diagram summarizing the review process

Nine articles included studies conducted in United States, one in Germany and one in Austria. Nine articles were retrospective cohort studies and two were prospective studies (Table 1). There was a substantial range in type of dressing methods and management of care discussed in the articles (Table 2). Three of the studies evaluated the whole care protocol, while others compared cleaning agents, covering materials, showering properties and the use of a dressing kit (Table 3). There was no an obvious change over time in the driveline exit-care protocols which made a substantial difference. INTERMACS and ISHLT criteria were used for definitions of driveline infections in the seven articles. Table 1 summarizes the final articles and STROBE scores. The mean number of patients described in the 11 articles was 145 LVAD patients (range, 44 to 285 patients). LVAD strategy was bridge to transplant/ candidacy/recovery (63%) and destination therapy (37%) in the articles. The median of driveline infection frequencies in the articles was 13.8% with a range of 0% to 52.6% in a follow-up of 6-44 months in this cohort. The causative microorganisms of driveline infections

were reported in 8 out of 11 articles. The organism reported as the most common causes of driveline infections were *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Table 3). The types of the devices were HeartMate (HM) II and 3, HeartWare (HW) and VentrAssist in the included articles; HM II in six, HM II and HW in two, HM II, 3 and HW HVAD in one and, HM II, HW and VentrAssist in one study. In one study none of the device type was reported (Table 1). The driveline infection readmission was evaluated according to the device type in one study. The study reported that HM 3 patients had a higher risk for driveline infection readmissions compared to HW HVAD or HM II [12].

Driveline exit-site cleaning agents

The most frequently used cleaning agent was chlorhexidine gluconate (CHG) (n=7) (Table 2) [4, 7, 8, 13-16]. CHG was used with the saline solution in the three studies [4, 7, 8]. CHG characteristics (saline or alcohol-based) was not reported in the articles. In two studies, if there was a skin irritation or CHG intolerance, povidone-iodine was used an alternative cleaning agent [14, 16]. Driveline infection frequency differed between the studies, with a range of 5.4%-21.3% in the studies using CHG as a cleaning agent (Table 3). Studies using CHG and silver-based dressing for the care of driveline exit-site reported driveline infection frequency of 6%-7.5% [7, 15]. In the studies using CHG and sterile gauze dressing for exist-site care, driveline infection frequencies were between 5.4%-21.3% [4, 8, 14, 15]. Son et al. reported with, povidone-iodine, used as an alternative cleaning agent in CHG intolerant patients, a higher driveline infection frequency (42.9%) [14]. Durand et al. evaluated effect of topical polymyxin-trimethoprim (poly) solution on driveline infections [17]. While the driveline infection rate was reported in n=9 patients (13.8%) in the group using poly solution and n=10 patients (52.6%) in non-poly group (p=0.001). Menon et al. compared merbromin with octenidine solutions for cleaning the driveline exit-site [18]. The driveline infection frequency in patients using octenidine was 11.8%, no infections were found in patients using merbromin solution. In the study by Schlöglhofer et al. octenidine was used as a cleaning agent and the driveline infection frequency was reported 27.3% [12]. Hozayen et al. reported a driveline infection frequency of 13% when soap and antimicrobial spray was used for driveline exit-site cleaning [19].

Dressings materials for the driveline exit-site

Sterile gauze pad (n=5) and silver-based dressing (n=3) were the most common used covering materials for dressing of driveline exit-site (Table 2). Cagliostro et al. compared driveline dressing protocols including silver-based dressing with sterile gauze dressing. The driveline infection frequency (7.5%) in silver-based group was lower than the group using sterile gauze (15.8%) [15]. In the study by Stahovich et al. silver-based dressing and CHG were used for the care of driveline exit-site. With this protocol, driveline infection frequency and time to first infection were 6% and 180 days, respectively [7]. Two studies evaluated driveline exit-site dressing protocol included foam- based dressing [8, 19]. Hozayen et al. compared foam and sterile gauze dressing for covering of driveline exit site. Driveline infection frequency was reported 19% for foam-based dressing and 13% for sterile gauze dressing (p=0.68) [19]. Lander et al., used foam-based dressing and CHG for dressing and, driveline infection frequency was reported 7.6% [8]. Schlöglhofer et al. reported a driveline infection rate of 27.3% when absorptive non-adherent compress and octenidine was used for the care of driveline exit-site [12].

Table 2. Summary of driveline exit-site dressing change methods described in the articles and at Erasmus University Medical Center

Article	Cleaning agent	Dressing closure	Anchoring device	Dressing change frequency	Showering	Sterile technique	Use of a dressing kit
Schlöglhofer et al. 2020 [12]	Octenidine solution	Absorptive non-adherent slit compress (Askina Pad™ 5x5 cm)	Secutape Nanoplast fixation™	Twice or three times weekly	N/R	Yes*	N/R
Lander et al. 2018 [8]	CHG and saline solution	Control: Sterile gauze pad dressing (The Telfa island™ occlusive sandwich dressing) Intervention: The Kendal™ fenestrated foam dressing	Control: Centurion™ foley holder Intervention: Centurion™ Secure view Port Window	Weekly	N/R	Yes**	N/R
Aburjania et al. 2017 [16]	CHG PVP-I (if there is a skin irritation)	N/R	N/R	N/R	Not allowed, exit site must kept dry (using a hand-held shower attachment to wash their hair and lower extremities)	Yes^	N/R
Durand et al. 2017 [17]	Polymyxin-trimethoprim solution (polymyxin B 10000 units/mL + trimethoprim 1mg/mL)	N/R	N/R	Once or twice weekly	Allowed once per week when the exit site healed.	N/R	N/R
Cagliostro et al. 2016 [15]	Control: CHG 2% Intervention: CHG 2% and 70% isopropyl alcohol	Control: Sterile gauze pad dressing Intervention: Silver-based dressing	Control: Bio-occlusive dressing, binder or StatLock™ device Intervention: Centurion™ foley holder	N/R	N/R	N/R	Yes
Son et al. 2016 [14]	CHG group: CHG 2% PVP-I group: Povidone-iodine 10%	Sterile gauze sponge dressing	Centurion™ foley holder	Three times weekly	Allowed with occlusive covering of the driveline exit site	Yes^	Yes
Stahovich et al. 2016 [7]	CHG 3.15%, saline solution and isopropyl alcohol 70%	Silver-based dressing SorbaView Ultimate dressing™	Centurion™ foley holder	Weekly	Allowed with occlusive covering of the driveline exit site	Yes#	Yes

Article	Cleaning agent	Dressing closure	Anchoring device	Dressing change frequency	Showering	Sterile technique	Use of a dressing kit
Menon et al. 2015 [18]	Control: Octenidine dihydrochloride 0.1% Intervention: Merbromin 2%	Silver-based dressing and sterile gauze pad dressing	Hollister™ plate stabilizer	Every 5-6 day	N/R	Yes**	N/R
Stulak et al. 2013 [13]	CHG 4%	N/R	N/R	N/R	N/R	Yes^	N/R
Sharma et al. 2012 [4]	CHG and saline swabs	Sterile gauze pad dressing	Abdominal binder	Daily	N/R	Yes**	N/R
Hozayen et al. 2012 [19]	Utah protocol: N/R Minnesota protocol: soap and antimicrobial spray	Utah protocol: Foam-based dressing Minnesota protocol: Sterile gauze pad dressing	N/R	Utah protocol: Every third day Minnesota protocol: Daily	N/R	Yes^	N/R
Erasmus University Medical Centre	CHG 4%	Silver-based and sterile gauze pad dressing	Hollister® plate stabilizer	Two times a week	Allowed once per week when the exit site healed.	Yes&	No

CHG: Chlorhexidine gluconate, PVP-I: Povidone-iodine, N/R: Not reported, *: Using sterile dressing closure, facemask, hair cover, sterile gloves **: Using sterile dressing closure, facemask and sterile gloves, #: Using sterile dressing closure, facemask, hair cover, non-latex gloves, ^: Using sterile dressing closure, &: Using sterile dressing closure and sterile gloves

Anchoring devices used for stabilization of driveline

For immobilization of the driveline, the Centurion™ foley holder, Hollister™ plate stabilizer, abdominal binder, Centurion™ secure view port and Secutape Nanoplast fixation™ were used (Table 2). The most frequently used anchoring device for stabilization of driveline was Centurion™ foley holder in 4 studies [7, 8, 14, 15]. In two studies, driveline exit-site dressing protocol included Centurion™ foley holder, silver-based dressing and CHG. These studies reported driveline infection frequency and time to first infection of 6%-7.5% and 180 days, respectively [7, 15]. Driveline care protocol included Centurion™ Foley holder, sterile gauze dressing and CHG was used in two studies. These studies reported driveline infection frequency between 5.4%-21.3% [8, 14]. The Hollister™ plate stabilizer was used for immobilizing the driveline in one study, driveline infection frequency reported was 0%-11.8%.[18] The study that used abdominal binder for immobilizing the driveline reported driveline infection rate 12% [4]. In the study of Schlöglhofer et al. Secutape Nanoplast fixation™ was used and a driveline infection frequency of 27.3% was reported [12].

Frequency of driveline exit-site dressing change

The frequencies of dressing changes differed between the studies and varied from daily to weekly (Table 2) [4, 7, 8, 12, 14, 17, 19]. Two studies reported weekly dressing change in driveline exit-site care protocol. Stahovich et al. evaluated effect of using a dressing kit and weekly dressing change in their study, they reported 6% driveline infection frequency and 180 days to first driveline infection [7]. In the study by Lander et al., weekly fenestrated foam dressing and weekly occlusive sterile gauze dressing were compared. While the driveline infection frequency in weekly fenestrated foam dressing group was 7.6%, an infection frequency of 21.3% was reported in weekly occlusive sterile gauze dressing group. [8] In two studies, with daily dressing changes, driveline infection frequencies of 12%-13% were reported [4, 19]. Hozayen et al. reported 3 times weekly foam-based dressing change and reported a 19% driveline infection frequency in their study [19]. In the study of Son et al. three times weekly dressing change protocol included CHG and povidone-iodine as cleaning agent was evaluated. The study reported a driveline infection frequency of 5.4% in the CHG group and 42.9% in the povidone-iodine group [14]. In the study of Schlöglhofer et al., 2-3 times weekly dressing change with octenidine solution and 27.3% driveline infection frequency was repeorted [12].

Showering strategies for LVAD patients

Showering strategies in the driveline exit-site care protocols were reported in four studies (Table 2) [7, 14, 16, 17]. Aburjania et al. investigated the effect of abstaining from conventional showers and keeping the driveline exit-site dry. Driveline infection frequency and *Pseudomonas* infection frequency were 14% and 1% in the intervention group, and 42% and 9% in the control group, respectively [16]. Occlusive covering over the driveline exit-site dressing during showering was used in two studies and, driveline infection frequencies reported were between 5.4%-42.9% [7, 14].

Table 3. Summary of results of the articles included in the systematic literature review

Article	Intervention / Implementation	Median Follow up time (months)	Driveline infection rate	Time to first infection (days)	Infection relapse rate	Microorganisms
Schlöglhofer et al. 2020 [12]	To characterize risk factors for DLI readmission 2 years postimplant	24	27.3% (50/183)	N/R	N/R	*S. aureus 56% (32/57) *P. aeruginosa 12% (7/57) *Others 32% (18/57)
Lander et al. 2018 [8]	Control: Historical LVAD patients (using Telfa™ Island dressing) Intervention: Fenestrated hydrophilic foam dressing	Control: 23.8 Intervention: 39.1	Control: 21.3% (13/61) Intervention: 7.6% (7/92) [p=0.032]	N/R	45% (9/20)	*MSSA 32%, *MRSA 11% *P. aeruginosa 14%, *Proteus 11% *CoNS 7%, *Others 25%
Aburjania et al. 2017 [16]	Control: Historical LVAD patients Intervention: Not to take conventional showers and to keep the exit site dry while bathing	Control: 44.4 Intervention: 13.2	Driveline infection [p=0.06] Control: 42% (69/163) Intervention: 14 % (17/120) Pseudomonas infection [p=0.077] Control: 9% (15/163) Intervention: 1% (1/120)	347 (entire sample)	N/R	P. aeruginosa Control: 17% (15/86) Intervention: 1.1% (1/86)
Durand et al. 2017 [17]	Control: No topical antibiotics Intervention: Topical polymyxin trimethoprim solution	12.3	Control: 52.6 (10/19) Intervention: 13.8% (9/65) [p=0.001]	Control: 164 Intervention: 320	37% (7/19)	P. aeruginosa: 37% (7/19) MSSA 16% (3/19) Skin flora: 26% (5/19) Others: 21% (4/19)
Cagliostro et al. 2016 [15]	Control: Historical LVAD patients (using gauze pad dressing and not using a standard kit) Intervention: Using of a standard kit for dressing (included silver-based gauze dressing and a standard anchoring device)	Control: 8.7 Intervention: 11.6	Control: 15.8% (17/107) Intervention: 7.5% (12/159)	Control: 154 Intervention:181	Control: 65% (11/17) Intervention: 50% (6/12)	N/R
Son et al. 2016 [14]	CHG group: Using CHG for cleaning PVP-I group: Using povidone-iodine in patients with CHG intolerance for cleaning	17.3	CHG group= 5.4% (2/37) PVP-I group= 42.9% (3/7) [p=0.02]	336 (entire sample)	N/R	CHG group: Acinetobacter 50% (1/2) Stenotrophomonas 50% (1/2) PVP-I group: S. aureus 100% (3/3)
Stahovich et al. 2016 [7]	Using the percutaneous lead management kit for dressing	6	6% (3/50)	180	N/R	N/R

Article	Intervention / Implementation	Median Follow up time (months)	Driveline infection rate	Time to first infection (days)	Infection relapse rate	Microorganisms
Menon et al. 2015 [18]	Control: Using Octenidine solution for cleaning Intervention: Using Merbromin solution for cleaning	Control: 6.7 Intervention: 6.5	Control: 11.8% (2/17) Intervention: 0% [p: 0.043]	Control: 130.5 Intervention: Infection free	N/R	S. aureus 100% (2/2)
Stulak et al. 2013 [13]	Control: Sterile dressing changes without continued (long-term) prophylactic antibiotics Intervention: Sterile dressing changes with continued (long-term) prophylactic antibiotics	Control: 11 Intervention: 12.3	Control: 13% (19/141) Intervention: 18% (26/144) [p=0.15]	N/R	N/R	Staphylococci (no rate)
Sharma et al. 2012 [4]	Experience with the management of driveline infections (sterile dressing changes with CHG and saline application, without prophylactic oral antibiotics)	11.3	12% (18/143)	182	22% (4/18)	CoNs: 44.5% (4/9#) S. aureus: 33.3% (3/9#) P. aeruginosa: 22.2% (2/9#)
Hozayen et al. 2012 [19]	Utah protocol: Foam-based dressing Minnesota protocol: Gauze-based dressing	18	Utah protocol: 19% (3/16) Minnesota protocol: 13% (6/47) [p=0.68]	N/R	N/R	N/R

N/R: Not reported, Chlorhexidine gluconate: CHG, Povidone-iodine: PVP-I, P aeruginosa: Pseudomonas aeruginosa, S. aureus: Staphylococcus aureus, MSSA: Methicillin-sensitive Staphylococcus aureus, MRSA: Methicillin-resistant Staphylococcus aureus, CoNS: Coagulase-negative staphylococci. *The study reported cultures with multiple organisms, #The study reported microorganisms for 9 cases.

Using a kit for driveline exit-site dressing

The utilization of a kit for driveline exit-site dressing was reported in two studies (Table 2) [7, 15]. Cagliostro et al. compared a group using a standard kit included silver-based dressing and an anchoring device with a historical control group. Driveline infection frequency and time to infection were 7.5% and 181 days in the standard dressing kit group, and 15.8% and 154 days in the historical control group, respectively [15]. In the study of Stahovich et al., the use of a percutaneous lead management kit for dressing was evaluated. They reported a driveline infection frequency and time to infection of 6% and 180 days, respectively [7].

DISCUSSION

In this systematic review we found a marked variability in the care protocols of LVAD driveline exit-site, without a standardized driveline dressing technique. But, driveline exit care protocols including chlorhexidine, silver-based dressing, the use of an anchoring device, and dressing kits might be the best in reducing driveline infection rates.

In this systematic review, CHG appeared to be the most commonly used cleaning agent for driveline care. CHG has a broad-spectrum of activity against gram-positive, gram-negative non spore-forming bacteria, yeast, and selective lipid envelope viruses [20, 21]. Furthermore, CHG is considered to be advantageous in the care because of poor absorption from the skin and no evidence of systemic accumulation and adverse events [20]. Additionally, the use of CHG has already been proposed as an effective agent in the prevention of surgical site infections [20, 21]. Unfortunately, data on the concentration of CHG, time of evaporation, and whether it was saline or alcohol-based or not, was not available in the included studies. In case of CHG intolerance, povidone-iodine was used for driveline care [14, 16]. Povidone-iodine is an effective bactericidal solution against gram-positive and gram-negative organisms and does not delay the healing of the. However, the absorption of iodine from the skin is a disadvantage in the care [22]. Studies comparing the efficacy of CHG and povidone-iodine in surgical site cleaning and prevention of infections show superiority of CHG [23, 24]. The use of merbromine in driveline exit-site care is controversial as it is a toxic agent due to the brome and mercury content, and is therefore prohibited in many countries [18, 25]. Octenidine, which has been used frequently as an antiseptic in recent years, is another cleaning agent used in driveline care. It is recommended for use in prophylactic antisepsis because it is not absorbed by the skin and mucosa, it is well tolerated and suitable for topical use [26, 27]. In addition, polymyxin-trimethoprim solution was effective in the prevention of driveline infections. However, no other studies suggested the use of either of these this solution in LVAD care. Based on the above, the standardized driveline care protocol should be the best to include CHG as the main cleaning and antiseptic agent, as it is advantageous over other solutions in view of both cost and effectiveness [23]. Alternatively, the use of octenidine or povidone-iodine solutions in CHG intolerant patients may be suggested.

In the current systematic review sterile gauze and silver-based dressings were the most frequently used materials to cover driveline exit-site. The use of sterile gauze dressing in a non-infected dry exit site that completed the healing process can be cost-effective in the driveline exit-site care protocol [28]. In our analysis, the silver-based dressing was more

effective. The use of silver-based dressing in the care was recommended for the prevention of colonization and improving healing [29, 30]. However, some studies assume the evidence for silver-based dressing in the prevention of infections as insufficient and the costs are too high [31, 32]. Foam-based dressing is generally recommended for exudate wounds due to its absorbent property and, is not recommended for use in dry wounds in the literature [28, 33]. According to the results of our study and the literature, wound characteristics should be taken into consideration when choosing the covering material in driveline care protocol. Therefore, the use of silver-based dressing only in the first 6 months after LVAD implantation may be (cost) effective in preventing driveline infections [34]. Silver or foam-based dressing may be preferred depending on whether the exit-site has infection or exudate.

Using an anchoring device is one of the methods to prevent driveline exit-site trauma and, thereby effective in reducing the driveline exit-site infections [34-37]. In our study, there was great variability in the anchoring devices used for the driveline stabilization. However, no clear data for the superiority of any one of the anchoring devices was found.

Driveline exit-site dressing change frequency varies considerably according to the institutions [9, 36, 38]. None of the particular dressing change frequencies was more effective than another in the prevention of driveline infections. The study by Wus et al, not included in the systematic review because of the short follow-up time and inclusion of hospitalized patients, reported that dressing change frequency had no effect on driveline infection frequencies [6]. In determining the optimal dressing change frequency, driveline exit-site features and whether there is infection should be taken into consideration [34, 36]. Daily dressing change is recommended until the driveline exit-site heals completely for effective exit-site cleaning and preventing wet dressings. Once driveline exit-site healed and there is no drainage, a lower dressing change frequency may be feasible and safe, and also increases caregiver and patient satisfaction [19, 36].

In the driveline exit-site care management, keeping the driveline exit-site dry should be considered in the prevention of driveline exit-site infections. Therefore, showers are recommended only after the driveline exit-site has healed completely in LVAD patients [34, 36]. Keeping the driveline exit-site as dry as possible during the shower and changing the dressing immediately after the shower may be effective in preventing driveline infections, in particular *Pseudomonas* infections.

The driveline care protocol requires the use of many different materials. This systematic review suggests that using of a dressing kit might be effective in reducing the driveline infections. The use of a dressing kit in driveline care can be effective in increasing patient compliance and reducing infection frequencies [7].

Clinical implications

Taking the findings of this systemic review in account, driveline exit-site care should preferably be best performed within a standardized protocol, using sterile dressing materials and sterile gloves and with the use of a dressing kit (Figure 2). CHG should be used for driveline exit-site cleaning, and octenidine or povidone-iodine in case of intolerance. The properties of the exit-site should be taken into consideration when choosing covering material. Silver-

based dressing can be used, particular in the first months after implantation. An anchoring device should be used to prevent driveline exit-site trauma. Driveline exit-site should be kept dry as reasonably possible. The dressing change frequency can be decided according to the properties of the exit-site. For a dry exit-site that has completed the healing process, the dressing change frequency can be once or twice a week. The proposed changes, despite the increased cost for materials and agents (e.g. silver-based dressings), may significantly reduce frequent re-admission and long hospitalization.

Figure 2. Recommendation based on the systematic review

Limitations

This systematic review has limitations that should be considered when interpreting the results. The studies included systematic review were mostly retrospective cohort studies. In addition, the studies had small sample size and did not compare the same exit-site care protocols. Due to the substantial heterogeneity in the exit-site care methods of the studies, a meta-analysis could not be performed, and the centre specific findings of the systematic review could perhaps not be generalizable. Furthermore, the studies had less percentage of destination therapy patients and hence might underrepresent these patients.

CONCLUSION

Based on this systematic review, driveline exit-site care protocols including chlorhexidine, silver-based dressing, the use of an anchoring device, and dressing kits might be the best in reducing driveline infection frequencies. However, no strong evidence for a standardized driveline exit-site care exist. Prospective studies with larger cohorts are needed to establish the optimal protocol for the LVAD driveline exit-site care.

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Supplementary Table 1. Summary of recommendations in the articles

Article	Recommendation
Lander et al. 2018, USA	A fenestrated hydrophilic foam dressing protocol is associated with a marked improvement in driveline infections.
Aburjania et al. 2017, USA	Stopping conventional showering and keeping dry the driveline exit site may reduce the rate of Pseudomonas LVAD exit-site infections.
Durand et al. 2017, USA	Using topical polymyxin-trimethoprim may be effective in preventing driveline infections.
Cagliostro et al. 2016, USA	Using of a standardized kit, including silver-based dressing and a standard anchoring device, decreases driveline infections.
Son et al. 2016, USA	Povidone-iodine can be used for driveline antisepsis patients with chlorhexidine intolerance.
Stahovich et al. 2016, USA	The percutaneous lead management kit may help reduce variability and simplify the process of driveline exit site management and increase patient compliance.
Menon et al. 2015, Germany	Using Merbromin solution in the driveline exit site wound care reduces driveline infections.
Stulak et al. 2013, USA	Chronic prophylactic antibiotics do not seem to play a significant role in preventing percutaneous DLI. The most important factor is likely maintenance of the exit-site and avoidance of trauma.
Sharma et al. 2012, USA	Driveline infections may be successfully managed with antibiotics and local wound care.
Hozayen et al. 2012, USA	There is non-inferiority of the foam dressing technique to the gauze dressing in the care of driveline exit-site.

Supplementary Table 2. Definition of LVAD driveline infections in the articles

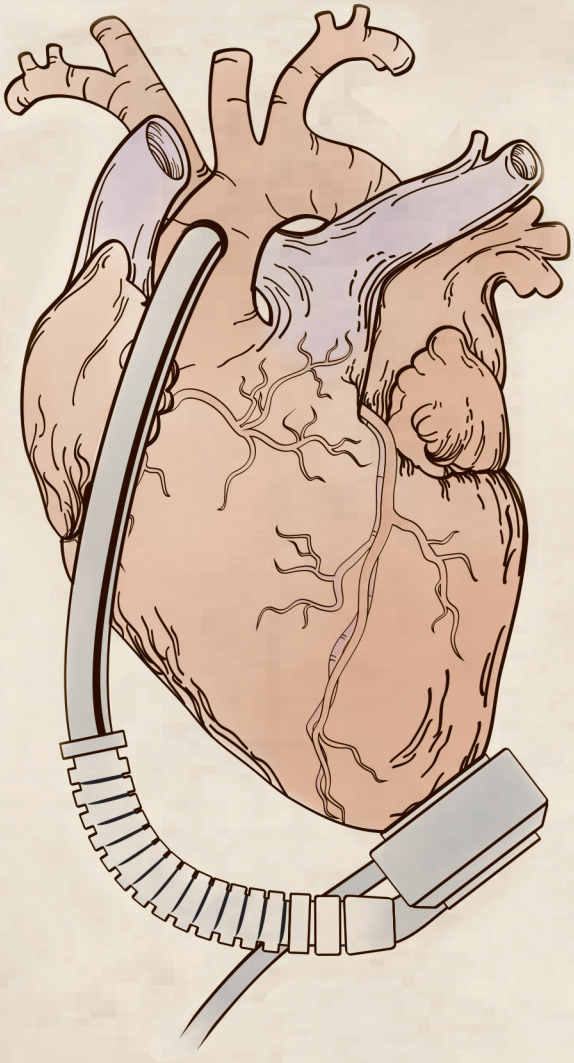
Definition	Articles
INTERMACS[1]	Cagliostro et al. 2016, Son et al. 2016
ISHLT[2]	Durand et al. 2017, Sharma et al. 2012, Hozayen et al. 2012
INTERMACS / ISHLT[1,2]	Lander et al. 2018
Cleveland Clinic classification of ventricular assist device infections[3]	Menon et al. 2015
Own institution's standard definition[4]	Aburjania et al. 2017
Not reported	Stahovich et al. 2016, Stulak et al. 2013

[1] A positive culture from the skin and/or tissue surrounding the driveline, the need for antimicrobial treatment, clinical signs and symptoms of infection (erythema, increased local temperature, pain, fever, or discharge)

[2] Histopathologic or radiologic examination, and isolation of organisms from culture fluid or tissue from the exit site, clinical signs (i.e., purulent drainage from the DLI site, an abscess, or other evidence of infection involving the driveline tract found on direct examination)

[3] Culture or histologic evidence of infection, local or systemic signs of infection, clinical response to antimicrobials, device removal, or both

[4] Purulent discharge from driveline site with one of the following: Erythema, pain and/or induration of skin around driveline



Chapter VIII

Intermittent Levosimendan treatment for late onset right ventricular failure in a patient supported with a left ventricular assist device

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We present a case of a 58-year-old male patient, with end-stage heart failure due to ischemic heart disease for which a HeartMate II left ventricular assist device (LVAD) was implanted in 2013. In 2018, he was admitted with recurrent red low-flow alarms. The differential diagnosis at the first admission was hypovolemia due to dehydration with anemia (hemoglobin 8.22 g/dL), without signs of active bleeding. He was treated with intravenous fluid administration and transfusion with 2 packed cells. Initially the low-flow alarms ceased, however, in the following 3 to 4 months, the patient experienced multiple red low-flow alarms, with LVAD parameters: 9000 RPM, Flow 2.0 L/min, PI 5.6 and Power 3.9. The LVAD log was send to the manufacturer, but no evidence was found for device or driveline related problems. Computed tomography showed no abnormalities. However, echocardiographic imaging displayed severely impaired right ventricular function (TAPSE 5 mm), left ventricular end-diastolic diameter (LVEDD) 57mm with moderate to severe tricuspid valve regurgitation. Right heart catheterization revealed mild pulmonary hypertension (PA 36/17/25 mmHg, wedge 23 mm Hg, extremely low cardiac output/index 3.3/1.8 L/min/kg2, mixed venous saturation (SVO2) of 23%) with inappropriate high right atrial pressures of 17 mm Hg. Low-dose Enoximone (1.0 µg/kg/min) intravenously was started, normalizing filling pressures, reducing congestion and subsequently cessation of his low flow alarms (PA 24/11/16 mmHg, wedge 9 mmHg, RA/CVP 10, CO 4.5, CI 2.5, SVR 977, PVR 119, LVEDD 62 mm, and SVO2 of 67%). Given the excellent response to the low dose Enoximone, we decided to intermittently administer Levosimendan infusions: every 4 weeks (0.1 µg/kg/min) for 24-hours, to support the right ventricle function. At discharge his LVAD parameters were: RPM 9000, Flow 5.3 L/min, PI 3.1 and Power 5.5. At 9 months of follow-up, with monthly intermittent Levosimendan infusions, no low-flow alarms have since been reported. Additionally, no clinical signs of right ventricular failure (RVF) have been observed since his initial treatment with Levosimendan.

Levosimendan has been used successfully to treat acute RVF in the several cardiac settings (1, 2) To the best of our knowledge, this is the first report of successful use of intermittent Levosimendan treatment in a LVAD patient with late RVF. However, this needs to be administered parenterally via a central-venous catheter, making it very cumbersome for long-term treatment. Furthermore, long-term treatment with intravenous inotropes increases mortality, probably due to the pro-arrhythmic and increased myocardial oxygen consumption.(3)

Levosimendan, a calcium sensitizer, functions as a positive inotrope without increased myocardial oxygen consumption, and due to its long-half life, its positive inotropic effects persist for at least 1 week and its hemodynamic/neuro-humoral effects up to 4 weeks.(4) In our case, intermittent low-dose Levosimendan could have increased the contractility of RV and effectively dilated the PA, with subsequent decreasing the afterload of the right ventricle. This may have restored adequate LV filling pressures and LVAD flow. Further investigation is needed to ensure the value of intermittent Levosimendan in patients on LVAD support, where RVF could be very cumbersome with high mortality and morbidity.

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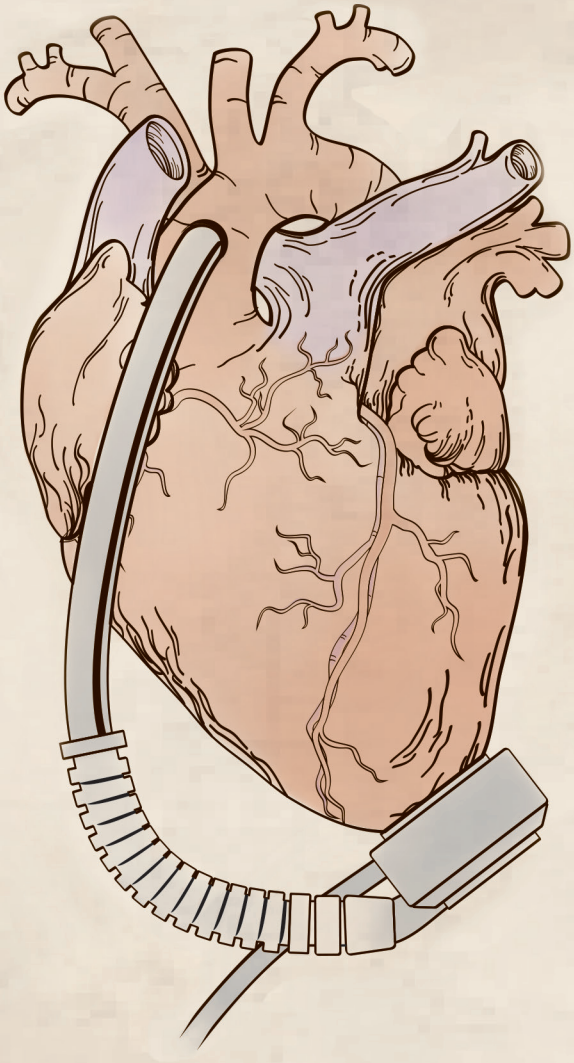

Chapter IX

Aortic root thrombus after left ventricular assist device implantation and aortic valve replacement

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ESC Heart Fail. 2020 Oct;7(5):3208-3212

Abstract

Data on the risk of aortic root thrombosis in patients with aortic valve replacement (AVR) and left ventricular assist device(LVAD) surgery are scarce. Two out of nine patients receiving AVR concomitant with LVAD surgery and two out of two patients receiving AVR on LVAD support, at our center, developed an aortic root thrombus, all diagnosed with computed tomography (CT) angiography. These results demonstrate that patients with concomitant AVR and LVAD surgery, or AVR on LVAD support, have an increased risk of aortic root thrombosis. Therefore, early anti-thrombotic therapy and vigilant diagnostic follow-up, using CT scans, are warranted to prevent thromboembolic events.

Introduction

Currently, contemporary left ventricular assist devices (LVADs) utilize continuous-flow, which are strongly associated with an increased risk for the development of aortic regurgitation (AR) (1). AR during LVAD therapy is associated with a negative impact on hemodynamics, hospitalization and overall survival. Therefore, concomitant aortic valve replacement (AVR) is recommended in patients with moderate to severe AR (2). Due to changes in blood flow in the aortic root, a blind sac can be formed, increasing the risk of thromboembolic events in patients. However, the information on the risk of aortic root thrombosis and stroke after AVR procedures concomitant with LVAD surgery are very limited. Therefore, we retrospectively reviewed all consecutive HeartMate II (HMII; n=62) and HeartMate 3 (HM3; n=42) implantations performed between December 2006 and December 2018 in our center.

Case Report

During this period, eleven (11%) patients received an AVR; nine concomitant procedures during LVAD surgery, one surgical AVR 520 days post-LVAD surgery and one trans catheter aortic valve replacement 337 days post-LVAD surgery (Table 1). After a median follow-up of 23.5 days (range: 20-654 days) post-LVAD surgery, four patients (36%) were diagnosed with an aortic root thrombosis; two patients with an AVR concomitant with LVAD surgery and two patients while on LVAD support. In all patients, aortic root thrombosis was diagnosed based on CT-angiogram results (Figure 1). In three patients the CT-angiogram was performed during regular follow-up, while in one patient transthoracic echocardiogram (TTE) results were suspicious for aortic root thrombosis, which was confirmed based on CT-angiogram.

Retrospectively, aspirin was later introduced in patients who were diagnosed with an aortic root thrombosis compared to patients free of aortic root thrombosis (median time till aspirin introduction 22 days (range: 12-32 days) vs. 10 days (5-39 days), respectively). The delayed introduction of aspirin in both groups was mainly caused due to a high bleeding risk or actual bleeding events (including tamponade and left-sided pleural bleeding). No difference was seen in the time-to-therapeutic heparin dosage between the groups: median time of 3.5 days (range: 1-5 days) and 4.0 days (range: 2-7 days) in patients with and with an aortic root thrombosis respectively. Post-operative bleeding events (tamponade (n=3), pleural bleeding (n=1) and substernal bleeding (n=1) caused temporary lowering of the heparin dosages in both groups. One patient diagnosed with an aortic root thrombosis suffered from an ischemic stroke 24 days post-AVR. Unfortunately, this patient suffered from extensive neurological damage and passed away 39 days post-AVR. One patient without an aortic root thrombosis suffered from a hemorrhagic stroke 454 days post-AVR and recovered without significant sequelae. The follow-up in the other patients was uneventful, without any thromboembolic events.

Table 1. Clinical features of individual patients with aortic valve replacement

Patient	Age (years); Gender	Etiology of HF	Type of LVAD; LVAD indication	Degree of AR (0-4)	Days; adequate heparin level; start aspirin	Days on LVAD support	Aortic valve opens at last TTE	MAP (mmHg); LVAD speed (RPM) at last TTE	ART on TTE	ART on CT-a	Stroke	Clinical outcome
1	55; M	DC	HM II; BTT	4	2; 11	750	No	-*; 9200	No	No	No	HTx
2	52; M	IC	HM II; BTT	3	6; 663†	2163	No	92; 9000	No	No	No	Ongoing LVAD support
3	61; M	DC	HM II; BTT	3	4; 5	939	No	88; 8600	No	No	Hemorrhagic stroke (454 days post LVAD)	HTX
4	52; M	DC	HM II; BTT	2	2; 13	1465	No	84; 9000	No	No	No	Ongoing LVAD support
5	39; M	DC	HM II; BTT	4	4; 5	1359	Minimal opening	88; 9000	No	No	No	Ongoing LVAD support
6	24; M	DC	HM 3; BTT	3	7; 39	622	No	87; 5300	No	No	No	Ongoing LVAD support
7	63; M	IC	HM 3; BTT	2	1; 32	564	No	83; 5200	No	Yes (654 days post LVAD)	No	Ongoing LVAD support
8	65; F	DC	HM 3; DT	3	3; 12	398	No	86; 5100	Yes (22 days post LVAD)	Yes (20 days post LVAD)	No	Ongoing LVAD support
9	53; M	DC	HM 3; BTC	2	2; 9	167	No	88; 5500	No	No	No	Ongoing LVAD support
10	56; M	IC	HM 3; BTT	4	4; -‡	559 (39 days with AVR)	Yes	84; 5300	Suspicion (26 days post AVR)	Yes (27 days post AVR)	Ischemic stroke (24 days post AVR)	Deceased

11	59; F	IC	HM 3; DT	4	5; ◊	953 (538 with TAVR)	No	-*; 5300	Yes (33 days post TAVR)	Yes (30 days post TAVR)	No	Ongoing LVAD support

HF, Heart Failure; AR, Aortic valve Regurgitation; LVAD, Left Ventricular Assist Device; ART, Aortic Root Thrombosis; TTE, TransThoracic Echocardiogram; MAP, Mean Arterial Pressure; RPM, Rounds Per Minute; CT-a Computed Tomography angiogram; M, Male; F, Female; DC, Dilated Cardiomyopathy; IC, Ischemic Cardiomyopathy; HM, HeartMate; BTT, Bridge-to-transplant; HTx; Heart Transplantation; LVAD, Left Ventricular Assist Device; DT, Destination Therapy; BTC, Bridge-to-Candidacy; AVR, Aortic Valve Replacement; TAVR, Transcatheter Aortic Valve Replacement

† Due to a PCI shortly prior to LVAD implantation, clopidogrel was continued instead of aspirin; ‡ Shortly after reaching a therapeutic heparin range, the patient was for another 7 days out of the therapeutic heparin range; ◊ Due to the TAVI procedure clopidogrel was started instead of aspirin, after diagnosis of aortic root thrombus clopidogrel was continued; * Blood pressure could not be measured due to LVAD continues flow

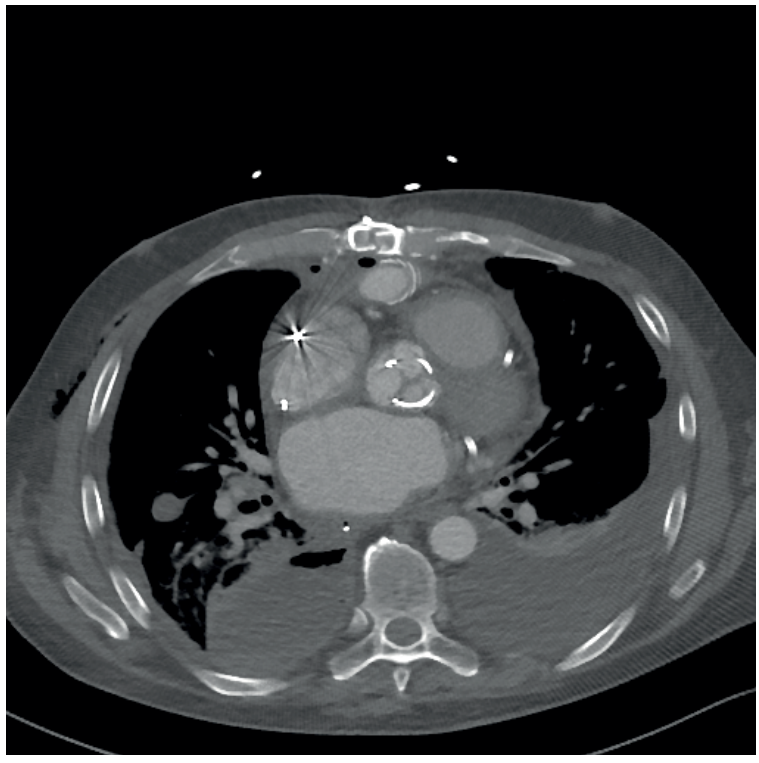

Figure 1 - Computed tomography-angiography, showing an aortic root thrombosis on the bioprosthetic aortic valve

Discussion

The increased risk for thrombus formation in patients with an AVR might be explained due to the material of bioprosthetic valves. This is thrombogenic and activates the coagulation cascade, increasing the risk for the formation of thrombi (3). It has been shown that thrombi might start forming as soon as in the first 24 hours after implantation. This underlines the importance of the early introduction of antiplatelet and anticoagulation therapy in patients with an AVR and LVAD implantation (4). Due to a lack of endothelialization, the risk of thrombus formation remains elevated in the first 3 months (3). Furthermore, post-LVAD implantation, blood flow in the aortic root changes. If the left ventricle (LV) is excessively unloaded by the LVAD, the LV is not able to unload itself. The minimal or lack of AV opening, causes a blind pouch in the aortic root, increasing the risk of aortic root thrombus formation. Ideally, LVAD speed-settings are optimized, resulting in an optimal unloading of the LV while the AV continuous to open intermittent. However, it can be challenging to obtain these optimal LVAD settings. In all our patients, optimal LVAD speed-settings were determined based on clinical and transthoracic echocardiogram (TTE) parameters. However, hardly any patient had an intermittent opening AV, both in the early post-operative setting as well as during follow-up visits.

TTE examination is commonly used in the follow-up of LVAD patients in the outpatient clinic. However, diagnosing an aortic root thrombosis based on TTE images can be difficult, leading to underdiagnosing of aortic root thrombosis. In non-LVAD patients, other techniques, such as trans esophageal echocardiography (TEE) or CT-angiogram have shown to be better in detecting aortic root thrombosis (5). Similar, in our patients, the diagnosis of aortic valve thrombosis was only made based on CT-angiogram results, indicating that CT-angiogram might be superior over TTE as a diagnostic tool for aortic root thrombosis in LVAD patients with an AVR. Additionally, CT-angiogram is less stressful for the patients and provides more detailed information on dynamic flows around the aortic valve compared with an echocardiogram (5). These flows could be used to identify patients at higher risk for the development of aortic root thrombosis, probably also in the non-AVR LVAD patients.

The use of anticoagulation therapy after AVR has shown to be effective in patients without a LVAD, and the ISHLT recommends starting aspirin and adequate heparin therapy within one day post-LVAD surgery (2). However, studies investigating the optimal timing of the start of anticoagulation and antiplatelet therapy strategies after an AVR in LVAD patients are lacking. The current ECS/EACTS Guidelines advice for very early, i.e. on day 1 postoperative AVR, introduction of aspirin (4). However, the early introduction of therapeutic heparin dosage and aspirin can be challenging due to post-operative bleeding complications. In our series, the delayed introduction of these therapies has most likely contributed to the development of aortic root thrombosis.

Conclusions

In conclusion, patients with concomitant AVR and LVAD implantation, or AVR while on LVAD support, had increased risk of aortic root thrombosis, and probably increased the risk for ischemic stroke. To prevent these thromboembolic events, early introduction of therapeutic anticoagulation and especially the anti-thrombotic therapy are needed. Furthermore, vigilant diagnostic follow-up, especially using CT-scans, are needed for the timely diagnosis of aortic root thrombosis. Prospective, multicenter studies are needed to elucidate aortic root thrombosis after AVR and LVAD implantation and the possible risk of thromboembolic events.

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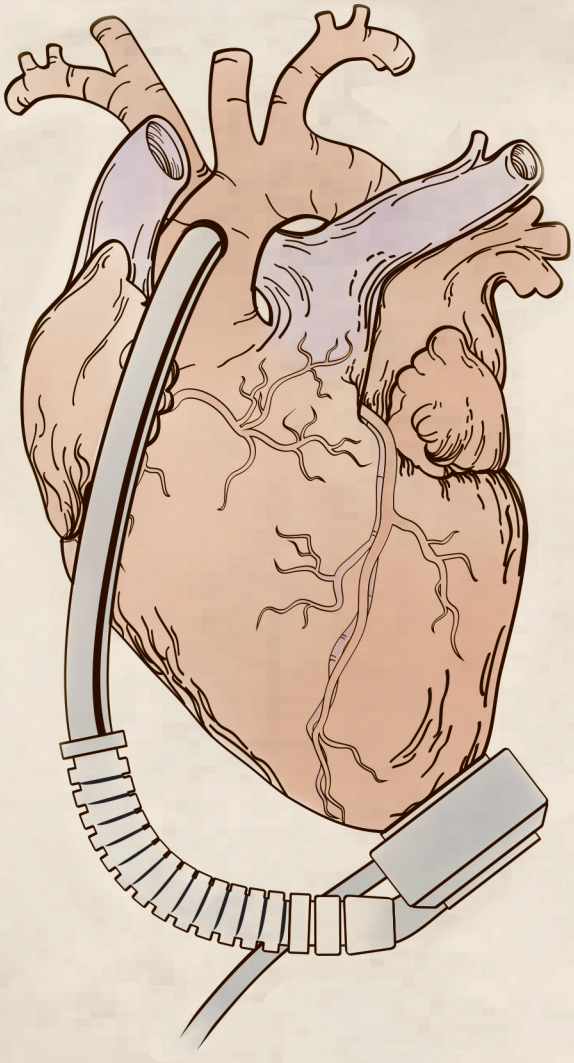

Chapter X

Survival following concomitant aortic valve procedure and left ventricular assist device implantation: an ISHLT Mechanically Assisted Circulatory Support (IMACS) Registry

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Abstract

Purpose: The aim of this study was to compare early- and late-term survival and causes of death between patients with and without a concomitant aortic valve (AoV) procedure during continuous-flow left ventricular assist device (LVAD) surgery.

Methods: All adult primary continuous-flow LVAD patients from the International Society of Heart and Lung Transplantation (ISHLT) Mechanically Assisted Circulatory Support (IMACS) registry (n=15,267) were included in this analysis and stratified into patients with a concomitant AoV procedure (being AoV replacement or AoV repair) and without AoV procedure. The primary outcome was early (≤90 days) survival post-LVAD surgery. Secondary outcomes were late survival, survival of patients alive 90 days post-LVAD surgery (conditional survival) and its determinants.

Result: Patients who underwent concomitant AoV replacement (n=457) or AoV repair (n=328) had a significantly reduced early survival compared with patients without an AoV procedure (n=14,482) (85%, 87%, 90%, respectively p<0.001). Although this difference sustained in the late postoperative period (56%, 61%, and 62%, respectively, Long-Rank: p=0.001), the biggest difference occurred in the early postoperative period. After adjustment for other significant predictors, concomitant AoV replacement remained an independent predictor for early (HR 1.226 [1.037-1.449]) and late mortality (HR 1.477 [1.154-1.890]). The main causes of early death were multisystem organ failure (28%), circulatory failure (17%) and neurological events (16%).

Conclusion: Concomitant AoV surgery in patients with an LVAD implantation was an independent predictor of worse outcome, mainly in the early postoperative period. Additional research is needed to determine the best AoV surgical strategy at the time of LVAD surgery.

Introduction

In the recent years, more and more patients received a left ventricular assist device (LVAD), as treatment for end-stage HF (1). However, significant aortic valve (AoV) regurgitation in patients with an LVAD causes a short circulation loop, in which blood is pumped into the aorta by the LVAD, and flows directly back into the left ventricle (2). This results in less unloading of the left ventricle and reduced systemic perfusion, indicated by an increased left ventricular end-diastolic diameter and higher levels of brain natriuretic peptide (3). Additionally, significant AoV regurgitation has been associated with increased mortality and higher hospitalization rates (3, 4). Therefore, it is recommended to perform a concomitant AoV procedure in patients with moderate to severe AoV regurgitation at the time of LVAD surgery (5). Additionally, it is recommended to perform a concomitant AoV procedure at the time of LVAD surgery in patients with a mechanical AoV (5), since mechanical AoV in LVAD patients is associated with an increased risk of thromboembolic events (6, 7).

Concomitant AoV replacement with a bioprosthetic valve, AoV repair, or overseewing of the AoV are all considered as treatment strategies, with associated risks and benefits (8). However, conflicting results have been reported on the outcomes of concomitant AoV procedures, and there is limited contemporary data available on the early and late survival outcomes of these concomitant AoV procedures.

The aim of this study was to compare early and late survival and causes of early and late death between patients with and without a concomitant AoV procedure during continuous-flow LVAD surgery in the International Society of Heart and Lung Transplantation (ISHLT) Mechanically Assisted Circulatory Support (IMACS) registry.

Methods

The IMACS registry is a multinational, multicenter database, prospectively collecting data, as has been prescribed previously (9). In short, the aim of the IMACS registry is to enroll and monitor patients implanted with durable mechanical circulatory support devices, worldwide. The registry receives data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), European Registry for Patients with Mechanical Circulatory Support (EUROMACS), United Kingdom (UK) registry and the Japanese Mechanically Assisted Circulatory Support (JMACS) registries as well as from individual hospitals worldwide.

All adult patients (age ≥18 years) who underwent primary implantation of a continuous-flow LVAD from January 2013 through November 2017 were included in this analysis. Patients with a total artificial heart, isolated right ventricular assist device or with missing information on concomitant AoV procedure were excluded from this analysis (**Supplementary Figure 1)**. The endpoint for this analysis was all-cause mortality post-LVAD surgery, device explantation or heart transplantation. The primary outcome was early (≤90 days post-LVAD surgery) survival. Secondary outcomes were late (survival during the entire follow-up period) and conditional survival (in patients who survived the first 90 days post-LVAD surgery), causes of early and late death post-LVAD surgery, device explantation and heart transplantation. The definitions of causes of death were defined earlier by the IMACS registry, no granular data on the causes of death were available (9).

Statistical analysis

Patient characteristics are presented as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on the distribution of the data, for continuous data and counts and percentages (%) for categorical data. The one-way ANOVA test or Kruskal-Wallis test was used to compare data for categorical variables, depending on the distribution of the data, and the Chi-square test was used to compare data for categorical variables. All included LVAD patients were stratified into those without a concomitant AoV procedure, AoV replacement of with a concomitant AoV repair.

The probability of survival was analyzed using the Kaplan-Meier method and compared using the log-rank test. A univariable Cox proportional hazard analysis was used to relate preoperative parameters, such as demographics, medication, echocardiographic, hemodynamic and laboratory characteristics with the study outcomes (**Supplementary Tables 1-2**). Variables with a p-value <0.20 were entered in a multivariable Cox proportional hazard analysis, in order to adjust the prediction of AoV procedures for cofounders, applying the stepwise forward method, with a $p<0.05$ model-entry criterion. Data were censored at heart transplantation or device explantation due to recovery. The competing outcomes methodology was used to estimate the probability of survival, mortality, heart transplantation or device explantation over time.

A sub-analysis, investigating the early, late and contemporary survival in patients with a documented moderate to severe AoV regurgitation has been performed.

Missing data in the baseline variables were imputed, using multiple imputation. If the missing variables showed a monotone pattern of missing values, the monotone method was used, otherwise, an iterative Markov chain Monte Carlo method was used with a number of 10 iterations. A total of five imputations was performed, and the pooled data were analyzed. Variables with less than 40% missing data in the entire population were accepted for multiple imputation (10). The vast majority of variables had less than 5% missing data. The imputed data were only used in the Cox proportional hazard analysis.

A two-tailed $p<0.05$ was considered statistically significant. All analyses were performed with SPSS statistical package version 25.0 (SPSS Inc., Chicago, IL, USA).

Results

In total, 15,267 LVAD patients were included in this analysis and were stratified into those without an AoV procedure (n=14,482, 94.9%), AoV replacement (n=457, 3.0%) or AoV repair (n=328, 2.1%). The median follow-up period was 13.2 [5.5-25.6] months. The baseline characteristics are summarized in (**Table 1**). Overall, the median age at LVAD surgery was 58 years, the majority of patients were men (79.3%) and the main etiology of HF was non-ischemic (61.5%). In patients without an AoV procedure, 67.2% had no AoV regurgitation, while in 15.9% of patients with an AoV replacement and 10.9% of the patients with an AoV repair, no AoV regurgitation prior to LVAD surgery was reported (p<0.001). Patients with an AoV repair were significantly older compared to patients without an AoV procedure or AoV replacement (p<0.001), had a lower body mass index (p<0.001), a lower platelets count (p=0.001), and received an LVAD more often as destination therapy (p=0.001). Patients who received an AoV replacement were more often men (p<0.001) and had a higher blood urea nitrogen level (p<0.001) compared with patients with an AoV procedure or AoV repair.

Early, late and conditional survival

In the combined cohort of patients, the early survival rate (≤90 days post-LVAD surgery) was 90.3%, the late survival rate (up to 36 months post-LVAD surgery) was 62.1%, while the conditional survival rate (up to 36 months post-LVAD surgery in patients alive at 90 days post-LVAD surgery) was 68.8%. The early survival rates were 90.4% for patients without an AoV procedure, 85.1% for patients with an AoV replacement and 87.4% for patients with an AoV repair (p<0.001), as shown in **Figure 1A**. Although the late survival rates differed significantly (**Figure 1B**, 62.4%, 55.5%, and 60.9%, respectively, p=0.001), the biggest difference occurred early post-LVAD surgery, with no additional difference observed in the conditional survival (**Supplementary Figure 2**, survival rates were 69.0%, 65.2%, and 69.7%, respectively, p=0.268).

As shown in **Supplementary Figure 3**, mechanical AoV replacements (82.7%, 50.6%, respectively) have the worse early and late survival followed by biological AoV replacement (85.6%, 56.4%, respectively), AoV repair (87.4%, 60.9%, respectively), while no AoV procedure (90.4%, 62.4%, respectively) has the best early and late survival (p<0.001, p=0.001, respectively).

The baseline and clinical characteristics of patients with a documented moderate to severe AoV regurgitation has been shown in **Supplementary Table 3**. As shown in **Supplementary Figure 4A-C**, no significant differences in the early, late or conditional survival rates were observed between patients without an AoV procedure, AoV replacement or AoV repair.

When competing outcomes are analyzed between the patient cohorts, patients with an AoV replacement (29.0%) and AoV repair (29.4%) were less often transplanted at 36 months post-LVAD surgery compared to patients without AoV procedure (36.3%) **(Figure 2A-C)**.

Table 1. Baseline and clinical characteristics stratified to AoV procedure in LVAD patients

	Overall population (n=15,267)	No AoV procedure (n=14,482)	AoV replacement (n=457)	AoV repair (n=328)	p-value
Demographics					
Age (years)	58.0 [49.0-66.0]	58.0 [48.0-66.0]	62.0 [53.0-69.0]	64.0 [57.0-69.0]	<0.001
Men	12,093 (79.3)	11,433 (79.1)	396 (87.0)	264 (80.5)	<0.001
BSA (m^2)	2.04 [1.85-2.25]	2.04 [1.86-2.25]	1.99 [1.83-2.18]	1.96 [1.81-2.16]	<0.001
BMI (kg/m^2)	27.4 [23.8-32.0]	27.5 [23.9-32.1]	26.1 [22.8-30.4]	25.1 [22.8-29.4]	<0.001
Ischemic etiology	5,721 (38.5)	5,451 (38.6)	147 (35.6)	123 (39.5)	0.437
Comorbidities					
CVA	655 (4.4)	621 (4.4)	21 (4.8)	13 (4.1)	0.877
DM	1,477 (9.9)	1,417 (10.0)	37 (8.3)	23 (7.0)	0.105
Current smoker	866 (5.9)	818 (5.9)	29 (6.9)	19 (5.8)	0.693
Dialysis	444 (2.9)	423 (2.9)	16 (3.5)	5 (1.5)	0.246
Current ICD therapy	10,392 (78.1)	9,860 (78.1)	279 (76.9)	253 (81.9)	0.393
History of CABG	2,544 (19.0)	2,415 (19.1)	68 (17.8)	61 (19.4)	0.814
NYHA-classification					
NYHA I/II	174 (1.2)	164 (1.2)	7 (1.6)	3 (1.0)	0.761
NYHA III	2,690 (19.2)	2,558 (19.3)	79 (18.6)	53 (17.0)	
NYHA IV	11,151 (79.6)	10,557 (79.5)	339 (79.8)	255 (82.0)	
INTERMACS classification					
INTERMACS 1	2,373 (15.6)	2,269 (15.8)	60 (13.3)	44 (13.4)	0.502
INTERMACS 2	5,173 (34.1)	4,887 (34.0)	165 (36.5)	121 (36.9)	
INTERMACS 3	5,179 (34.1)	4,914 (34.1)	156 (34.5)	109 (33.2)	
INTERMACS 4	1,968 (13.0)	1,873 (13.0)	55 (12.2)	40 (12.2)	
INTERMACS 5	315 (2.1)	296 (2.1)	9 (2.0)	10 (3.0)	
INTERMACS 6	95 (0.6)	86 (0.6)	6 (1.3)	3 (0.9)	
INTERMACS 7	68 (0.4)	66 (0.5)	1 (0.2)	1 (0.3)	
IABP prior to LVAD surgery	4,302 (28.9)	4,109 (29.1)	105 (24.0)	88 (26.8)	0.049
ECMO prior to LVAD surgery	891 (6.0)	853 (6.0)	18 (4.1)	20 (6.1)	0.238
Ventilator prior to LVAD surgery	1,934 (12.7)	1,845 (12.8)	48 (10.5)	41 (12.5)	0.364

	Overall population (n=15,267)	No AoV procedure (n=14,482)	AoV replacement (n=457)	AoV repair (n=328)	p-value
Laboratory					
Creatinine, mg/dL	1.20 [0.98-1.50]	1.20 [0.97-1.50]	1.27 [1.05-1.57]	1.20 [1.00-1.50]	0.003
BUN, mg/dL	25.0 [18.0-37.3]	25.0 [18.0-37.0]	29.0 [21.0-40.0]	26.0 [18.0-36.0]	<0.001
ASAT, U/L	29.0 [21.0-44.0]	29.0 [21.0-44.0]	30.0 [22.0-46.0]	30.0 [21.5-42.0]	0.226
ALAT, U/L	29.0 [19.0-49.0]	29.0 [19.0-49.0]	28.5 [18.8-46.3]	29.0 [20.0-52.0]	0.782
LDH, (U/L)	279.0 [220.0-391.0]	279.0 [220.0-391.0]	289.5 [222.8-390.3]	276.5 [216.3-395.0]	0.753
Total bilirubin, mg/dL	1.0 [0.6-1.6]	1.0 [0.6-1.6]	1.1 [0.7-1.7]	1.1 [0.7-1.7]	0.010
WBC, $x10^9$/L	7.9 [6.3-10.2]	7.9 [6.3-10.2]	7.8 [6.2-9.8]	7.5 [6.0-10.4]	0.167
Platelets, $x10^9$/L	188.0 [142.0-242.0]	188.0 [142.0-242.0]	187.0 [132.0-232.0]	176.5 [131.3-226.0]	0.001
INR	1.2 [1.1-1.4]	1.2 [1.1-1.4]	1.3 [1.1-1.5]	1.2 [1.1-1.4]	<0.001
Albumin, g/dL	3.5 [3.0-3.8]	3.5 [3.0-3.8]	3.4 [3.0-3.8]	3.4 [3.0-3.8]	0.552
Hemoglobin, g/dL	11.3 [9.8-12.8]	11.3 [9.8-12.8]	11.2 [9.9-12.6]	11.2 [9.7-12.5]	0.539
Hemodynamics					
RA pressure, mmHg	11.0 [7.0-16.0]	11.0 [7.0-16.0]	11.0 [7.0-17.0]	10.5 [7.0-15.0]	0.295
PCWP, mmHg	25.0 [19.0-31.0]	25.0 [19.0-31.0]	25.0 [20.0-31.0]	25.0 [19.0-32.0]	0.551
Systolic PAP, mmHg	50.0 [40.0-60.0]	50.0 [40.0-60.0]	51.0 [41.0-63.0]	50.0 [40.0-60.0]	0.012
Diastolic PAP, mmHg	25.0 [19.0-30.0]	25.0 [19.0-30.0]	25.0 [20.0-32.0]	24.0 [18.0-29.0]	0.026
Cardiac output, L/min	3.93 [3.14-4.80]	3.96 [3.15-4.80]	3.90 [3.20-4.71]	3.79 [3.00-4.55]	0.077
Echocardiographic					
LVEF					
≥40%	347 (8.5)	327 (8.5)	18 (14.4)	2 (1.8)	0.012
30-39%	484 (11.8)	460 (11.9)	12 (9.6)	2 (10.7)	
20-29%	3,260 (79.7)	3,067 (79.6)	95 (76.0)	98 (87.5)	
RVEF					
Normal	2,941 (26.0)	2,790 (26.1)	73 (22.4)	78 (28.4)	0.400
Mild	3,272 (29.0)	3,086 (28.9)	108 (33.1)	78 (28.4)	
Moderate	3,473 (30.8)	3,283 (30.7)	103 (31.6)	87 (31.6)	
Severe	1,606 (14.2)	1,532 (14.3)	42 (12.9)	32 (11.6)	

	Overall population (n=15,267)	No AoV procedure (n=14,482)	AoV replacement (n=457)	AoV repair (n=328)	p-value
Mitral valve regurgitation					
None	1,070 (7.6)	1,021 (7.6)	32 (7.7)	17 (5.4)	0.067
Mild	4,960 (35.2)	4,689 (35.1)	164 (39.7)	107 (34.3)	
Moderate	4,689 (33.3)	4,431 (33.2)	138 (33.4)	120 (38.5)	
Severe	3,368 (23.9)	3,221 (24.1)	79 (19.1)	68 (21.8)	
Tricuspid valve regurgitation					
None	1,257 (9.0)	1,210 (9.1)	31 (7.5)	16 (5.1)	0.172
Mild	6,865 (49.2)	6,491 (49.1)	207 (49.8)	167 (53.4)	
Moderate	4,197 (30.1)	3,969 (30.0)	134 (32.2)	94 (30.0)	
Severe	1,640 (11.7)	1,560 (11.8)	44 (10.6)	36 (11.5)	
AoV regurgitation					
None	8,426 (64.4)	8,330 (67.2)	63 (15.9)	33 (10.9)	<0.001
Mild	4,084 (31.2)	3,747 (30.2)	182 (45.8)	155 (51.3)	
Moderate	492 (3.8)	270 (2.2)	119 (30.0)	103 (34.1)	
Severe	91 (0.7)	47 (0.4)	33 (8.3)	11 (3.6)	
LVEDD (mm)	68.0 [61.0-75.0]	68.0 [61.0-75.0]	69.0 [63.0-77.0]	68.0 [62.0-74.0]	0.009
Main LVAD strategy					
BTT	4,272 (28.0)	4,087 (28.2)	116 (25.4)	69 (21.0)	0.001
BTC	4,221 (27.7)	4,016 (27.7)	126 (27.6)	79 (24.1)	
Destination therapy	6,563 (43.0)	6,177 (42.7)	206 (45.1)	180 (54.9)	
Rescue therapy	125 (0.8)	122 (0.8)	3 (0.7)	0 (0.0)	
Bridge to recovery	55 (0.4)	51 (0.4)	4 (0.9)	0 (0.0)	
Other	28 (0.2)	26 (0.2)	2 (0.4)	0 (0.0)	

AoV, Aortic Valve; LVAD, Left Ventricular Assist Device; BSA, Body Surface Area; BMI, Body Mass Index; CVA, CerebroVascular Accident; DM, Diabetes Mellitus; ICD, Implantable Cardioverter Defibrillator; CABG, Coronary Artery Bypass Graft; NYHA, New York Heart Association; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; IABP, Intra-Aortic Balloon Pump; ECMO, Extracorporeal Membrane Oxygenator; BUN, Blood Urea Nitrogen; ASAT, Asparate Aminotransferase; ALAT, Alanine AminoTransaminase; LDH, Lactate DeHydrogenase; WBC, White Blood Count; RA, Right Atrial; PCWP, Pulmonary Capillary Wedge Pressure; PAP, Pulmonary Artery Pressure; LVEF, Left Ventricular Ejection Fraction; RVEF, Right Ventricular Ejection Fraction; LVEDD, Left Ventricular End Diastolic Diameter; BTT, Bridge to Transplant; BTC, Bridge to Candidacy

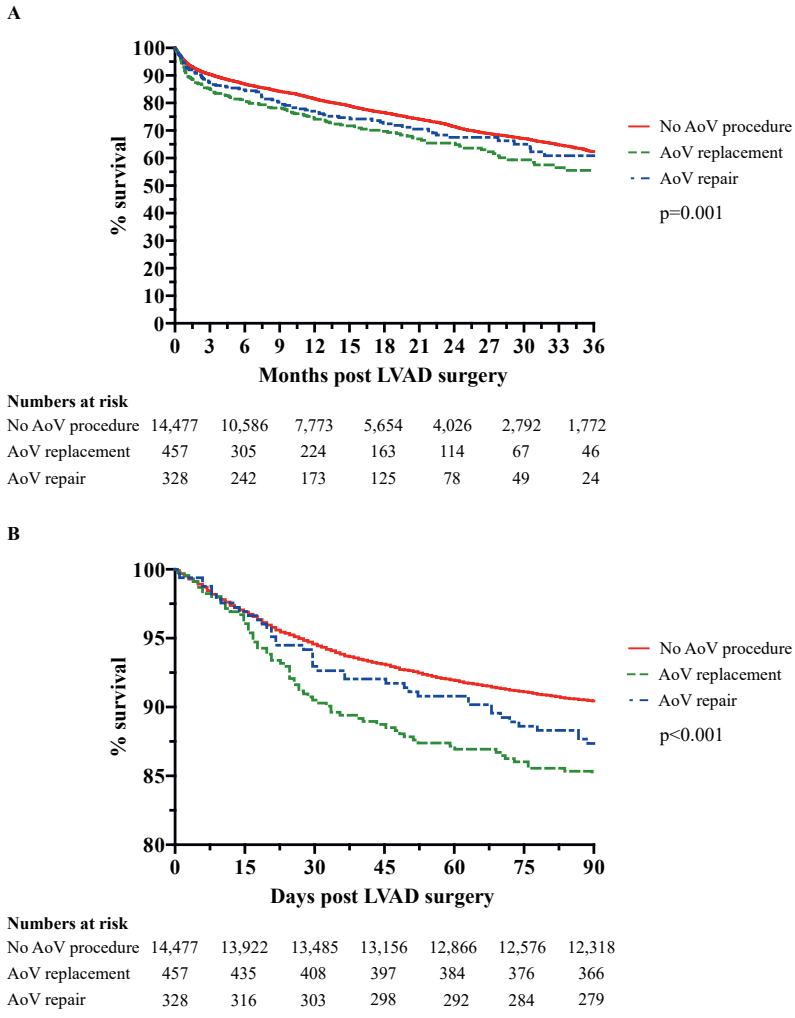

Figure 1. A Early and **B** late survival stratified according to AoV procedure post-LVAD surgery

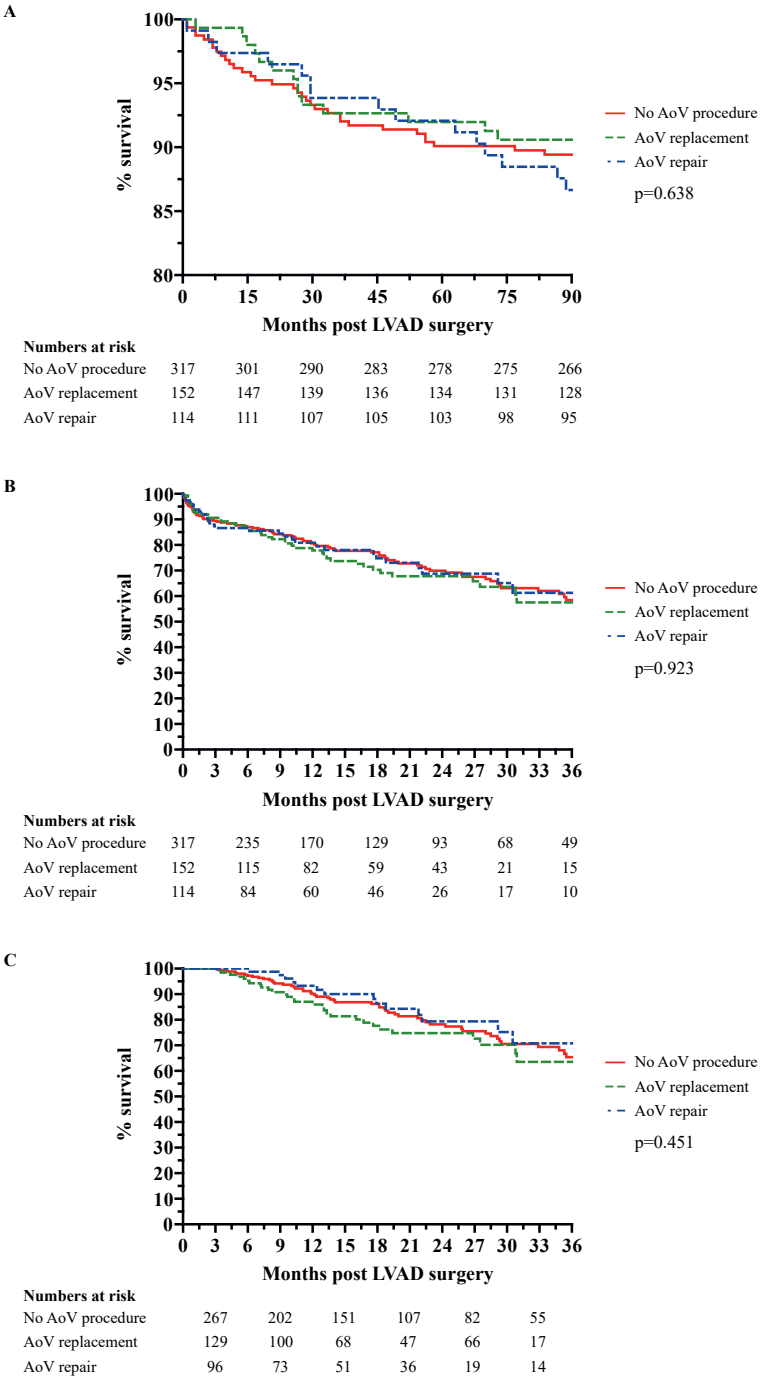

Figure 2. Competing outcomes for patients with **A** no AoV procedure, **B** AoV replacement, and **C** AoV repair

Causes of death

The causes of early and late death post-LVAD surgery are shown in **Tables 2** and **3**. Multisystem organ failure was the most frequent cause of early death (27.7%), followed by circulatory failure (16.9%) and neurological events (15.9%). The most frequent cause of late death was neurological events (19.2%) followed by multisystem organ failure (17.5%) and circulatory failure (17.2). The causes of death in patients surviving the first 90 days post-LVAD surgery are shown in **Supplementary Table 4**.

Table 2. Causes of early death stratified to AoV procedure in LVAD patients post-LVAD surgery

	Overall population (n=1,452)	No AoV procedure (n=1,344)	AoV replacement (n=67)	AoV repair (n=41)
Multisystem Organ Failure	402 (27.7)	368 (27.4)	22 (32.8)	12 (29.3)
Circulatory failure	246 (16.9)	230 (17.1)	7 (10.4)	9 (22.0)
Neurological events	231 (15.9)	220 (16.4)	7 (10.4)	4 (9.8)
Withdrawal of support	161 (11.1)	150 (11.2)	6 (9.0)	5 (12.2)
Major infection	110 (7.6)	101 (7.5)	4 (6.0)	5 (12.2)
RV-failure	80 (5.5)	76 (5.7)	3 (4.5)	1 (2.4)
Respiratory failure	72 (5.0)	66 (4.9)	4 (6.0)	2 (4.9)
Digestive/liver failure*	21 (1.4)	21 (1.6)	0 (0.0)	0 (0.0)
Device related	10 (0.7)	9 (0.7)	1 (1.5)	0 (0.0)
Hematologic failure	8 (0.6)	7 (0.5)	1 (1.5)	0 (0.0)
Cancer	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Other	110 (7.6)	95 (7.1)	12 (17.9)	3 (7.3)

p-value for distribution between groups: 0.454
AoV, Aortic Valve; LVAD, Left Ventricular Assist Device; RV, Right Ventricular
* including hepatic dysfunction, renal dysfunction, pancreatitis

Table 3. Causes of late death stratified to AoV procedure in LVAD patients post-LVAD surgery

	Overall population (n=3,890)	No AoV procedure (n=3,657)	AoV replacement (n=143)	AoV repair (n=90)
Neurological events	748 (19.2)	713 (19.5)	25 (17.5)	10 (11.1)
Multisystem Organ Failure	681 (17.5)	635 (17.4)	28 (19.6)	18 (20.0)
Circulatory failure	688 (17.2)	627 (17.1)	18 (12.6)	23 (25.6)
Withdrawal of support	441 (11.3)	419 (11.5)	12 (8.4)	10 (11.1)
Major infection	322 (8.3)	304 (8.3)	10 (7.0)	8 (8.9)
Respiratory failure	207 (5.3)	196 (5.4)	6 (4.2)	5 (5.6)
RV-failure	171 (4.4)	162 (4.4)	6 (4.2)	3 (3.3)
Device related	82 (2.1)	73 (2.0	7 (4.9)	2 (2.2)
Digestive/liver failure*	50 (1.3)	49 (1.3)	1 (0.7)	0 (0.0)
Cancer	43 (1.1)	42 (1.1)	1 (0.7)	0 (0.0)
Hematologic failure	24 (0.6)	20 (0.5)	4 (2.8)	0 (0.0)
Other	453 (11.6)	417 (11.4)	25 (17.5)	11 (12.2)

p-value for distribution between groups: 0.028
AoV, Aortic Valve; LVAD, Left Ventricular Assist Device; RV, Right Ventricular
* including hepatic dysfunction, renal dysfunction, pancreatitis

Multivariable model

Independent risk factors for early mortality post-LVAD surgery after multivariable adjustment are shown in **Table 4**. The replacement of the AoV was significantly associated with an increased risk for early all-cause mortality, both unadjusted (HR 1.604 [1.255-2.050], p<0.001) as adjusted for other significant predictors (HR 1.477 [1.154-1.890], p=0.002, while AoV repair was no significant predictor, compared to no AoV procedure. Similarly, AoV replacement was an predictor for late all-cause mortality, unadjusted (HR 1.360 [1.152-1.605], p<0.001) and adjusted 1.226 [1.037-1.449], p=0.017) (**Table 5**).

Table 4. Multivariable predictors of early all-cause mortality post-LVAD surgery, stratified to AoV procedure

			95% CI for HR		
	Variables	**HR**	**Lower**	**Upper**	**p-value**
Univariable	No AoV procedure	ref	ref	ref	ref
	AoV replacement	1.604	1.255	2.050	<0.001
	AoV repair	1.331	0.976	1.816	0.071
Multivariable	No AoV procedure	ref	ref	ref	ref
	AoV replacement	1.477	1.154	1.890	0.002
	AoV repair	1.209	0.885	1.652	0.233
	Age (years)	1.030	1.025	1.035	<0.001
	Sex (men vs. women)	0.817	0.718	0.930	0.002
	BMI (kg/m^2)	1.019	1.011	1.028	<0.001
	Creatinine (mg/dL)	1.148	0.990	1.333	0.068
	BUN (mg/dL)	1.007	1.005	1.010	<0.001
	ASAT (U/L)	1.000	1.000	1.001	0.003
	Total bilirubin (mg/dL)	1.197	1.127	1.272	<0.001
	Platelet (x10^9/L)	0.999	0.998	1.000	0.001
	Albumin (g/dL)	0.728	0.663	0.800	<0.001
	Hemoglobin (g/dL)	0.924	0.898	0.951	<0.001
	Mean RA pressure (mmHg)	1.011	1.004	1.019	0.004
	Pulmonary artery wedge pressure (mmHg)	0.990	0.983	0.996	0.002
	Moderate/severe tricuspid regurgitation	1.285	1.148	1.438	<0.001
	Moderate/severe mitral regurgitation	0.796	0.712	0.889	<0.001
	ECMO	1.612	1.345	1.932	<0.001
	LVAD strategy				
	BTT	ref	ref	ref	ref
	BTC	0.936	0.802	1.093	0.402
	DT	1.109	0.966	1.274	0.143
	Rescue therapy	2.233	1.147	4.347	0.018
	Bridge to recovery	2.527	1.781	3.585	<0.001
	Other	1.325	0.423	4.152	0.629

LVAD, Left Ventricular Assist Device; AoV, Aortic Valve; CI, Confidence Interval; HR, Hazard Ratio; BMI, Body Mass Index; INTERMACS, Interagency Registry for Mechanical Assisted Circulatory Support; IABP, Intra-Aortic Balloon Pump; ECMO, Extra Corporeal Membrane Oxygenator; BUN, Blood Urea Nitrogen; ASAT, Asparate Transaminase; RA, Right Atrial; BTT, Bridge to Transplant; BTC, Bridge to Candidacy; DT, Destination Therapy

Table 5. Multivariable predictors of late all-cause mortality post-LVAD surgery, stratified to AoV procedure

			95% CI for HR		
	Variables	**HR**	**Lower**	**Upper**	**p-value**
Univariable	No AoV procedure	ref	ref	ref	ref
	AoV replacement	1.360	1.152	1.605	<0.001
	AoV repair	1.150	0.933	1.418	0.190
Multivariable	No AoV procedure	ref	ref	ref	ref
	AoV replacement	1.226	1.037	1.449	0.017
	AoV repair	1.052	0.853	1.298	0.635
	Age (years)	1.024	1.021	1.028	<0.001
	BMI (kg/m^2)	1.016	1.011	1.022	<0.001
	Ischemic etiology	1.070	1.001	1.144	0.047
	INTERMACS class (1-3 vs. 4-7)	1.101	1.005	1.207	0.040
	Creatinine (mg/dL)	1.111	1.014	1.217	0.024
	BUN (mg/dL)	1.006	1.004	1.007	<0.001
	Total bilirubin (mg/dL)	1.085	1.042	1.129	<0.001
	Platelet (x10^9/L)	0.999	0.999	1.000	0.016
	INR	1.062	0.995	1.134	0.070
	Albumin (g/dL)	0.872	0.822	0.924	<0.001
	Hemoglobin (g/dL)	0.938	0.922	0.954	<0.001
	Mean RA pressure (mmHg)	1.011	1.006	1.015	<0.001
	Pulmonary artery wedge pressure (mmHg)	0.992	0.988	0.996	<0.001
	Moderate/severe tricuspid regurgitation	1.144	1.068	1.226	<0.001
	Moderate/severe mitral regurgitation	0.845	0.790	0.904	<0.001
	IABP	1.074	1.000	1.154	0.050
	ECMO	1.354	1.185	1.546	<0.001
	LVAD strategy				
	BTT	ref	ref	ref	ref
	BTC	0.979	0.889	1.077	0.661
	DT	1.145	1.050	1.248	0.002
	Rescue therapy	1.484	0.873	2.521	0.145
	Bridge to recovery	1.599	1.201	2.128	0.001
	Other	0.806	0.301	2.159	0.668

LVAD, Left Ventricular Assist Device; AoV, Aortic Valve; CI, Confidence Interval; HR, Hazard Ratio; BMI, Body Mass Index; INTERMACS, Interagency Registry for Mechanical Assisted Circulatory Support; IABP, Intra-Aortic Balloon Pump; ECMO, Extra Corporeal Membrane Oxygenator; BUN, Blood Urea Nitrogen; RA, Right Atrial; BTT, Bridge to Transplant; BTC, Bridge to Candidacy; DT, Destination Therapy

Discussion

This is the largest, contemporary study investigating the outcomes after continuous-flow LVAD implantation with and without a concomitant AoV procedure. The main findings from this study were decreased, mainly in the early, survival rate of patients with an AoV replacement or repair compared to patients without an AoV procedure. Following adjustment for other significant predictors, AoV replacement remained an independent predictor for all-cause mortality. Furthermore, the main causes of early death included multi organ failure, circulatory failure, and neurological events.

Untreated significant AoV regurgitation could be very hemodynamically compromising due to the short circulation loop, while less severe AoV regurgitation might be less cumbersome. Surprisingly, in up to 15% of our patients who underwent an AoV procedure, no AoV regurgitation was reported prior to LVAD surgery. In these patients, the decision for an AoV procedure could have been made based on the peri-operative echocardiogram, showing a significant AoV regurgitation. Additionally, these patients might have undergone a concomitant AoV procedure in order to replace or oversew the AoV due to a pre-existing mechanical AoV, as is recommended (5). However, both peri-operative echocardiographic data as well as replacement of a mechanical AoV were not collected in the IMACS database, so these hypotheses could not be tested. However, as our results indicate that AoV replacement is an independent predictor for mortality, stringent criteria for a concomitant AoV procedure at the time of LVAD surgery might be warranted, especially in patients with only a mild AoV regurgitation. Additionally, less invasive procedures for the treatment of significant AoV regurgitation in LVAD patients have been suggested. Only small studies have investigated the usage of a transcatheter aortic valve replacement (TAVR) procedure to treat significant AoV regurgitation in patients already on LVAD support, showing promising results (11-13). Using a TAVR procedure concomitant with LVAD surgery could reduce the circulatory bypass time, reducing the risk of myocardial ischemia, as shown in a recent case-report (14). However, additional trials are highly needed in order to determine the optimal strategy for the treatment of significant AoV regurgitation at the time of LVAD surgery. Especially since our results demonstrated that in patients with a significant AoV regurgitation, the survival rates between patients with and without an AoV procedure was similar.

Early and late survival

Previous studies investigating the association between survival and AoV procedures reported conflicting results, with some studies indicating a worse survival (15-18), while others reported similar or better survival rates in patients with a concomitant AoV procedure (19-23). However, most of these studies were single-center studies and were limited by the lower number of patients with a concomitant AoV procedure (with only one of them including more than 100 patients with an AoV procedure), and some reported only outcomes of multiple concomitant cardiac procedures combined. The largest study used the INTERMACS dataset, and included 6,721 adult LVAD patients, with 125 patients undergoing concomitant AoV closure, 95 AoV repair, and 85 AoV replacement between June 2006 and December 2012 (15). In the INTERMACS study, patients undergoing a concomitant AoV procedure had significantly lower 1-year survival rates (patients with an AoV repair 79%, AoV replacement 72% and AoV closure 64%) compared to patients without an AoV

procedure (81%, p=0.0003). In comparison to the INTERMACS study, our study reflects a more contemporary, worldwide LVAD population, a much higher number of LVAD patients were included, with a higher number of AoV procedures. The late survival rates in our study were higher compared to the INTERMACS study, most likely reflecting the improvement in LVAD management and survival over time. Similar to the INTERMACS study, our results demonstrated a lower survival rate in patients with an AoV procedure, although, in our study, patients with an AoV replacement had the lowest survival, compared to patients with an AoV closure in the INTERMACS study.

Multiple closure and repair techniques have been reported in LVAD patients, each with their own risks and benefits (8). A variation in the used operating techniques might explain the observed variation in outcome after AoV repair between INTERMACS and IMACS study. However, this hypothesis could not be tested since both databases do not have sufficient data to discriminate between different operating techniques. Additionally, our results did not discriminate between AoV repair or closure, which might have contributed to the observed variation. However, in patients with an AoV closure, native ejection from the heart is not possible, especially during catastrophic pump dysfunction. A catastrophic pump dysfunction, although rare, is a severe complication and is in 2% of all LVAD patients the cause of death (1). Therefore, the decision for the closure of the AoV should not be taken lightly.

Causes of death

In our combined cohort of LVAD patients, the most common causes of early death were multisystem organ failure, circulatory failure, and neurological events post-LVAD surgery, similar to previous report (24). The lower survival in patients with an AoV replacement appears to be accompanied by an increase in multisystem organ failure, while patients with an AoV repair died more often due to a circulatory failure compared to patients without an AoV procedure. Unfortunately, no granular data was available in the IMACS database for more specification of the causes of early and late death.

The most common causes of late death were neurological events, multi organ failure, and circulatory failure, which are similar as previously reported by the INTERMACS, EUROMACS and IMACS databases (1, 24, 25). Patients with an AoV replacement and repair died more often due to multisystem organ failure, and patients with an AoV repair died more often due to a circulatory failure compared to patients without an AoV procedure.

Competing outcomes

In this cohort, LVAD patients with an AoV procedure were less often transplanted in comparison to patients without an AoV procedure. As previously suggested, AoV regurgitation might be treated more aggressively in patients with an LVAD as destination therapy (15). However, the observed difference between those without an AoV procedure and replacement could not fully be explained by the difference in device strategy. Potentially, the significantly higher age in the patients with an AoV replacement might have influenced the decision not to proceed towards transplantation after LVAD implantation.

Limitations

This study has some limitations. First, due to the retrospective nature of this study, some data was missing in our study. Although, we used multiple imputation to deal with the missing data, this might have caused a minor bias might have been caused due to the missing data. Additionally, some errors might have occurred during data entry. Second, in order to ensure data anonymization, LVAD brand information was not available in the research database. Therefore, brand-specific sub-analysis could not be performed. Data on the presence and severity of AoV regurgitation was available for all patients, however, information on why surgeons decided for an AoV replacement or repair was not available. It is likely that this might have varied between the participating centers due to local experiences and preferences. Lastly, no discrimination between AoV repair or closure was made in the database.

Conclusion

This is the largest study comparing the short- and long-term survival of concomitant AoV procedures in continuous-flow LVAD patients with pre-existing AoV regurgitation. Concomitant AoV surgery, especially replacement, is associated with lower survival rates compared to patients without an AoV procedure. Therefore, additional research is urgently needed to determine the optimal strategy in order to treat or not to treat AoV regurgitation at the time of LVAD surgery.

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Disclosures

All authors had no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Univariable predictors of early all-cause mortality post-LVAD surgery

Supplementary Table 2. Univariable predictors of late all-cause mortality post-LVAD

Supplementary Table 3. Baseline and clinical characteristics stratified to AoV procedure in LVAD patients with moderate to severe AoV regurgitation at baseline

Supplementary Table 4. Causes of death in patients alive 90 days post-LVAD surgery

Supplementary Figure 1. Inclusion flowchart

Supplementary Figure 2. Conditional survival of patients alive at 90 days post-LVAD surgery stratified to AoV procedure

Supplementary Figure 3. A Early, **B** late, and **C** conditional survival stratified to no AoV procedure, biological AoV replacement, mechanical AoV replacement and AoV repair post-LVAD surgery

Supplementary Figure 4. A Early, **B** late, and **C** conditional survival in patients with moderate to severe AoV regurgitation at baseline, stratified to no AoV procedure, AoV replacement and AoV repair post-LVAD surgery.

Supplementary Table 1. Univariable predictors of early all-cause mortality post-LVAD surgery

		95% CI for HR		
Variables	**HR**	**Lower**	**Upper**	**p-value**
Demographics				
Age (years)	1.030	1.025	1.035	<0.001
Sex (men vs. women)	0.914	0.808	1.034	0.153
BSA (m^2)	0.936	0.790	1.110	0.448
BMI (kg/m^2)	1.007	0.999	1.015	0.076
Ischemic etiology	1.317	1.188	1.459	<0.001
Blood type				
O	ref	ref	ref	ref
A	1.067	0.952	1.195	0.265
B	1.133	0.969	1.325	0.118
AB	1.091	0.839	1.419	0.515
INTERMACS class (1-3 vs. 4-7)	1.404	1.201	1.641	<0.001
IABP	1.337	1.201	1.489	<0.001
ECMO	2.580	2.216	3.002	<0.001
≥3 inotropic use	1.526	1.263	1.843	<0.001
Laboratory				
Creatinine (mg/dL)	1.801	1.597	2.032	<0.001
BUN (mg/dL)	1.013	1.011	1.015	<0.001
ASAT (U/L)	1.001	1.001	1.001	<0.001
Total bilirubin (mg/dL)	1.294	1.226	1.365	<0.001
WBC ($_{x10}^{9}$/L)	1.000	0.999	1.000	0.698
Platelets ($_{x10}^{9}$/L)	0.997	0.996	0.998	<0.001
INR	1.296	1.192	1.411	<0.001
Albumin (g/dL)	0.552	0.509	0.600	<0.001
Hemoglobin (g/dL)	0.852	0.831	0.874	<0.001
Hemodynamic				
Mean RA pressure (mmHg)	1.020	1.013	1.026	<0.001
Pulmonary artery wedge pressure (mmHg)	0.996	0.991	1.002	0.185
Systolic pulmonary artery pressure (mmHg)	0.997	0.994	1.001	0.131
Diastolic pulmonary artery pressure (mmHg)	0.993	0.987	0.999	0.015
Cardiac output (L/min)	1.028	0.985	1.073	0.201
Severe RV dysfunction	1.204	1.047	1.383	0.009
Severe LV dysfunction (<20%)	0.884	0.794	0.983	0.023
Moderate or severe tricuspid regurgitation	1.258	1.136	1.394	<0.001
Moderate or severe mitral regurgitation	0.799	0.722	0.885	<0.001
Device strategy				
BTT	ref	ref	ref	ref
BTC	1.097	0.941	1.279	0.236
DT	1.598	1.401	1.823	<0.001
Rescue therapy	2.473	1.275	4.797	0.007
Bridge to recovery	4.937	3.526	6.913	<0.001
Other	1.492	0.479	4.651	0.490

LVAD, Left Ventricular Assist Device; CI, Confidence Interval; HR, Hazard Ratio; BSA, Body Surface Area; BMI, Body Mass Index; INTERMACS, Interagency Registry for Mechanical Assisted Circulatory Support; IABP, Intra-Aortic Balloon Pump; ECMO, Extra Corporeal Membrane Oxygenator; BUN, Blood Urea Nitrogen; ASAT, Asparate Transaminase; WBC, White Blood Count; RA, Right Atrial; RV, Right Ventricle; LV Left Ventricle; BTT, Bridge to Transplant; BTC, Bridge to Candidacy; DT, Destination Therapy

Supplementary Table 2. Univariable predictors of late all-cause mortality post-LVAD surgery

		95% CI for HR		
Variables	**HR**	**Lower**	**Upper**	**p-value**
Demographics				
Age (years)	1.027	1.024	1.030	<0.001
Sex (men vs. women)	0.969	0.897	1.047	0.425
BSA (m^2)	1.005	0.907	1.113	0.929
BMI (kg/m^2)	1.006	1.001	1.010	0.020
Ischemic etiology	1.347	1.265	1.434	<0.001
Blood type				
O	ref	ref	ref	ref
A	1.140	1.064	1.222	<0.001
B	1.081	0.980	1.193	0.120
AB	1.121	0.951	1.321	0.174
INTERMACS class (1-3 vs. 4-7)	1.217	1.116	1.327	<0.001
IABP	1.214	1.135	1.299	<0.001
ECMO	1.707	1.517	1.921	<0.001
≥3 inotropic use	1.258	1.103	1.434	0.001
Laboratory				
Creatinine (mg/dL)	1.614	1.498	1.739	<0.001
BUN (mg/dL)	1.009	1.008	1.010	<0.001
ASAT (U/L)	1.001	1.000	1.001	<0.001
Total bilirubin (mg/dL)	1.106	1.067	1.147	<0.001
WBC ($_{x10}^{9}$/L)	1.000	0.999	1.000	0.393
Platelets ($_{x10}^{9}$/L)	0.999	0.998	0.999	<0.001
INR	1.161	1.093	1.233	<0.001
Albumin (g/dL)	0.716	0.680	0.754	<0.001
Hemoglobin (g/dL)	0.897	0.883	0.910	<0.001
Hemodynamic				
Mean RA pressure (mmHg)	1.015	1.011	1.019	<0.001
Pulmonary artery wedge pressure (mmHg)	0.997	0.994	1.001	0.122
Systolic pulmonary artery pressure (mmHg)	1.000	0.998	1.002	0.909
Diastolic pulmonary artery pressure (mmHg)	0.995	0.991	0.998	0.004
Cardiac output (L/min)	1.032	1.006	1.060	0.017
Severe RV dysfunction	1.108	1.015	1.209	0.022
Severe LV dysfunction (<20%)	0.903	0.846	0.965	0.002
Moderate or severe tricuspid regurgitation	1.117	1.049	1.189	0.001
Moderate or severe mitral regurgitation	0.829	0.779	0.883	<0.001
Device strategy				
BTT	ref	ref	ref	ref
BTC	1.072	0.975	1.179	0.149
DT	1.541	1.420	1.672	<0.001
Rescue therapy	1.519	0.895	2.576	0.121
Bridge to recovery	2.335	1.763	3.091	<0.001
Other	0.743	0.278	1.984	0.553

LVAD, Left Ventricular Assist Device; CI, Confidence Interval; HR, Hazard Ratio; BSA, Body Surface Area; BMI, Body Mass Index; INTERMACS, Interagency Registry for Mechanical Assisted Circulatory Support; IABP, Intra-Aortic Balloon Pump; ECMO, Extra Corporeal Membrane Oxygenator; BUN, Blood Urea Nitrogen; ASAT, Asparate Transaminase; WBC, White Blood Count; RA, Right Atrial; RV, Right Ventricle; LV Left Ventricle; BTT, Bridge to Transplant; BTC, Bridge to Candidacy; DT, Destination Therapy

Supplementary Table 3. Baseline and clinical characteristics stratified to AoV procedure in LVAD patients with moderate to severe AoV regurgitation at baseline

	Overall population (n=583)	No AoV procedure (n=317)	AoV replacement (n=152)	AoV repair (n=114)	p-value
Demographics					
Age (years)	62.0 [53.0-69.0]	63.0 [53.5-69.0]	60.0 [52.0-66.0]	63.0 [56.8-69.0]	0.094
Men	477 (82.0)	260 (82.3)	131 (86.2)	864 (75.4)	0.077
BSA (m^2)	1.97 [1.80-2.16]	1.98 [1.78-2.18]	2.00 [1.83-2.19]	1.90 [1.80-2.09]	0.081
BMI (kg/m^2)	25.4 [22.5-29.5]	25.3 [22.2-29.4]	26.6 [23.3-30.0]	24.6 [22.0-27.7]	0.059
Ischemic etiology	213 (39.7)	124 (42.3)	44 (32.4)	45 (41.7)	0.130
Comorbidities					
CVA	17 (3.0)	9 (2.9)	5 (3.4)	3 (2.7)	0.930
DM	49 (8.5)	32 (10.1)	12 (8.2)	5 (4.4)	0.168
Current smoker	30 (5.3)	8 (2.6)	12 (8.2)	10 (8.8)	0.008
Dialysis	15 (2.6)	9 (2.8)	3 (2.0)	3 (2.6)	0.857
Current ICD therapy	391 (75.0)	208 (74.0)	95 (73.1)	88 (80.0)	0.608
History of CABG	108 (20.4)	67 (23.8)	23 (16.8)	18 (16.4)	0.125
NYHA-classification					
NYHA I/II	7 (1.3)	4 (1.3))	2 (1.4)	1 (1.0)	0.804
NYHA III	98 (18.1)	59 (19.8)	23 (16.8)	16 (15.2)	
NYHA IV	435 (80.6)	235 (78.9)	112 (81.8)	88 (83.8)	
INTERMACS classification					
INTERMACS 1	84 (14.6)	50 (16.0)	20 (13.3)	14 (12.3)	0.780
INTERMACS 2	202 (35.1)	107 (34.3)	57 (38.0)	38 (33.3)	
INTERMACS 3	188 (32.6)	95 (30.4)	51 (34.0)	42 (36.8)	
INTERMACS 4	78 (13.5)	45 (14.4)	18 (12.0)	15 (13.2)	
INTERMACS 5	17 (3.0)	9 (2.9)	3 (2.0)	5 (4.4)	
INTERMACS 6	4 (0.7)	3 (1.0)	1 (0.7)	0 (0.0)	
INTERMACS 7	3 (0.5)	3 (1.0)	0 (0.0)	0 (0.0)	
IABP prior to LVAD surgery	130 (22.7)	75 (23.7)	36 (25.4)	19 (16.7)	0.210
ECMO prior to LVAD surgery	28 (4.9)	17 (5.4)	4 (2.8)	7 (6.1)	0.395
Ventilator prior to LVAD surgery	66 (11.3)	36 (11.4)	15 (9.9)	15 (13.2)	0.704

	Overall population (n=583)	No AoV procedure (n=317)	AoV replacement (n=152)	AoV repair (n=114)	p-value
Laboratory					
Creatinine, mg/dL	1.22 [1.00-1.53]	1.27 [1.00-1.59]	1.27 [1.05-1.56]	1.18 [1.00-1.50]	0.113
BUN, mg/dL	27.0 [20.0-42.0]	28.0 [20.0-43.0]	26.7 [19.0-37.5]	27.0 [19.0-35.3]	0.449
ASAT, U/L	31.0 [22.0-46.0]	30.0 [22.0-44.0]	33.0 [23.0-50.8]	33.0 [24.0-42.0]	0.293
ALAT, U/L	30.0 [20.0-51.0]	28.5 [19.0-46.0]	32.5 [19.3-51.0]	33.0 [22.0-63.0]	0.113
LDH, (U/L)	287.0 [220.5-426.5]	309.0 [229.0-464.3]	280.5 [213.0-395.0]	260.0 [216.0-395.0]	0.207
Total bilirubin, mg/dL	1.1 [0.7-1.7]	1.1 [0.7-1.6]	1.1 [0.7-2.0]	1.2 [0.7-1.9]	0.548
WBC, $x10^9$/L	7.8 [6.1-10.3]	7.8 [6.1-10.4]	8.1 [6.5-9.8]	7.5 [5.7-10.6]	0.463
Platelets, $x10^9$/L	188.0 [141.0-241.0]	186.0 [136.5-252.0]	198.0 [153.0-231.5]	175.5 [141.0-229.3]	0.412
INR	1.2 [1.1-1.4]	1.2 [1.1-1.4]	1.2 [1.1-1.4]	1.2 [1.1-1.3]	0.234
Albumin, g/dL	3.4 [3.0-3.8]	3.3 [3.0-3.7]	3.4 [3.0-3.8]	3.5 [3.0-3.8]	0.270
Hemoglobin, g/dL	11.0 [9.7-12.6]	10.7 [9.4-12.3]	11.1 [10.0-12.8]	11.6 [10.0-12.9]	0.021
Hemodynamics					
RA pressure, mmHg	11.0 [7.0-17.0]	12.0 [7.0-18.0]	10.0 [7.0-15.0]	12.0 [6.0-15.0]	0.272
PCWP, mmHg	25.0 [18.5-32.0]	24.0 [18.0-31.0]	26.0 [20.0-32.0]	25.0 [18.0-31.0]	0.359
Systolic PAP, mmHg	50.0 [40.0-62.0]	50.0 [40.0-62.0]	50.0 [40.0-61.0]	50.0 [40.0-62.0]	1.000
Diastolic PAP, mmHg	25.0 [20.0-30.0]	25.0 [20.0-31.0]	24.0 [20.0-30.0]	24.0 [19.0-30.0]	0.844
Cardiac output, L/min	3.90 [3.00-4.70]	3.90 [3.00-4.60]	4.10 [3.13-4.80]	3.60 [2.80-4.80]	0.298
Echocardiographic					
LVEF					
≥40%	13 (7.0)	4 (4.4)	8 (15.0)	1 (2.5)	0.034
30-39%	27 (14.6)	19 (20.7)	4 (7.5)	4 (10.0)	
20-29%	145 (78.4)	69 (75.0)	41 (77.4)	35 (87.5)	
RVEF					
Normal	117 (26.3)	66 (27.4)	23 (27.4)	28 (28.9)	0.182
Mild	131 (29.4)	66 (27.4)	43 (40.2)	22 (22.7)	
Moderate	135 (30.3)	76 (31.5)	28 (26.2)	31 (32.0)	
Severe	62 (13.9)	33 (13.7)	13 (12.1)	16 (16.5)	
Mitral valve regurgitation					

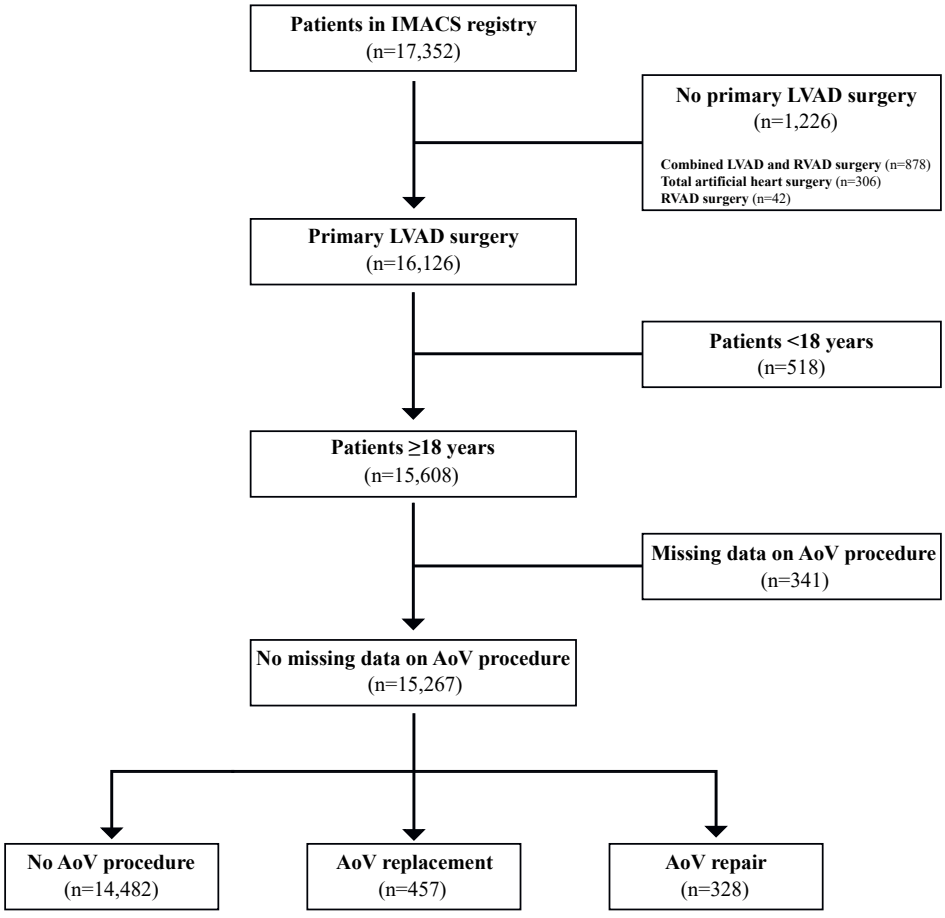
	Overall population (n=583)	No AoV procedure (n=317)	AoV replacement (n=152)	AoV repair (n=114)	p-value
None	24 (4.2)	11 (3.6)	8 (5.5)	5 (4.5)	0.581
Mild	193 (34.0)	107 (34.6)	54 (37.0)	32 (28.6)	
Moderate	211 (37.2)	114 (36.9)	55 (37.7)	42 (37.5)	
Severe	139 (24.5)	77 (24.9)	29 (19.9)	33 (29.5)	
Tricuspid valve regurgitation					
None	34 (6.1)	21 (7.1)	9 (6.1)	4 (3.5)	0.178
Mild	238 (42.7)	114 (38.4)	66 (44.9)	58 (50.9)	
Moderate	201 (36.0)	108 (36.4)	55 (37.4)	38 (33.3)	
Severe	85 (15.2)	54 (18.2)	17 (11.6)	14 (12.3)	
AoV regurgitation					
Moderate	493 (84.4)	270 (85.2)	119 (78.3)	103 (90.4)	0.023
Severe	91 (15.6)	47 (14.8)	33 (21.7)	11 (9.6)	
LVEDD (mm)	68.0 [62.0-75.0]	67.0 [60.1-74.0]	70.5 [63.0-78.0]	68.0 [63.0-75.0]	0.037
Main LVAD strategy					
BTT	135 (23.2)	73 (23.0)	40 (26.3)	22 (19.3)	0.373
BTC	160 (27.4)	86 (27.1)	43 (28.3)	31 (27.2)	
Destination therapy	278 (47.7)	150 (47.3)	67 (44.1)	61 (53.5)	
Rescue therapy	5 (0.9)	5 (1.6)	0 (0.0)	0 (0.0)	
Bridge to recovery	4 (0.7)	3 (0.9)	1 (0.7)	0 (0.0)	
Other	1 (0.2)	0 (0.0)	1 (0.7)	0 (0.0)	

AoV, Aortic Valve; LVAD, Left Ventricular Assist Device; BSA, Body Surface Area; BMI, Body Mass Index; CVA, CerebroVascular Accident; DM, Diabetes Mellitus; ICD, Implantable Cardioverter Defibrillator; CABG, Coronary Artery Bypass Graft; NYHA, New York Heart Association; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; IABP, Intra-Aortic Balloon Pump; ECMO, Extracorporeal Membrane Oxygenator; BUN, Blood Urea Nitrogen; ASAT, Asparate Aminotransferase; ALAT, Alanine AminoTransaminase; LDH, Lactate DeHydrogenase; WBC, White Blood Count; RA, Right Atrial; PCWP, Pulmonary Capillary Wedge Pressure; PAP, Pulmonary Artery Pressure; LVEF, Left Ventricular Ejection Fraction; RVEF, Right Ventricular Ejection Fraction; LVEDD, Left Ventricular End Diastolic Diameter; BTT, Bridge to Transplant; BTC, Bridge to Candidacy

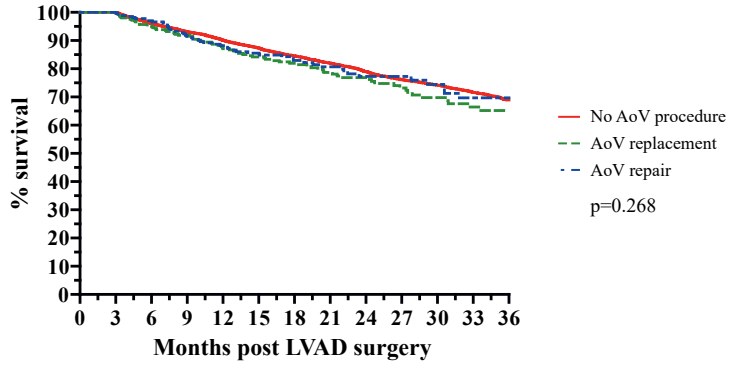
Supplementary Table 4. Causes of death in patients alive 90 days post-LVAD surgery

	Overall population (n=3,890)	No AoV procedure (n=3,657)	AoV replacement (n=143)	AoV repair (n=90)
Device related	72 (3.0)	64 (2.8)	6 (7.9)	2 (4.1)
RV-failure	91 (3.7)	86 (3.7)	3 (3.9)	2 (4.1)
Withdrawal of support	280 (11.5)	269 (11.6)	6 (7.9)	5 (10.2)
Circulatory failure	422 (17.3)	397 (17.2)	11 (14.5)	14 (28.6)
Multisystem Organ Failure	279 (11.4)	267 (11.5)	6 (7.9)	6 (12.2)
Neurological events	517 (21.2)	493 (21.3)	18 (23.7)	6 (12.2)
Major infection	212 (8.7)	203 (8.8)	6 (7.9)	3 (6.1)
Respiratory failure	135 (5.5)	130 (5.6)	2 (2.6)	3 (6.1)
Digestive/liver failure	29 (1.2)	28 (1.2)	1 (1.3)	0 (0.0)
Cancer	42 (1.7)	41 (1.8)	1 (1.3)	0 (0.0)
Hematologic failure	16 (0.7)	13 (0.6)	3 (3.9)	0 (0.0)
Other	343 (14.1)	322 (13.9)	13 (17.1)	8 (16.3)

p-value for distribution between groups: 0.081
LVAD, Left Ventricular Assist Device; AoV, Aortic Valve; RV, Right Ventricular



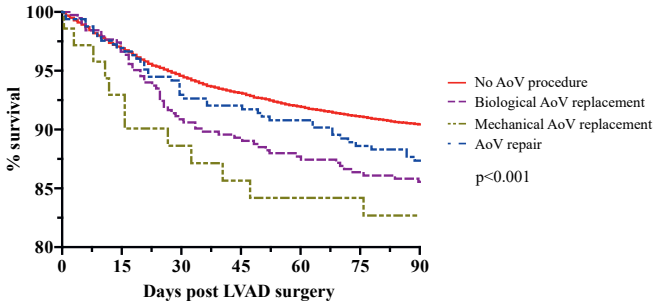
Supplementary Figure 1. Inclusion flowchart



Numbers at risk						
No AoV procedure	12,318	9,077	6,631	4,806	3,357	2,252
AoV replacement	366	305	194	135	91	56
AoV repair	279	203	143	103	57	36

Supplementary Figure 2. Conditional survival of patients alive at 90 days post-LVAD surgery stratified to AoV procedure

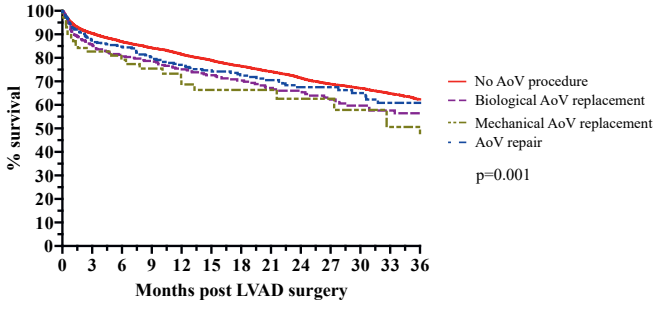
A



Numbers at risk

No AoV procedure	14,477	13,922	13,485	13,156	12,866	12,576	12,318
Biological AoV replacement	386	370	348	339	327	320	312
Mechanical AoV replacement	71	65	60	58	57	56	54
AoV repair	328	316	303	298	292	284	279

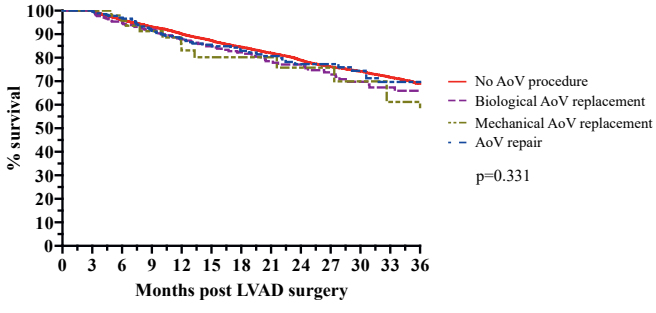
B



Numbers at risk

No AoV procedure	14,477	10,586	7,773	5,654	4,026	2,795	1,772
Biological AoV replacement	386	260	194	144	98	58	42
Mechanical AoV replacement	71	45	30	19	16	9	4
AoV repair	328	242	173	125	78	49	24

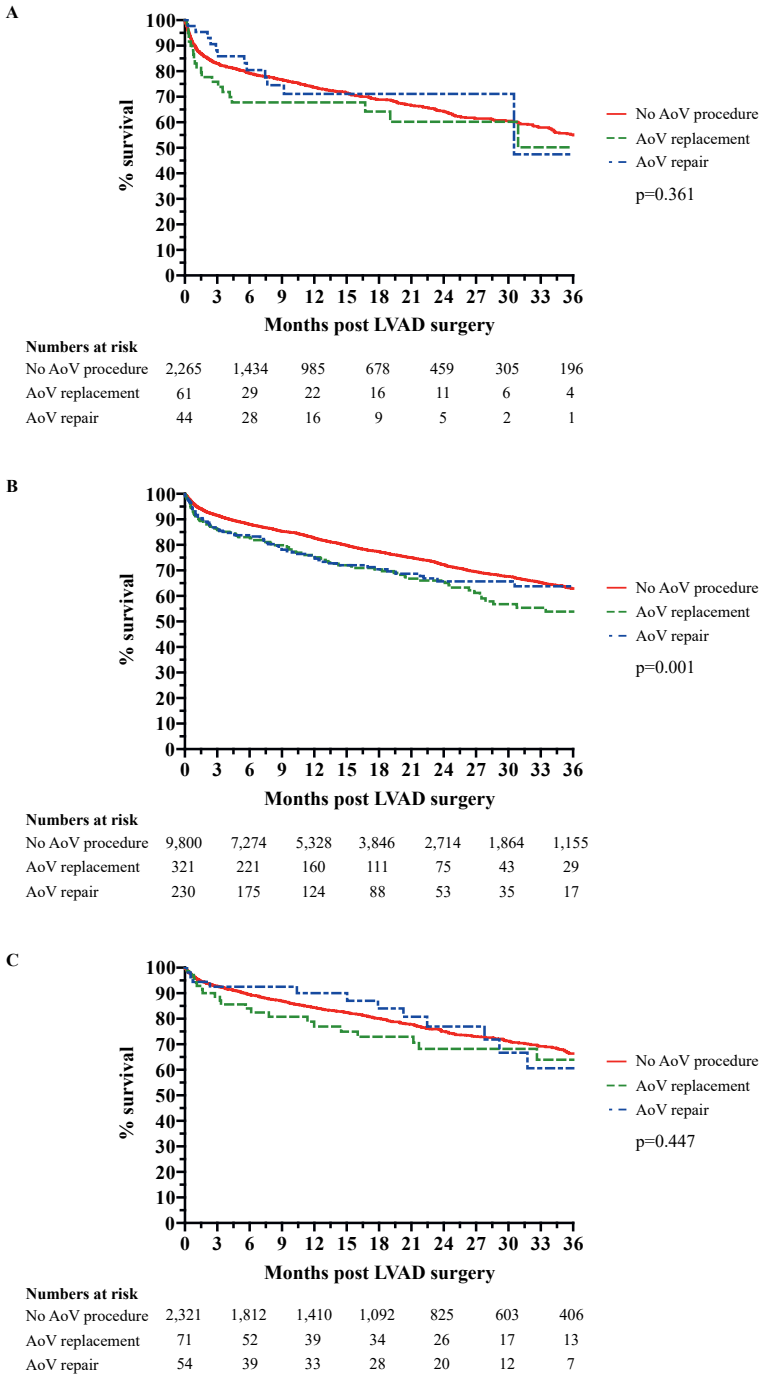
C



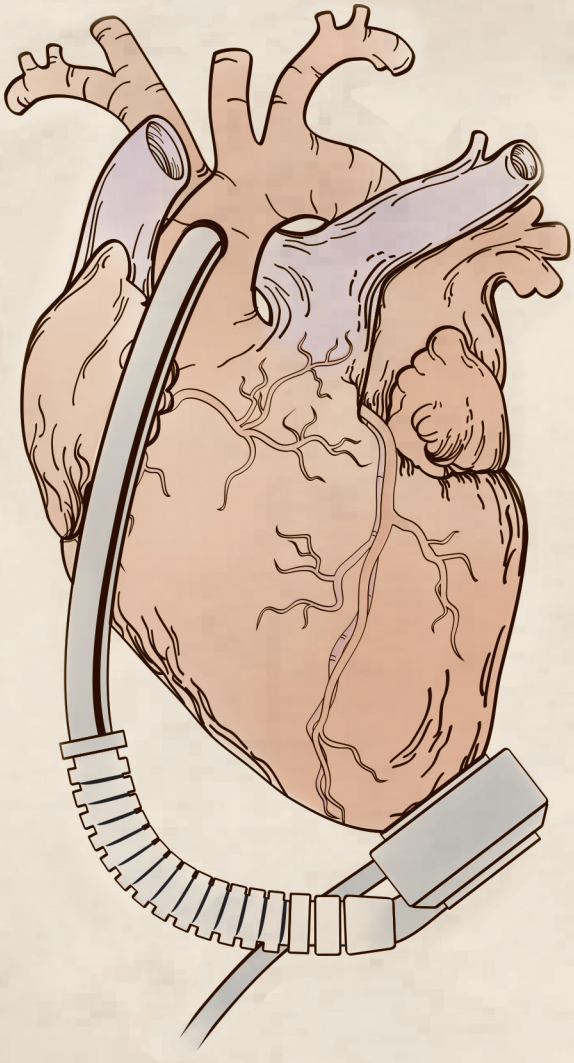
Numbers at risk

No AoV procedure	12,318	9,077	6,631	4,806	3,357	2,252
Biological AoV replacement	312	231	169	117	76	49
Mechanical AoV replacement	54	36	25	18	15	7
AoV repair	279	203	143	103	57	36

Supplementary Figure 3. A Early, **B** late, and **C** conditional survival stratified to no AoV procedure, biological AoV replacement, mechanical AoV replacement and AoV repair post-LVAD surgery



Supplementary Figure 4. A Early, **B** late, and **C** conditional survival in patients with moderate to severe AoV regurgitation at baseline, stratified to no AoV procedure, AoV replacement and AoV repair post-LVAD surgery.



Chapter XI

Thromboembolic Versus Bleeding Events in Patients with Concomitant Aortic Valve Surgery and Left Ventricular Assist Device Implantation: An Analysis of the IMACS Database

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ABSTRACT

Background: Significant aortic regurgitation at the time of left ventricular assist device (LVAD) implantation, requires concomitant aortic valve (AoV) replacement or repair. However, the impact of concomitant AoV surgery on morbidity remains unknown. Therefore, our aim is to determine the impact of concomitant AoV surgery on thromboembolic and bleeding events.

Methods: A retrospective IMACS registry study, including patients implanted from 2013 until September 2017. Differences between different concomitant AoV surgery modalities were analyzed.

Results: In total, 785 (5.1%) out of 15.267 patients (median age 58 IQR 49-66 years, 79% male) underwent concomitant AoV surgery (median age 63 IQR 54-69 years, 84% male); 386 (49%) patients received biological prostheses, 71 (9%) mechanical prostheses and 328 (42%) AoV repairs. In total, 54 (8%) patients with AoV surgery experienced a thromboembolic event and 1016 (9%) patients with no AoV surgery. Furthermore, concomitant AoV surgery was associated with an increased rate of all and nonsurgical bleedings. Following a multivariable Cox regression, concomitant AoV surgery remained an independent predictor for bleeding events.

Conclusions: In LVAD patients undergoing concomitant AoV surgery, thromboembolic event rates were not higher, however both all and nonsurgical bleeding event rates were higher.

Introduction

During the last decade, the number of durable left ventricular assist device (LVAD) implantations has increased to unprecedented heights.[1] Valvular diseases including aortic regurgitation (AR) are associated with increased morbidity and mortality following LVAD implantation, due to a circulatory shortcut with the continuous flow.[2,3] Therefore, the International Society for Heart and Lung Transplantation [4] and the European Association for Cardio-Thoracic Surgery (EACTS) recommend that greater than mild AR, should prompt concomitant aortic valve replacement (AVR) or -repair during LVAD surgery.[5,6] However, concomitant aortic valve (AoV) surgery during LVAD implantation is not without risks as concomitant surgeries during LVAD surgery are associated with an increased mortality rate.[7,8] Moreover, reports on the impact of concomitant AoV surgery past the early period are scarcely available and were conducted with rather small number of patients. Therefore, the aim of the current study is to elucidate the impact of concomitant AoV surgery on, both early and late, thromboembolic (TE) events and bleeding events in patients undergoing LVAD surgery.

Patients and Methods

The IMACS registry is a multinational, multicenter database collecting prospective data, as has been described previously.[9] The goal of the IMACS registry is to gather data of patients treated with mechanical circulatory support (MCS) worldwide and consecutively conduct studies with the aim of improving outcomes. The registry receives data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) [10], European Registry for Patients with Mechanical Circulatory Support (EUROMACS), United Kingdom registry and the Japanese Mechanically Assisted Circulatory Support (JMACS) registries and various individual hospitals worldwide.

Ethical statement

This analysis was reviewed and approved by the IMACS Steering Committee. Informed consent was obtained by each of the participating registries and centers.

Study design, definitions, and endpoints

All patients who were scheduled for a continuous-flow LVAD implantation from January 2013 through September 2017 were selected. **Supplemental figure 1** shows the inclusion flowchart. Definitions of events were predetermined by the IMACS registry. The aim of the current study was to investigate the effect of concomitant aortic valve surgery on the primary endpoint. Subsequently, a sub-analysis, analyzing each aortic valve surgery modality separately was conducted. The primary endpoint of the study was the first occurrence of thromboembolic (TE) events. Thromboembolic events were defined as either early (during the first 90 days of follow-up) or late (up until 2 years of follow-up) ischemic strokes. Secondary endpoints included all major bleeding events (defined as mediastinal, pump pocket, pleural space, intra-abdominal, pulmonary, retroperitoneal, device anastomosis, urinary tract, and all gastrointestinal bleedings), nonsurgical bleeding events (defined as urinary tract or gastrointestinal bleeding), early and late pump thrombosis (defined as either suspected or

confirmed cases), hemorrhagic stroke events, intensive care stay duration, total admission duration and mortality. Major bleeding events were predefined by the IMACS database: a suspected internal or external bleeding which resulted in one or more of the following things: death, re-operation, hospitalization, or transfusion with red blood cells. Furthermore, hemocompatibility related adverse events (HRAE's) were compared between the groups. The HRAEs, a composite endpoint, was defined as either a nonsurgical bleeding event, a neurologic event (i.e., hemorrhagic, or ischemic stroke) or pump thrombosis (suspected or confirmed). Lastly, independent predictors for bleeding events were evaluated.

Statistical analysis

Baseline characteristics are presented as mean, standard deviation (SD) or median with interquartile range (IQR) depending on the distribution of the continuous variables, and count and percentages (%) for categorical variables. Differences between patients' groups were compared with One-way ANOVA (Gaussian distribution) or Kruskal-Wallis (non-Gaussian distribution) for continuous variables. Categorical variables were compared with the Chi squared test. Kaplan-Meier curves were plotted for the occurrence of any of the primary or secondary endpoints. Differences in the rate of endpoints were compared with the Log-Rank test. Patients were censored at the time of transplantation, ventricular recovery, or death. The Fine-Gray method was applied for the competing outcomes analysis.

To determine the most optimal predictive model, a univariable cox hazard regression model was applied. Each individual baseline was tested for its predictive value. Following the univariable regression, a combined multivariable cox hazard regression model was built. The enter method was used to avoid the rather opportunistic nature of the forward and backward method. The multivariable Cox proportional hazards analysis was performed for the identification of covariates independently associated with bleeding events. Missing data were handled by performing multiple imputations, which was only performed for the missing variables used in the univariable and multivariable analysis (see **Supplementary Table 1** for percentages missing). A maximum of 30% missing was deemed acceptable for inclusion to be imputed. Variables were only included in the multivariable models if their respective p was ≤0.10 in the univariable analysis. All multivariable models were constructed by using the enter method. A 2-tailed value of $p<0.05$ was considered statistically significant. The analyses were performed using SPSS statistics version 26 for MacOS (IBM Corp, Armonk, NY) and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Results

In total, 15.267 patients were treated with a primary continuous-flow LVAD implantation and were subsequently included. Concomitant AoV surgery was performed in 785 (5.1%) patients; 386 patients of them (49.2%) were treated with a biological prosthesis, 71 (9.0%) patients with a mechanical prosthesis and 328 (41.8%) patients were treated with concomitant AoV repair surgery. At the time of LVAD implantation, 38% of all patients undergoing concomitant AoV surgeries had a moderate-to-severe AR. The remainder of patients were reported to have only mild or even no AR. There was no specific information retrievable regarding the

surgical indication for AoV surgery. Differences in baseline characteristics are displayed in **Table 1**. The differences in baseline characteristics for each individual modality are displayed in **Supplementary table 2**.

Table 1. Baseline characteristics of the cohort, comparing LVAD patients who underwent no concomitant aortic valve surgery with those who underwent concomitant aortic valve surgery.

Baseline Characteristics	No Concomitant Aortic Valve Surgery (N=14.482)	Concomitant Aortic Valve Surgery (n=785)	P-Value
Age (years)	58.0 [48.0-66.0]	63.0 [54.0-69.0]	<0.001
Male	11.433 (79%)	660 (84%)	<0.001
Continent			<0.001
• America's	12259 (85%)	656 (83%)	
• Asia-Pacific	411 (3%)	45 (6%)	
• Europe	1812 (12%)	84 (11%)	
Body mass index	27.5 [23.9-32.1]	25.8 [22.8-29.9]	<0.001
Ischemic etiology	5.451 (38%)	270 (35%)	0.094
Centrifugal device	5275 (36%)	230 (29%)	<0.001
Other concomitant surgery	3705 (28%)	266 (37%)	<0.001
Comorbidities			
• CVA	621 (4%)	34 (5%)	0.838
• Diabetes	1.417 (10%)	60 (8%)	0.042
• Chronic kidney disease	2882 (21%)	182 (25%)	0.009
• Current ICD	9.860 (78%)	532 (80%)	0.463
• CABG	2.415 (19%)	129 (19%)	0.733
• Atrial arrhythmia	2953 (20%)	172 (23%)	0.161
NYHA			0.430
• Class ≤III	2.722 (20%)	142 (19%)	
• Class IV	10.557 (79%)	594 (81%)	
INTERMACS			0.141
• Profile 1	2.269 (16%)	104 (13%)	
• Profile 2	4.887 (34%)	286 (37%)	
• Profile 3	4.914 (34%)	265 (34%)	
• Profile ≥4	2321 (16%)	125 (16%)	
Strategy			0.003
• Bridge-to-transplantation	4.087 (28%)	185 (24%)	
• Bridge-to-candidacy	4.016 (28%)	205 (26%)	
• Destination therapy	6.177 (42%)	386 (49%)	
• Other	199 (2%)	9 (1)	
IABP	4.109 (29%)	216 (29%)	0.778
ECMO	853 (6%)	58 (8%)	0.045
Laboratory variables			
• Creatinine mg/dl	1.20 [0.97-1.50]	1.24 [1.00-1.54]	0.002
• Blood urea nitrogen mg/dl	25.0 [18.0-37.0]	28.0 [19.0-39.0]	0.004
• Lactate dehydrogenase (u/l)	279.0 [220.0-391.0]	282.0 [218.0-395.0]	0.602
• Total bilirubin mg/dl	1.00 [0.60-1.58]	1.1 [0.7-1.7]	0.010
• WBC count x109/l	7.9 [6.3-10.2]	7.7 [6.1-10.1]	0.962

Baseline Characteristics	No Concomitant Aortic Valve Surgery (N=14.482)	Concomitant Aortic Valve Surgery (n=785)	P-Value
• Platelets x109/l	188.0 [142.0-242.0]	183.0 [132.0-228.5]	<0.001
• International normalized ratio	1.2 [1.1-1.4]	1.2 [1.1-1.4]	0.005
• Albumin g/dl	3.5 [3.0-3.8]	3.4 [3.0-3.8]	0.556
• Hemoglobin g/dl	11.3 [9.8-12.8]	11.2 [9.7-12.5]	0.202
Echocardiogram			
LVEDD (mm)	68.0 [61.0-75.0]	69.0 [63.0-76.0]	0.009
LV ejection fraction			0.837
• Mild (≥40%)	327 (3%)	20 (3%)	
• Moderate (30-39%)	460 (4%)	24 (4%)	
• Moderate/severe (<30%)	11.429 (94%)	610 (93%)	
RV ejection fraction			
• Normal	2.790 (26%)	151 (25%)	0.417
• Mild	3.086 (29%)	186 (31%)	
• Moderate	3.283 (31%)	190 (32%)	
• Severe	1.532 (14%)	74 (12%)	
Mitral valve regurgitation			0.067
• None	1.021 (8%)	49 (7%)	
• Mild	4.689 (35%)	271 (37%)	
• Moderate	4.431 (33%)	258 (36%)	
• Severe	3.221 (24%)	147 (20%)	
Tricuspid valve regurgitation			0.070
• None	1.210 (9%)	47 (7%)	
• Mild	6.491 (49%)	374 (51%)	
• Moderate	3.969 (30%)	228 (31%)	
• Severe	1.560 (12%)	80 (11%)	
Aortic valve regurgitation			<0.001
• None	8.330 (67%)	96 (14%)	
• Mild	3.747 (30%)	337 (48%)	
• Moderate	270 (2%)	222 (32%)	
• Severe	47 (1%)	44 (6%)	

Continuous variables are depicted as median [interquartile range] and categorical variables as count (percentage). Cva denotes cerebrovascular accident; icd, implantable cardioverter defibrillator; cabg, coronary artery bypass graft; nyha, new-york heart association; INTERMACS, interagency registry for mechanically assisted circulatory support; iabp, intra-aortic balloon pump; ecmo, extra corporeal membrane oxygenation; lvad, left ventricular assist device; wbc, white blood cell; lvedd, left ventricular end diastolic diameter; lv, left ventricle; rv, right ventricle.

Thromboembolic events and pump thrombosis

See **Table 2** for a complete overview of the following clinical outcomes. Overall, TE rates were similar in all groups, regardless of concomitant AoV surgery. The rate of TE events (**Supplemental Figure 2a)** was similar with (54 (8%)) or without (1016 (9%)) concomitant AoV surgery in LVAD patients (p=0.66). Additionally, no difference in TE rate was observed between the different AoV surgical modalities. The rate of hemorrhagic strokes was comparable (**Supplemental Figure 2b**). Furthermore, the rate of hemorrhagic stokes did not differ between the different AoV surgical modalities. To account for competing outcomes, a competing risk analysis (including stroke, death, or transplantation) was performed for both

concomitant AVR and concomitant repair surgery, which revealed comparable outcomes between all groups (**Supplemental Figures 3a & 3b).**

Table 2 Overview of the clinical outcomes following LVAD implantation, comparing the patients with and without concomitant aortic valve surgery.

Clinical outcomes	No concomitant aortic valve surgery (n=14.482)	Concomitant aortic valve surgery (n=785)	P-value
Follow-up (months)	9.1 [3.1-19.0]	7.2 [1.6-15.4]	<0.001
Intensive care stay (days)	7 [5-13]	9 [5-16]	0.002
Hospital stay (days)	20 [14-30]	23 [16-36]	<0.001
Transplanted	3178 (22%)	131 (17%)	<0.001
Death	3146 (27%)	213 (33%)	<0.001
Ischemic CVA			
• Early (≤30 days)	311 (3%)	13 (2%)	0.271
• Early (≤90 days)	484 (4%)	22 (3%)	0.280
• Late	1016 (9%)	54 (8%)	0.660
Hemorrhagic CVA			
• Early (≤30 days)	167 (1%)	8 (1%)	0.639
• Early (≤90 days)	515 (4%)	17 (3%)	0.600
• Late	939 (8%)	53 (7%)	0.900
All bleeding events			
• Early (≤30 days)	2377 (20%)	175 (27%)	<0.001
• Early (≤90 days)	3329 (28%)	231 (36%)	<0.001
• Late	4998 (42%)	315 (48%)	<0.001
Nonsurgical bleedings			
• Early (≤30 days)	1357 (12%)	98 (15%)	0.082
• Early (≤90 days)	1922 (16%)	129 (20%)	0.006
• Late	2913 (25%)	184 (28%)	0.002
Pump thrombosis			
• Early (≤30 days)	197 (2%)	13 (2.1%)	0.378
• Early (≤90 days)	489 (4%)	31 (5%)	0.200
• Late	1326 (11%)	73 (12%)	0.170
Hemocompatibility related adverse events			
• Early (≤30 days)	2379 (20%)	167 (25%)	0.002
• Early (≤90 days)	3590 (31%)	232 (35%)	0.001
• Late	6593 (56%)	373 (56%)	0.669
P-values of ischemic & hemorrhagic CVA, all bleeding & nonsurgical bleeding events, pump thrombosis and hemocompatibility related adverse events were determined by Log-Rank test.			

The pump thrombosis rates, (73 (12%) vs 1326 (11%), p=0.170, **Supplemental Figure 4**) were comparable between patients with and without concomitant AoV surgery. However, pump thrombosis rates were significantly higher in the AoV repair group (**Supplemental Figure 5**).

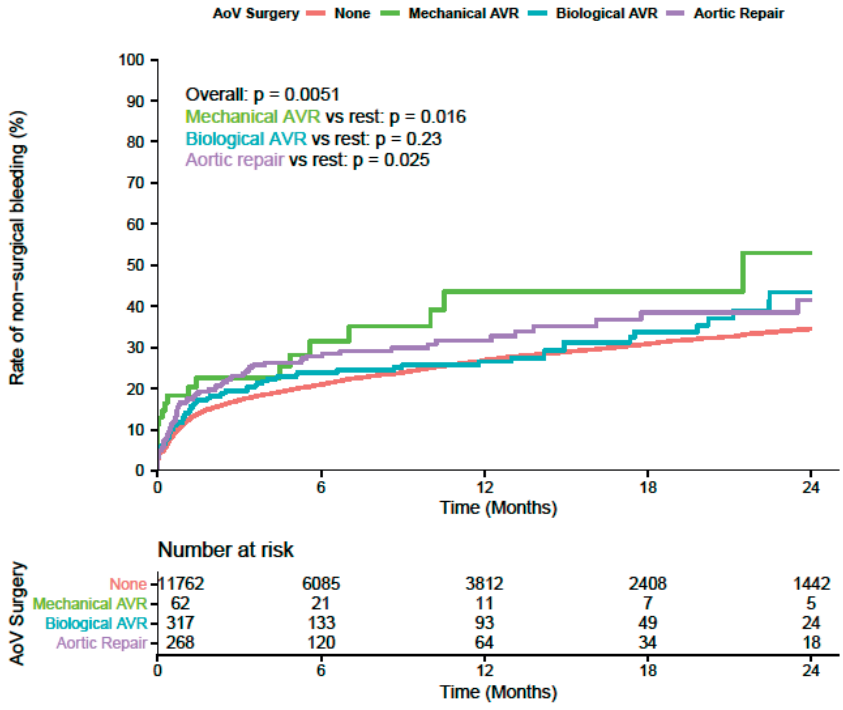

Figure 1 Rate of nonsurgical bleedings, during the first 2 years of support.

Bleeding events

The overall bleeding rate was higher in the concomitant AoV surgery group (315 (48%) vs 4998 (42%)**,** p<0.001) (**Supplemental figure 6a**). The increased bleeding rate was present in all three AoV surgical modalities (**Supplemental Figure 6b**).

The nonsurgical bleeding rate (**Supplemental Figure 7**), showed that concomitant AoV surgery patients had a higher rate (184 (28%) vs 2913 (25%), p=0.002). The early nonsurgical bleeding rate was higher in the AoV repair group, whereas both concomitant biological and mechanical AVR were not associated with an increased rate. However, the late nonsurgical bleeding rate (**Figure 1**) was significantly higher in both the concomitant AoV repair and mechanical prosthesis group.

Lastly, we looked at the international normalized ratio (INR). At the time of bleeding events, INR values were not significantly different, with a median INR of 2,0 [1,5-2,8], 1,9 [1,4-2,8] and 2,0 [1,4-2,6] for no concomitant surgery, concomitant AVR and concomitant repair surgery, respectively (One-Way ANOVA, p=0.248). However, the administered oral anticoagulation and platelet aggregation inhibitors at the time of the bleeding events did differ between groups, with 2637 (22.4%) patients in the no concomitant AoV surgery group

on dual therapy, 103 (27.2%) patients in the concomitant AVR group and 79 (29.5%) in the concomitant AoV repair group (Chi squared test, p=0.003).

Predictors for bleeding events

An exploratory univariable Cox proportional hazard model was built to investigate potential predictors for bleeding events. See **Table 3** for an overview of these predictors. Following a multivariable analysis, AoV surgery remained as an independent predictor for bleeding events.

Clinical outcomes

Overall, patients treated with concomitant AoV surgery had a longer intensive care unit [11] stay than those without. Furthermore, patients with concomitant AoV surgery were hospitalized longer. The outcomes of individual modalities of AoV surgery are listed in **Supplemental Table 3**. The overall occurrence of HRAEs were additionally analyzed and while the early period favored no concomitant AoV surgery, at 2-years of follow-up, no significant difference was observed between both groups. See **Table 2** for an overview of the clinical outcomes.

Patients without concomitant AoV surgery were transplanted significantly more often compared with those who did undergo this procedure; 3178 (22%) vs. 131 (17%), respectively (p<0.001). Lastly, the 2-year mortality rates (**Supplemental Figure 8**) were significantly different, favoring no concomitant AoV surgery to concomitant AoV surgery; 3146 (27%) vs 213 (33%), respectively (Log-Rank, p=0.001).

Table 3 Predictors for bleeding events following LVAD surgery showing both the univariable analysis and the multivariable analysis.

	Univariable			Multivariable		
Baseline characteristics	**Hazard Ratio**	**95% CI**	**p-value**	**Hazard Ratio**	**95% CI**	**p-value**
Age (years)	1.026	1.024 - 1.028	<0.001	1,017	1.015 - 1.020	<0,001
Male	0.936	0.877 - 0.999	0.046	0.897	0.836 – 0.963	0.003
Continent						
• Americas	ref			ref		
• Asia-Pacific	0.845	0.709 – 1.007	0.060	1.075	0.847 - 1.294	0.442
• Europe	0.420	0.368 – 0.479	<0.001	0.471	0.405 - 0.548	<0.001
Body mass index	0.996	0.991 - 1.000	0.051	0.999	0.994 – 1.004	0.707
Ischemic etiology	1.324	1.254 - 1.399	<0.001	1,080	1.018 - 1.146	0,011
Centrifugal device	0.662	0.623 – 0.704	<0.001	0.913	0.847 - 0.984	0.017
Comorbidities						
• CVA	1.009	0.882 - 1.154	0.896			
• Diabetes	1.198	1.1 - 1.304	<0.001	1,091	1.000 - 1.189	0,050
• Chronic kidney disease	1.448	1.359 - 1.542	<0.001	1,224	1.147 - 1.307	<0,001

	Univariable			Multivariable		
Baseline characteristics	**Hazard Ratio**	**95% CI**	**p-value**	**Hazard Ratio**	**95% CI**	**p-value**
• Current ICD	1.092	1.019 - 1.171	0.013	1,006	0.927 - 1.093	0,877
• CABG	1.425	1.335 - 1.522	<0.001	1.119	1.036 – 1.208	0.004
• Atrial arrhythmia	1.2	1.124 - 1.281	<0.001	1,071	1.002 - 1.146	0,045
NYHA						
• Class ≤III	ref			ref		
• Class IV	1.206	1.118 - 1.300	<0.001	1.031	0.957 – 1.111	0.418
INTERMACS						
• Profile 1	1.233	1.120 - 1.357	<0.001	1,394	1.261 - 1.541	<0,001
• Profile 2	1.12	1.031 - 1.216	0.007	1,193	1.098 - 1.297	<0,001
• Profile 3	1.016	0.935 - 1.104	0.715	1,049	0.965 - 1.140	0,261
• Profile ≥4	ref			ref		
Strategy						
• Bridge-to-transplantation	ref			ref		
• Bridge-to-candidacy	1.196	1.105 - 1.295	<0.001	1,190	1.097 - 1.290	<0,001
• Destination therapy	1.806	1.687 - 1.934	<0.001	1,512	1.408 - 1.625	<0,001
• Other	0.832	0.602 - 1.149	0.265	0,836	0.603 - 1.160	0,284
IABP	1.015	0.956 - 1.077	0.633			
ECMO	1.081	0.967 - 1.208	0.171			
Laboratory variables						
• Creatinine mg/dl	1.389	1.300 - 1.483	<0.001	1.101	1.014 - 1.196	0.022
• Blood urea nitrogen mg/dl	1.005	1.003 - 1.006	<0.001	1.003	1.002 – 1.005	<0.001
• Total bilirubin mg/dl	1.002	0.969 - 1.036	0.923			
• Wbc count x109/l	1	0.998 - 1.001	0.545			
• Platelets x109/l	0.999	0.999 - 0.999	<0.001	1.000	0.999-1.000	0.160
• International normalized ratio	0.94	0.880 - 1.004	0.067	0.938	0.874 – 1.008	0.080
• Albumin g/dl	0.801	0.763 - 0.840	<0.001	0.968	0.918 – 1.022	0.238
• Hemoglobin g/dl	0.9	0.888 - 0.912	<0.001	0.927	0.913 – 0.941	<0.001
Echocardiogram						
LVEDD (mm)	0.907	0.881 - 0.934	<0.001	0.974	0.945 – 1.000	0.050
LV ejection fraction						
• Mild (≥40%)	ref			ref		
• Moderate (30-39%)	1.551	1.118 - 2.023	0.002	1,065	0.733 - 1.549	0,723
• Moderate/severe (<30%)	1.372	1.090 - 1.728	0.008	0,981	0.707 - 1.361	0,903
RV ejection fraction						
• Normal	ref			ref		

	Univariable			Multivariable		
Baseline characteristics	**Hazard Ratio**	**95% CI**	**p-value**	**Hazard Ratio**	**95% CI**	**p-value**
• Mild	1.029	0.947 - 1.119	0.492	1.044	0.958 – 1.139	0.321
• Moderate	1.082	0.998 - 1.174	0.057	1.105	1.019 – 1.198	0.016
• Severe	1.043	0.939 - 1.157	0.427	1.085	0.978 – 1.205	0.123
Mitral valve regurgitation						
• None	ref					
• Mild	0.973	0.870 - 1.089	0.638			
• Moderate	1.005	0.897 - 1.126	0.938			
• Severe	1.012	0.900 - 1.137	0.847			
Tricuspid valve regurgitation						
• None	ref			ref		
• Mild	0.989	0.876 - 1.115	0.849	1,021	0.906 - 1.150	0,726
• Moderate	1.1	0.969 - 1.248	0.137	1,136	1.003 - 1.287	0,045
• Severe	1.257	1.127 - 1.444	<0.001	1,309	1.158 - 1.479	<0,001
Aortic valve regurgitation						
• None	ref			ref		
• Mild	1.115	1.040 - 1.195	0.003	0,997	0.931 - 1.067	0,927
• Moderate	1.372	1.194 - 1.578	<0.001	1,080	0.935 - 1.248	0,294
• Severe	1.28	0.939 - 1.745	0.117	1,127	0.825 - 1.539	0,453
Concomitant AoV surgery	1.327	1.184 - 1.487	<0.001	1,158	1.018 - 1.317	0,026
Other concomitant surgery	1.055	0.994 – 1.121	0.079	1.133	1.064 - 1.206	<0.001

Cva denotes cerebrovascular accident; icd, implantable cardioverter defibrillator; cabg, coronary artery bypass graft; nyha, new-york heart association; INTERMACS, interagency registry for mechanically assisted circulatory support; iabp, intra-aortic balloon pump; ecmo, extra corporeal membrane oxygenation; lvad, left ventricular assist device; wbc, white blood cell; lvedd, left ventricular end diastolic diameter; lv, left ventricle; rv, right ventricle.

Discussion

The main finding of this study was that concomitant AoV surgery during LVAD surgery was not associated with a higher rate of TE. However, concomitant AoV surgery was associated with an increased rate of bleeding events following LVAD implantation.

Thromboembolic events and pump thrombosis

This study was conducted with an initial hypothesis that concomitant AoV surgery could increase the rate of TE events following LVAD implantation. Prior, smaller studies revealed that aortic root thrombosis during LVAD support is not uncommon and that concomitant AoV surgery could play a role in the formation.[12,13] However, our current findings reveal similar rates of TE events between patients with and without concomitant AoV surgery.

The analysis revealed that concomitant AoV repair surgery was associated with a significantly increased rate of pump thrombosis following LVAD implantation. Previous studies have linked AoV closure at the time of LVAD implantation with an increased rate of pump thrombosis and decreased survival.[7,14] However, given the differences in patient characteristics (the AV repair patients were older, and were least likely to have a centrifugal device), this apparent increase in pump thrombosis is most likely explained due to these differences. Nonetheless, it remains possible that the AoV repair surgery is an instigator as well. The inherent risks of sutures tearing, and possible reoccurrence of AR could make patients more at risk for hematological complications such as pump thrombosis.[15,16] However, the underlying mechanisms are far from being elucidated.

Bleedings events

We found concomitant AoV surgery to be associated with an increased rate of bleeding events. To elucidate the underlying cause, we subsequently conducted a second analysis to only include nonsurgical bleeding. This revealed that, with prolonged support, both concomitant mechanical prostheses and AoV repair surgery were associated with an increased rate of nonsurgical bleeding. This is visible on the Kaplan Meier curves, showing an impact especially in the early period following surgery. Interestingly, a prior investigation stated that concomitant AoV surgery was not associated with an increased rate of bleedings in HeartMate II patients.[17] To validate our findings, we conducted a multivariable Cox regression analysis. After adjusting for multiple covariates, concomitant AoV surgery was found to be independent predictor for bleedings events following LVAD implantation. We postulate that the initiation of an intensified regimen of platelet inhibitors and oral anticoagulation most likely plays a part, as both are associated with increased bleeding rates.[18] Moreover, concomitant AV surgery is more extensive, needs more suturing, aortic cross-clamping and cardioplegia with dilution, and possibly more transfusion with possible impact on the blood homeostasis even in the days following the surgery. However, the increased shear stress and subsequent greater degree of acquired of von Willebrand factor deficiency could be contributors.[19-21] Lastly, the impact of intraoperative factors, such as the use of a cardiopulmonary bypass (CPB) machine, the duration of the CPB machine and the possible use of cardioplegia could all play a substation roll in the increased bleeding events, however these data were not available in this cohort.

Indications

We want to preface this section with the notion that the decision for concomitant AoV surgery is multifactorial and driven by more than the degree of AR. Nonetheless, to our surprise, this study revealed that the majority (48%) of concomitant AoV surgeries were performed in patients with a preoperative diagnosis of mild AR. This was unanticipated, since the current guidelines recommend concomitant AoV surgery only in patients with moderate-to-severe AR. Plausible explanations for deferring form this recommendation include the caution of heart teams in this obscure clinical entity in the era of LVAD surgery. Furthermore, during the perioperative period, surgeons can defer, or schedule concomitant surgeries based on the current perioperative condition of patients. The introduction of improved left ventricular flow could reveal a higher severity of aortic regurgitation, which might have been concealed previously due to poor left ventricular function.[22] Secondly, the data of this current study are provided from 2013 until 2017 and are subject to evolving indications and experience. Moreover, there seems to be evidence that concomitant AoV surgery is perhaps warranted in select LVAD candidates with mild AR. Previous studies found that mild preoperative AR is a significant predictor for worsening AR during LVAD support.[3,23] Nonetheless, these findings highlight the disparities between contributing centers.

Of note, inclusion of mechanical prosthesis as a treatment modality was highly unanticipated. The ISHLT guidelines and the EACTS expert consensus recommend replacement of mechanical prostheses with biological prosthesis at the time of LVAD surgery and recommends the use of a biological prosthesis in case of a scheduled AoV surgery.[6,24] These findings underline the far from crystallized indications for concomitant aortic valve surgery in patients undergoing LVAD implantation.

Clinical implications

Concomitant AoV surgery is associated with significantly higher mortality, longer need of ICU stay and hospital stay and bleedings rates, most noticeably in the early period following LVAD implantation. Furthermore, patients who had not undergone concomitant aortic valve surgery were more likely to be transplanted. This most likely derives from their baseline differences as patients who had not undergone concomitant aortic surgery were younger and more frequently implanted as bridge-to-transplantation. Therefore, the decision for concomitant aortic valve surgery should warrant thorough evaluation of bleeding risks prior to surgery. Lastly, the deployment of less invasive intervention such as transcatheter aortic valve implantation (TAVI) can provide a solution in some patient who are prone to complication when undergoing concomitant aortic valve surgery. Rather than extending the operation time, increase CPB time and aortic cross-clamping, the TAVI procedure can be scheduled either prior to surgery or following surgery.[25]

Limitations

The current study is the performed with data from registries allowing for the inclusion of a large number of concomitant AoV surgeries. However, it's important to note that the data supplied by every center is subject to erroneous and missing data. Furthermore, the retrospective nature of this study does not allow for establishing causality. Secondly, no detailed information was available on the indications for aortic valve surgery, implanted device type, and therefore no further analyses could be conducted between the differences

regarding device types. Furthermore, the use and the duration of a cardiopulmonary bypass machine, and possible off-pump implantations were not captured in the database. Therefore, no separate analyses could be conducted to account for the effect of CPB in this cohort. Additionally, no information was available on the decision-making process during concomitant aortic valve surgery. Third, some data were missing for end points used in this study and therefore could have altered the results of the study. Furthermore, no data on prior aortic valve surgery or aortic root dilation were provided. Fourth, missing data were imputed. Nonetheless, the percentage of missing data was limited, with most covariates missing less than 10%. Of note, the imputed data was solely used in the Cox regression models. Lastly, no data was available on the reasoning for concomitant AoV surgery modality and the registry did not distinguish a separate AoV closure group.

Conclusion

In LVAD patients, concomitant AoV surgery was not associated with an increased rate of TE events. However, concomitant AoV surgery was associated with an increased rate of bleeding events, especially in the early postoperative period. Prospective, randomized trials are required to determine the appropriate indications and management of concomitant AoV surgery at the time of LVAD implantation.

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Conflict of interest: None

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Supplemental Legend

Supplemental Table 1. Overview of the percentage of missing data of the baseline variables, which were imputed solely for the uni- and multivariable cox proportional hazard model.

Supplemental Table 2. Baseline characteristics of patients who underwent no vs biological prostheses, mechanical prostheses and aortic valve repair surgery concomitantly during LVAD surgery.

Supplemental Table 3. Overview of clinical outcomes in patients who did have concomitant aortic valve surgery, stratified according to the respective modalities.

Supplemental Figure 1. Flowchart describing the inclusion and exclusion criteria for the current study.

Supplemental Figure 2a Rate of thrombotic events during the first 24 months of support, in patients with and without concomitant aortic valve surgery at the time of LVAD implantation.

Supplemental Figure 2b Rate of hemorrhagic strokes, during the first 24 months of support, in patients with and without concomitant aortic valve surgery at the time of LVAD implantation.

Supplemental Figure 3a. Competing outcomes analysis including CVA, death and transplantation for patients with and without concomitant AVR surgery.

Supplemental Figure 3b. Competing outcomes analysis including CVA, death and transplantation for patients with and without concomitant repair surgery.

Supplemental Figure 4 Rate of pump thrombosis, during the first 24 months of support, in patients with and without concomitant aortic valve surgery at the time of LVAD implantation.

Supplemental Figure 5 Rate of pump thrombosis, during the first 24 months of support, in patients with biological, mechanical valve replacements or aortic valve repair surgery and patients without concomitant aortic valve surgery at the time of LVAD implantation.

Supplemental Figure 6a Rate of bleeding, during the first 24 months of support in patients with and without concomitant aortic valve surgery at the time of LVAD implantation.

Supplemental Figure 6b Rate of all bleeding, during the first 2 years of support, in patients with biological, mechanical valve replacements or aortic valve repair surgery and patients without concomitant aortic valve surgery at the time of LVAD implantation.

Supplemental Figure 7 Rate of nonsurgical bleeding during the first 24 months of support, in patients with and without concomitant aortic valve surgery at the time of LVAD implantation.

Supplemental Figure 8. The cumulative survival rate during the first 24 months of support, in patients with and without concomitant aortic valve surgery with LVAD surgery

Supplemental Table 1

Baseline characteristics	Missing %
Age (years)	0
Male gender	0.03
Body mass index (kg/m2)	2.76
Ischemic etiology	1.68
Comorbidities	
• CVA	2.28
• Diabetes mellitus	2.19
• Chronic kidney disease	3.84
• Current ICD therapy	13.43
• History of CABG	12.43
• Atrial arrhythmia	4.21
NYHA-classification	8.2
INTERMACS classification	0.63
Strategy	0.02
IABP	2.53
ECMO	2.55
Laboratory variables	
• Creatinine mg/dl	8.63
• Blood urea nitrogen mg/dl	2.64
• Lactate dehydrogenase (u/l)	41.8
• Total bilirubin mg/dl	10.76
• WBC count $x10^9$/l	1.24
• Platelets $x10^9$/l	1.17
• International normalized ratio	5.44
• Albumin g/dl	11.3
• Hemoglobin g/dl	2
Echocardiogram	
LVEDD (mm)	23.4
LV ejection fraction	15.7
RV ejection fraction	26.04
Mitral valve regurgitation	7.73
Tricuspid valve regurgitation	8.57
Aortic valve regurgitation	14.24

CVA denotes cerebrovascular accident; ICD, implantable cardioverter defibrillator; CABG, coronary artery bypass graft; NYHA, New-York heart association; INTERMACS, interagency registry for mechanically assisted circulatory support; IABP, intra-aortic balloon pump; ECMO, extra corporeal membrane oxygenation; LVAD, left ventricular assist device; WBC, white blood cell; LVEDD, left ventricular end diastolic diameter; LV, left ventricle; RV, right ventricle.

Supplemetary Table 2

Baseline Characteristics	No Aortic Valve Surgery (N=14.482)	Biological Prosthesis (N=457)	Mechanical Prosthesis (N=71)	Aortic Valve Repair (N=328)	P-Value
Age (years)	58.0 [48.0-66.0]	62.0 [53.0-69.0]	63.0 [53.0-69.0]	64.0 [57.0-69.0]	<0.001
Male	11.433 (79%)	396 (87%)	63 (91%)	264 (80%)	<0.001
Continent					<0.001
• America's	12259 (85%)	285 (74%)	64 (90%)	307 (94%)	
• Asia-Pacific	411 (3%)	30 (8%)	2 (3%)	13 (4%)	
• Europe	1812 (12%)	71 (18%)	5 (7%)	8 (2%)	
Body mass index	27.5 [23.9-32.1]	26.1 [22.8-30.4]	26.0 [23.2-30.6]	25.1 [22.8-29.4]	<0.001
Ischemic etiology	5.451 (38%)	121 (32%)	26 (38%)	123 (38%)	<0.001
Centrifugal device	5275 (36%)	136 (35%)	20 (28%)	74 (23%)	<0.001
Other concomitant surgery	3705 (28%)	125 (37%)	25 (37%)	116 (36%)	<0.001
Comorbidities					
• CVA	621 (4%)	21 (5%)	1 (1)	13 (4%)	0.450
• Diabetes	1.417 (10%)	37 (8%)	7 (10%)	23 (7$)	0.193
• Chronic kidney disease	2882 (21%)	100 (24%)	18 (25%)	82 (26%)	0.057
• Current ICD	9.860 (78%)	279 (77%)	50 (76%)	253 (82%)	0.594
• CABG	2.415 (19%)	68 (18%)	12 (18%)	61 (19%)	0.936
• Atrial arrhythmia	2953 (20%)	100 (22%)	23 (32%)	72 (22%)	0.124
NYHA					0.726
• Class ≤III	2.722 (20%)	73 (21%)	13 (19%)	56 (18%)	
• Class IV	10.557 (79%)	282 (79%)	57 (81%)	255 (82%)	
INTERMACS					0.669
• Profile 1	2.269 (16%)	60 (13%)	10 (14%)	44 (14%%)	
• Profile 2	4.887 (34%)	165 (36%)	23 (33%)	121 (37%)	
• Profile 3	4.914 (34%)	156 (34%)	25 (36%)	109 (33%)	
• Profile ≥4	2321 (16%)	71 (16%)	11 (16%)	54 (16%)	
Strategy					<0.001
• Bridge-to-transplantation	4.087 (28%)	106 (27%)	10 (14%)	69 (21%)	
• Bridge-to-candidacy	4.016 (28%)	104 (27%)	22 (31%)	79 (24%)	
• Destination therapy	6.177 (42%)	169 (44%)	37 (52%)	180 (55%)	
• Other	199 (2%)	7 (2%)	2 (3%)	0 (0.0)	
IABP	4.109 (29%)	105 (24%)	21 (30%)	88 (27%)	0.063
ECMO	853 (6%)	18 (4%)	4 (6%)	20 (6%)	0.359
Laboratory variables					

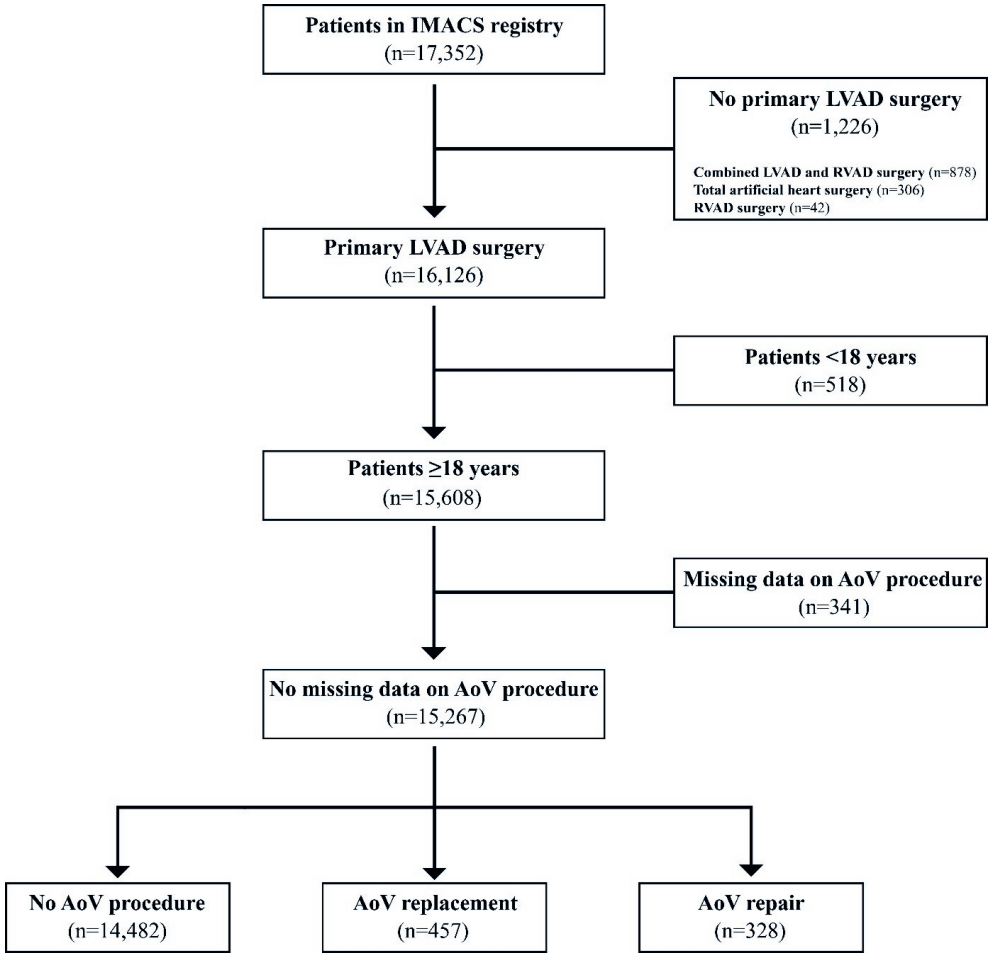
Baseline Characteristics	No Aortic Valve Surgery (N=14.482)	Biological Prosthesis (N=457)	Mechanical Prosthesis (N=71)	Aortic Valve Repair (N=328)	P-Value
• Creatinine mg/dl	1.20 [0.97-1.50]	1.27 [1.05-1.57]	1.3 [1.0-1.59]	1.20 [1.00-1.50]	0.011
• Blood urea nitrogen mg/dl	25.0 [18.0-37.0]	29.0 [21.0-40.0]	31.0 [22.0-40.0]	26.0 [18.0-36.0]	<0.004
• Lactate dehydrogenase (u/l)	279.0 [220.0-391.0]	289.50 [222.8-390.3]	283.0 [218.0-419.0]	276.5 [216.3-395.0]	0.790
• Total bilirubin mg/dl	1.00 [0.60-1.58]	1.1 [0.7-1.7]	1.1 [0.7-1.7]	1.1 [0.7-1.7]	0.036
• WBC count x109/l	7.9 [6.3-10.2]	7.8 [6.2-9.8]	8.2 [6.4-10.0]	7.5 [6.0-10.4]	0.962
• Platelets x109/l	188.0 [142.0-242.0]	187.0 [132.0-232.0]	166.0 [131.0-236.0]	176.5 [131.3-226.0]	<0.001
• International normalized ratio	1.2 [1.1-1.4]	1.3 [1.1-1.5]	1.2 [1.1-1.4]	1.2 [1.1-1.4]	0.001
• Albumin g/dl	3.5 [3.0-3.8]	3.4 [3.0-3.8]	3.5 [3.2-3.9]	3.4 [3.0-3.8]	0.648
• Hemoglobin g/dl	11.3 [9.8-12.8]	11.2 [9.9-12.6]	11.2 [9.7-12.6]	11.2 [9.7-12.5]	0.623
Echocardiogram					
LVEDD (mm)	68.0 [61.0-75.0]	69.0 [63.0-77.0]	69.0 [65.0-79.0]	68.0 [62.0-74.0]	0.006
LV ejection fraction					0.007
• Mild (≥40%)	327 (3%)	16 (6%)	2 (3%)	2 (1%)	
• Moderate (30-39%)	460 (4%)	7 (2%)	5 (8%)	12 (4%)	
• Moderate/severe (<30%)	11.429 (94%)	267 (92%)	57 (89%)	286 (95%)	
RV ejection fraction					
• Normal	2.790 (26%)	73 (22%)	11 (21%)	78 (28%)	0.210
• Mild	3.086 (29%)	108 (33%)	17 (31%)	78 (28%)	
• Moderate	3.283 (31%)	103 (32%)	17 (31%)	87 (32%)	
• Severe	1.532 (14%)	42 (13%)	9 (17%)	32 (12%)	
Mitral valve regurgitation					0.045
• None	1.021 (8%)	29 (8%)	3 (5%)	17 (6%)	
• Mild	4.689 (35%)	143 (41%)	21 (32%)	107 (34%)	
• Moderate	4.431 (33%)	116 (33%)	22 (34%)	120 (38%)	
• Severe	3.221 (24%)	60 (17%)	19 (29%)	68 (22%)	
Tricuspid valve regurgitation					0.277
• None	1.210 (9%)	25 (7%)	6 (9%)	16 (5%)	
• Mild	6.491 (49%)	172 (50%)	35 (51%)	167 (53%)	
• Moderate	3.969 (30%)	110 (32%)	24 (35%)	94 (30%)	
• Severe	1.560 (12%)	40 (11%)	4 (6%)	36 (12%)	
Aortic valve regurgitation					<0.001
• None	8.330 (67%)	52 (15%)	11 (19%)	33 (11%)	
• Mild	3.747 (30%)	153 (45%)	29 (50%)	155 (51%)	
• Moderate	270 (2%)	102 (30%)	17 (29%)	103 (34%)	
• Severe	47 (1%)	32 (9%)	1 (2%)	11 (4%)	

Continuous variables are depicted as median [interquartile range] and categorical variables as count (percentage). Cva denotes cerebrovascular accident; icd, implantable cardioverter defibrillator; cabg, coronary artery bypass graft; nyha, new-york heart association; intermacs, interagency registry for mechanically assisted circulatory support; iabp, intra-aortic balloon pump; ecmo, extra corporeal membrane oxygenation; lvad, left ventricular assist device; wbc, white blood cell; lvedd, left ventricular end diastolic diameter; lv, left ventricle; rv, right ventricle.

Supplemental Table 3

Clinical outcomes	Biological prosthesis (n=386)	Mechanical prosthesis (n=71)	AoV repair surgery (n=328)	P-value
Follow-up (months)	6,0 [1,3-15,8]	5 [1,0-14,2]	7,6 [2,3-14,9]	0.883
Intensive care stay (days)	10 [5-17]	10 [7-17]	8 [5-14]	0.010
Hospital stay (days)	23 [16-40]	23 [15-40]	22 [15-32]	0.358
Transplanted	65 (17%)	10 (14%)	56 (17%)	0.824
Death	120 (38%)	25 (40%)	90 (34%)	0.860
Ischemic CVA				
• Early (≤90 days)	10 (3%)	3 (5%)	9 (3%)	0.066
• Late	24 (7%)	6 (9%)	24 (9%)	0.194
Hemorrhagic CVA				
• Early (≤90 days)	8 (3%)	2 (3%)	7 (3%)	0.960
• Late	23 (7%)	4 (6%)	26 (9%)	0.500
All bleeding events				
• Early (≤90 days)	109 (34%)	21 (34%)	101 (38%)	0.674
• Late	151 (48%)	31 (50%)	133 (50%)	0.870
Nonsurgical bleedings				
• Early (≤90 days)	55 (17%)	16 (26%)	60 (22%)	0.136
• Late	80 (25%)	24 (39%)	80 (30%)	0.079
Pump thrombosis*				
• Early (≤90 days)	9 (3%)	4 (7%)	18 (7%)	0.087
• Late	28 (9%)	8 (14%)	37 (14%)	0.188
Hemocompatibility related adverse events				
• Early (≤90 days)	108 (35%)	26 (42%)	98 (37%)	0.053
• Late	174 (57%)	36 (58%)	163 (61%)	0.016

Continuous variables are depicted as median [interquartile range] and categorical variables as count (percentage, based on the available cases within each group). Late events were defined as occurring within 2 years post-operatively. Follow-up was truncated at 2-years. P-values of ischemic & hemorrhagic CVA, all bleeding & nonsurgical bleeding events, pump thrombosis and hemocompatibility related adverse events were determined by Log-Rank test. *suspected or confirmed cases.



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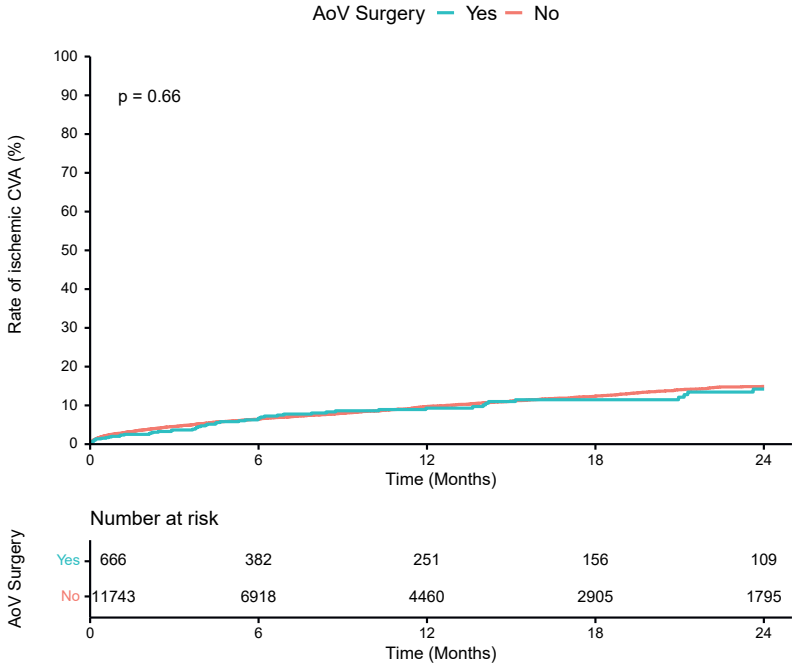

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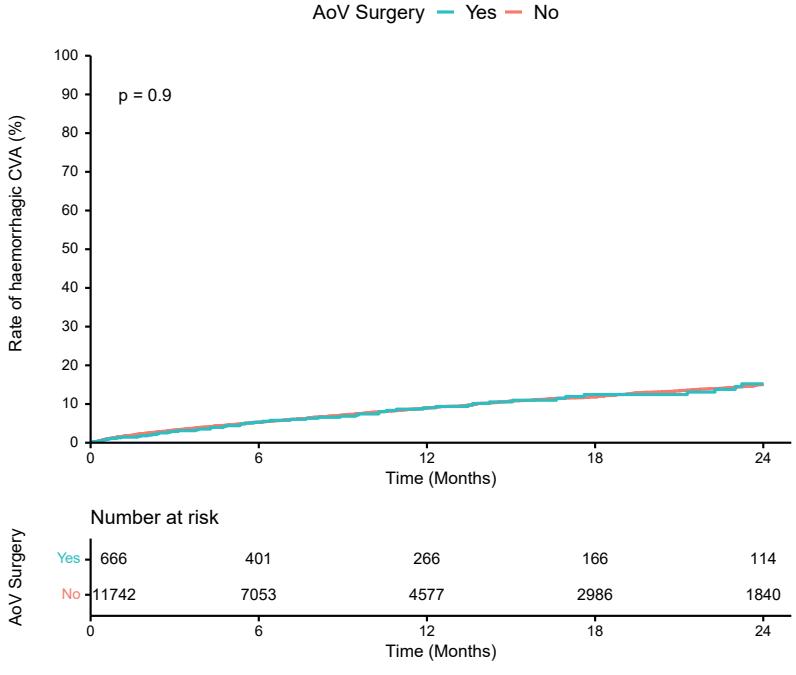

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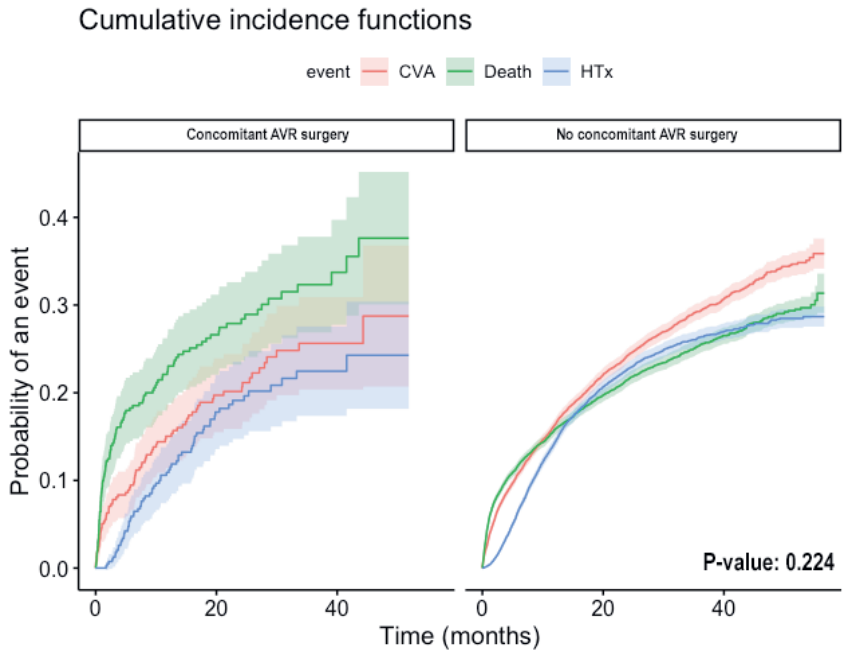

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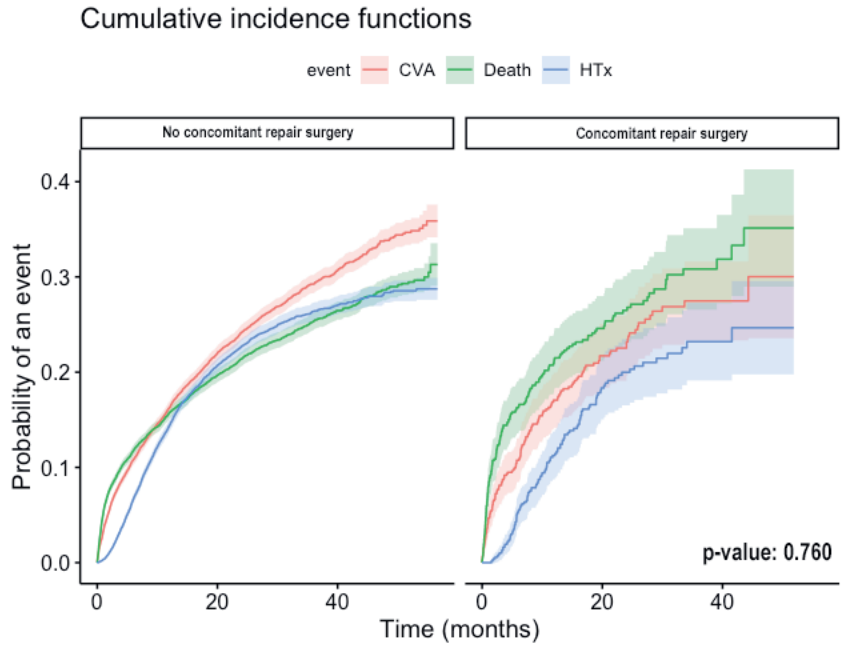

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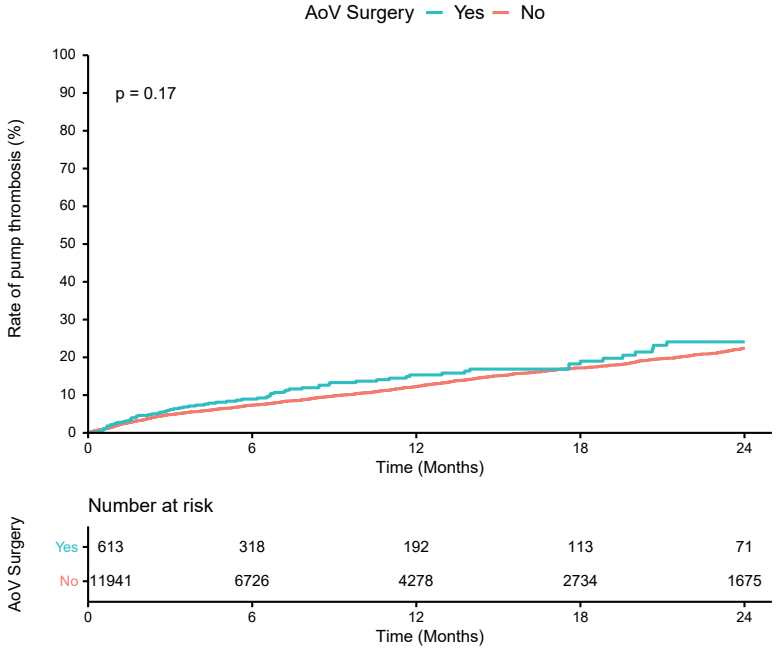

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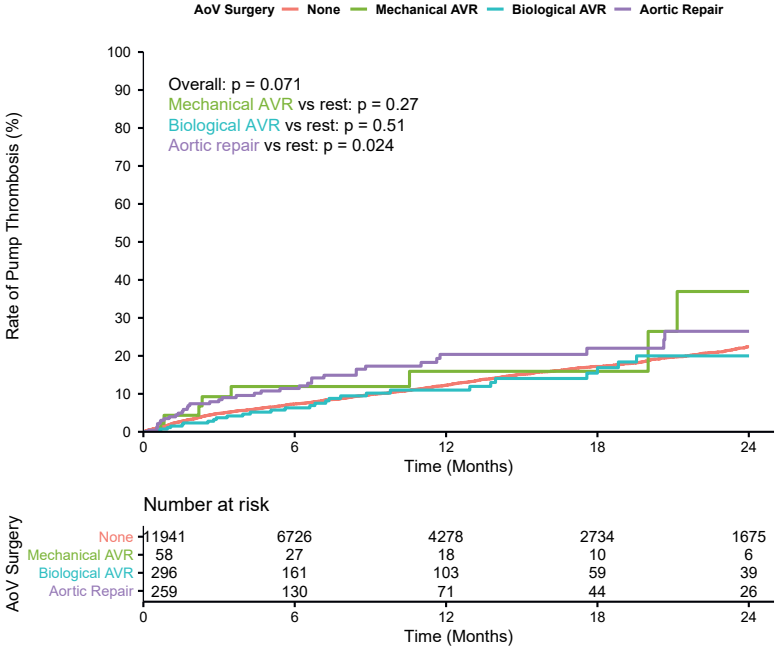

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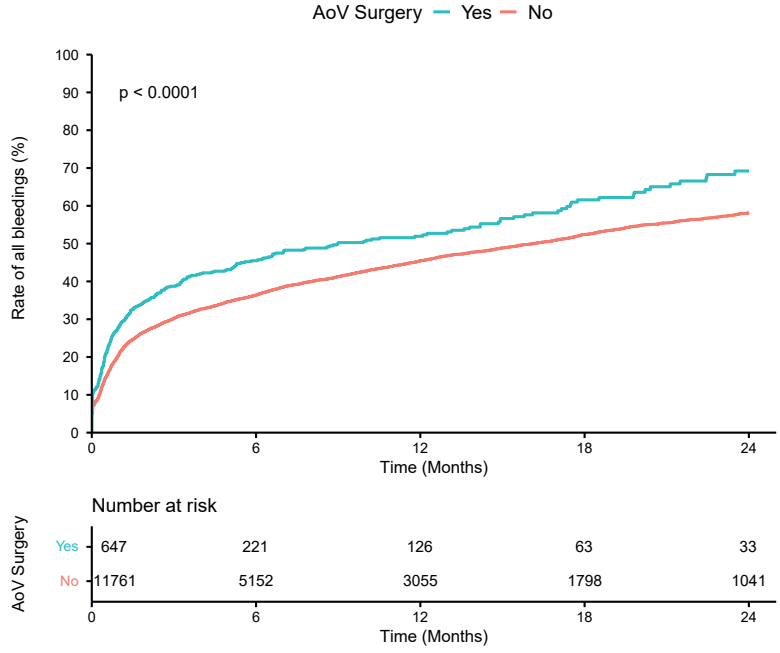

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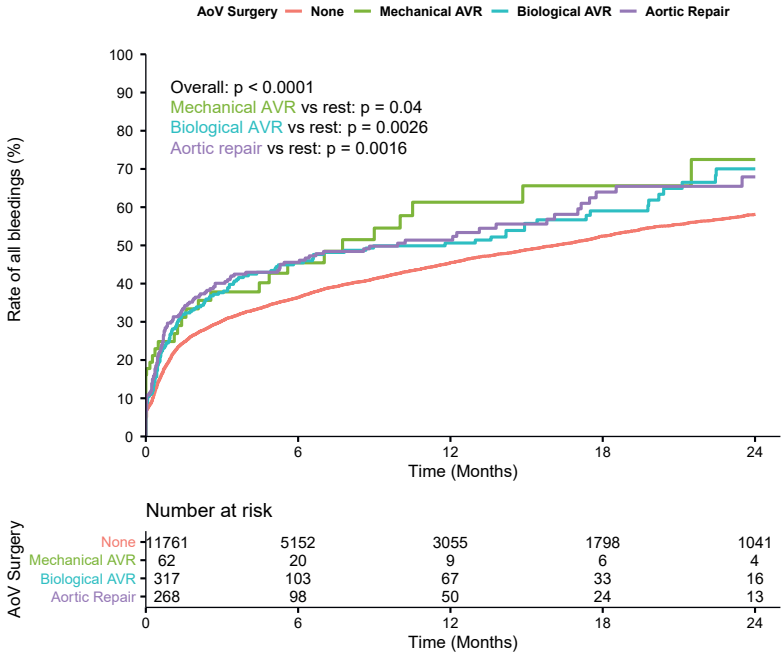

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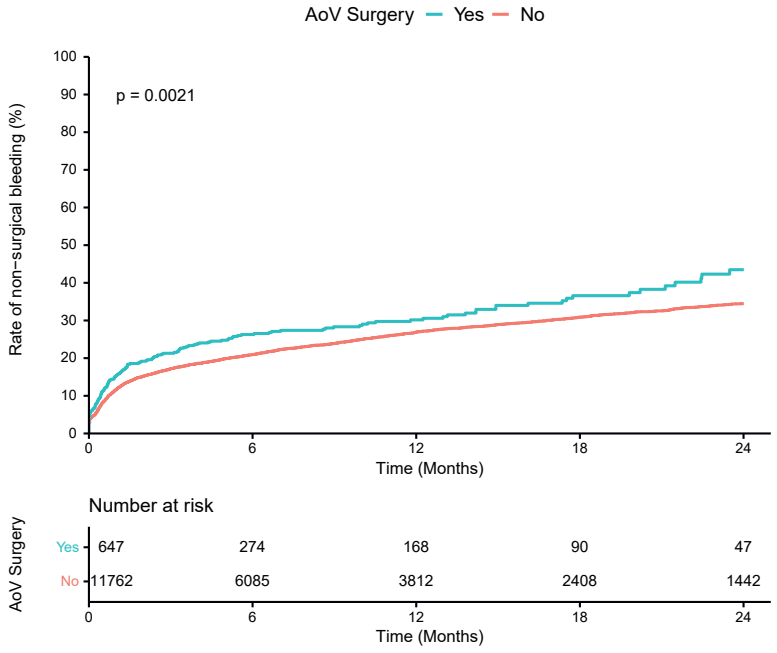
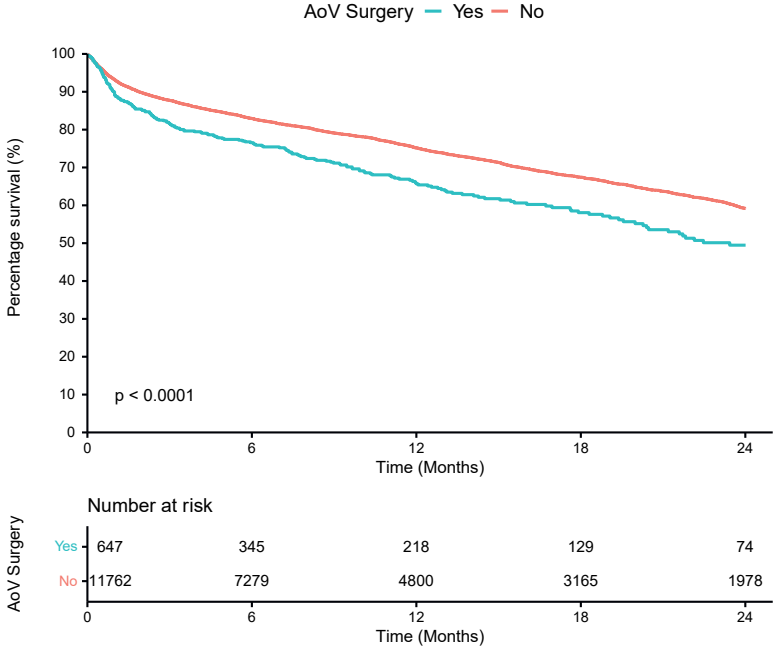
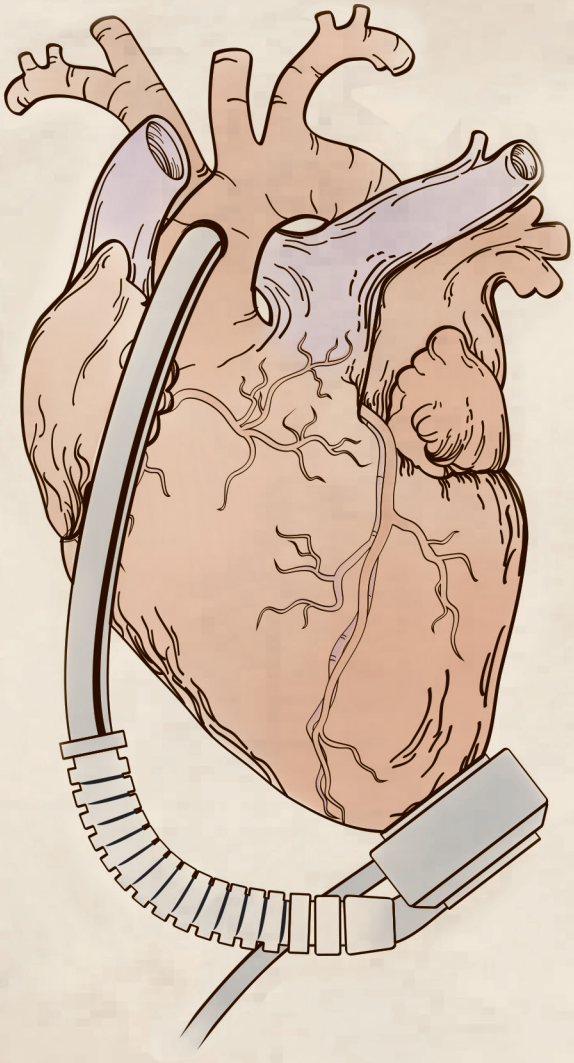


Supplemental Figure 7



Supplemental Figure 8



Chapter XII

Sufficient Methods for Monitoring Aortic Insufficiency

Veen KM, **Yalcin YC**, Mokhles MM

Ann Thorac Surg 2021;111:1098

To the Editor:

Left ventricular assist device therapy has become a well-established treatment for patients with end-stage heart failure. However, a cumbersome sequela is the development of aortic insufficiency (AI) after implantation.

Kawaga and colleagues[1] reported that patients with mild preoperative AI had higher rate of significant AI after left ventricular assist device implantation. Furthermore, they found that the postoperative development of significant AI is associated with a higher subsequent mortality rate.

The development of AI is dynamic in nature and prone to measurement error. Time-to-event analyses in this setting are not the preferred approach because they neglect the AI measurements after the first event of AI. Analyses of repeated measurement data, such as repeated echocardiograms over time, ideally should be done with longitudinal data, as was proposed by the guidelines for reporting after cardiac valve interventions more than a decade ago.[2] Generalized mixed models provide the most sophisticated method to perform these analyses.

Linking the development of AI to the survival probability is not a straightforward task, and simply stratifying patients who developed AI at some point during the follow-up versus patients who did not may lead to spurious conclusions. The development of AI varies in different patients, and the measurement of AI depends on the survival status, complicating adequate inference. A powerful method that accounts for these properties is the joint model. These models basically combine longitudinal models and a relative risk model.[3]

It is time to move beyond insufficient time-to-event analyses in the setting of repeated measurements and use sufficient methods combining longitudinal data (AI) and time-to-event data (mortality) to derive unbiased conclusions.

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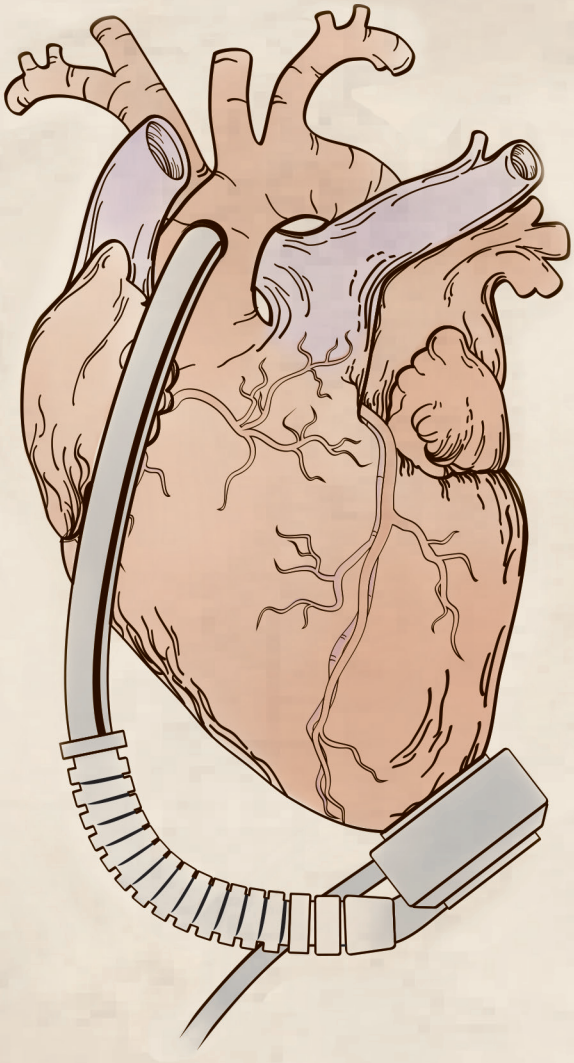

Chapter XIII

Aortic regurgitation associated outcomes following the implantation of left ventricular assist device implantation: An Analysis of the IMACS Database

Yalcin YC, Veenis JF, Veen KM, Soliman OI, Birim O, Bekkers JA, Bogers AJJC, Brugts JJ, Caliskan K.

Submitted

Abstract

Aims: The development of significant, defined as moderate-to-severe aortic regurgitation (AR) following left ventricular assist device (LVAD) implantation has detrimental effects. Therefore, we aim to quantify the impact of significant AR in LVAD patients.

Methods and results: Data from the IMACS registry was used. All adult LVAD patients, implanted between January 2013 until September 2017, with at least follow-up 1 echocardiogram available were included. Advanced joint-model analyses were used to elucidate the impact of significant AR on mortality.

In total, 12.810 patients (median age 58, IQR [48-66], 78.5% male) were included, with 36.343 echocardiograms available. Significant AR following LVAD implantation was observed in 1.660 patients (12.9%) on 2.660 echocardiograms. The development of significant AR was associated with a simulated excess mortality of 20% (60% vs 80%, $p<0.001$) at 20 months, with the strongest predictor being the speed of development of significant AR, with a hazard ratio per 1 Δlog(odds) of 3.34 (95% CI 1.87-6.48, $p<0.001$). Predictors for the development of significant AR included mild AR before LVAD, and prolonged LVAD support. Concomitant aortic valve replacement was associated with a significant lower risk for the development of significant AR, while aortic valve repair was not.

Conclusion: This analysis of the IMACS LVAD registry shows that significant AR occurs frequently and is associated with a significant excess in mortality. Additionally, this analysis shows that the speed of development of AR after LVAD implantation is an important predictor of worse outcome and mortality.

Introduction

Since the introduction of the durable left ventricular assist device (LVAD), many patients with end-stage heart failure have benefitted from this life saving treatment.[1] The success of long-term support however has yet to be optimized. One of the major concerns following the implantation of an LVAD remains the development of aortic regurgitation (AR). The retrograde flow from the aorta results in a loop circuit, effectively decreasing cardiac output, possibly elevating pulmonary arterial pressures resulting in a relapse of heart failure symptoms.[2] A recent study, using data provided by the Interagency Registry for Mechanically Assisted Circulatory Support [3], found that almost 15% of LVAD patients developed significant AR following LVAD implantation.[4] In a cohort comprising of almost 11.000 patients, they found an association between the development of significant AR and worse overall outcomes. Several other studies have investigated AR following LVAD implantation, with contradictory results.[5-7] However, a major limitation of the aforementioned studies resides in the limited methodology, as the varying time factor related to AR development after surgery as well as the potential of survival bias was not taken into account, as not all patients may have survived long enough to develop AR. To account for the dynamic nature of AR, a longitudinal data analysis approach should be preferred, as is proposed by the contemporary guidelines for reporting morbidity and mortality after cardiac valve interventions.[8] The current study is the first study to adjust for and include time to onset of AR as a covariate for the risks for morbidity following AR. Therefore, the aim of the current study was to elucidate the natural course, impact and predictors for mortality following significant AR development in LVAD patients.

Methods

The IMACS registry

The IMACS registry is a multinational, multicenter database collecting prospective data, as has been prescribed previously.[9] The goal of the IMACS registry is to gather data of patients treated with mechanical circulatory support (MCS) worldwide, to conducted studies with the aim of improving both the quality of life and the outcomes of the treated patients. The registry receives data from the Interagency Registry for Mechanically Assisted Circulatory Support, European Registry for Patients with Mechanical Circulatory Support (EUROMACS), United Kingdom (UK) registry and the Japanese Mechanically Assisted Circulatory Support (JMACS) registries as well as various individual hospitals worldwide.[10-12] Definitions for the endpoints and clinical events have been predetermined by the registry protocols. [9]

Study design

We included all adult (≥18 years) patients who were implanted with a primary LVAD, from January 2013 until September 2017. **Figure 1** shows the inclusion flowchart. Patients who were implanted with either an isolated right ventricular assist device, biventricular assist device or a total artificial heart implant were excluded from this analysis. Additionally, patients without baseline and/or follow-up echocardiogram data were excluded from further analyses.

The primary endpoint was to evaluate the impact of significant AR post LVAD implantation on survival. Additionally, we aimed to identify the independent predictors for mortality following the development of significant AR with respect to the time passed following surgery. Significant AR was defined as moderate or severe AR, confirmed on echocardiography. Secondary outcomes included clinical predictors of significant AR following LVAD implantation. To achieve this, the use of contemporary analyses methods, such as joint modeling, is necessary. This approach takes into consideration all the available echocardiography data and adjust for the correlations within measurements of patients and between the measurements of patients.

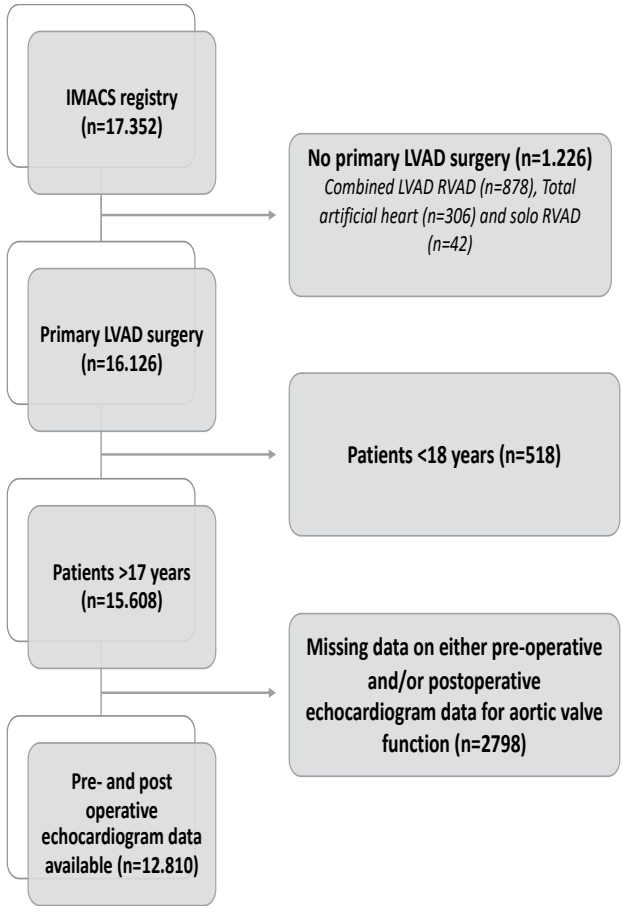

Figure 1. The inclusion flowchart, showing the derivation of the cohort from the International mechanically assisted circulatory support registry.

Missing values

To account for the missing values within the registry, multiple imputations by chained equations was used.[13] All preselected clinical variables had <30% missing values, and were imputed accordingly. Clinical variables with more than 30% missing were excluded from any further analyses. **Supplemental Figure 1** provides an overview of the selected covariates and their respective percentage of missing data. In case of highly correlate variables, the variable with the highest clinical value was chosen as the predictor. Correlation was tested with Pearson R or Spearman rho, where appropriate. In total, 5 imputed datasets were generated, using 5 iterations each. The imputation was visually checked by strip plots and density plots and no major deviations were noticed between the imputed and the original data (**Supplemental Figure 2**). Analyses were performed on the first dataset as the difference between datasets was minimal, therefore the datasets were not pooled according to Rubin's rules.[14]

Statistical analysis

Baseline characteristics are presented as mean ± standard deviation for or median with interquartile range (IQR) depending on the distribution of the continuous variables, and count and percentages (%) for categorical variables. Differences between patients' groups were compared with One-way ANOVA (Gaussian distribution) or Kruskal-Wallis (non-Gaussian distribution) for continuous variables. Categorical variables were compared with the Chi^2 Test. Logistic mixed-effect models were used to assess probability of AR over time and investigate determinants of the longitudinal evolution over time. These models included random intercept for patients and slope effects (if these improved the model) to capture the correlation of the repeated measurements in each patient. Natural splines with 2 knots placed at the 1st and 3rd quartiles were used to allow for flexibility of AR trajectory over time. Splines allow for non-linear trajectories over time. This is achieved by allowing a different spline-coefficient for each time interval defined by the knots (e.g., two knots define 3 such intervals). Survival probabilities were estimated and visualized by the Kaplan-Meier method. A joint model was developed to investigate determinants of mortality. More specifically, the mixed-effects model of AR and a relative risk model for the hazard of death (e.g., Cox model) were jointly modelled using shared-random effects. The subject-specific estimated longitudinal profiles were included in the relative risk model as predictors. Joint modelling has several benefits, such as the appropriate inclusion of endogenous covariates in relative risk models (AR), reduced bias and increased efficiency, while it can be used to derive dynamic predictions.[15] At time point *t* one can investigate the effect of the current value of AR, the effect of the slope/speed of AR and the cumulative effect of AR Hence, the speed at which AR is changing at a certain timepoint is defined as the change in probability of AR expressed as log (odd of moderate to severe AR per month (**Supplementary Figure 3**). The unbalanced nature of the data of the collected echocardiograms, which differ in intervals between patients, does not hinder the aforementioned analysis. **Supplemental Figure 4** explains the concept of joint modelling in a more visual manner.

Results

In total, 12.810 LVAD patients met the inclusion requirements and were included in the current study. Overall, 36.343 echocardiograms, with an average of almost 3 echocardiograms per person, were available with a 12.6 [interquartile range (IQR) 5.1-24.7] months median follow-up. The baseline characteristics are presented in **Table 1**. The median age was 58 [(IQR) 48-66], 78.5% male and 56.4% of patients were treated with either a bridge-to-transplantation or bridge-to-candidacy strategy. Overall, 8.790 (68.6%) of patients had no preoperative AR, with 3.514 (27.4%) having mild, and 506 patients (3.9%) of patients having moderate-to-severe preoperative AR. The development of significant AR was observed on 2.660 echocardiograms in 1.660 patients. Of all patients with no preoperative AR, 903 (10.2%) developed significant AR during follow-up. In patients with mild preoperative AR, 636 (18.1%) patients developed AR, with moderate preoperative AR developing significant AR during follow-up in 112 (25.4%) of patients. In the patients with severe preoperative AR, significant AR following LVAD implantation occurred in 9 (13.6%) of patients**.** In these groups, 344 (2.7%) patients underwent concomitant aortic valve replacement (AVR) surgery and 301 (2.3%) underwent concomitant aortic valve (AoV) repair surgery. In the first year of follow-up only 5.2% of all performed echocardiograms showed significant AR (**Figure 2a)**. However, in the fourth year of follow-up, this percentage had increased to 19.2%, demonstrating a 4-fold increase in significant AR occurrence. The number of echocardiograms performed over the entire follow-up period are showed in **Figure 2b**.

Lastly, at the end of follow-up, 3.111 (24.2%) of patients had died, 2816 patients (21.9%) had received an orthotopic heart transplantations and 420 (3.3%) had experienced ventricular recovery. The remaining 6.463 patients were still alive at the end of their respective follow-up.

Table 1. Baseline characteristics of the cohort comprised of patients with an left ventricular assist device with available post-implant echocardiogram data.

Baseline characteristics	Overall population (n=12.810)
Age (years)	58 [48-66]
Male sex	10.050 (78.5)
Body mass index (kg/m^2)	27.4 [23.7-32.1]
Ischemic etiology	5.722 (36.7)
Concomitant AVR surgery	344 (2.7)
Concomitant AoV repair surgery	301 (2.3)
Main LVAD strategy	
• BTT/BTC	8.807 (56.4)
• Destination therapy	6.567 (41.1)
• Other	234 (2.5)
Comorbidities	
• Current ICD therapy	9.349 (73.0)
• Atrial arrhythmia	2.509 (19.6)
INTERMACS classification	4.586 (35.8)
• Profile 1	1.949 (15.2)

Baseline characteristics	Overall population (n=12.810)
• Profile 2	4.374 (34.1)
• Profile 3	4.586 (35.8)
• Profile 4 – 7	1.901 (14.8)
Temporary MCS	4.080 (31.9)
Laboratory	
• Creatinine, mg/dl	1.20 [0.98-1.50]
• Total bilirubin, mg/dl	1.00 [0.60-1.50]
Hemodynamics	
• RA pressure, mmHg	8.0 [0.00-15.00]
• Mean PA pressure, mmHg	36.5 [28.5-44.0]
Echocardiographic	
Left ventricular ejection fraction	
• Mild (≥40%)	242 (1.9)
• Moderate (30-39%)	482 (3.8)
• Moderate/severe (20-29%)	12.086 (94.3)
Right ventricular ejection fraction	
• Normal	3.473 (27.1)
• Mild	3.738 (29.2)
• Moderate	3.869 (30.2)
• Severe	1.730 (13.5)
Baseline mitral valve regurgitation	
• None	979 (7.6)
• Mild	4.426 (34.6)
• Moderate	4.301 (33.6)
• Severe	3.104 (24.2)
Baseline tricuspid valve regurgitation	
• None	1.173 (9.2)
• Mild	6.329 (49.4)
• Moderate	3.858 (30.1)
• Severe	1.450 (11.3)
Baseline aortic valve regurgitation	
• None	8.790 (68.6)
• Mild	3.514 (27.4)
• Moderate	440 (3.4)
• Severe	66 (0.5)

AVR denotes aortic valve replacement, AoV; aortic valve, LVAD; left ventricular assist device, BTT; bridge-to-transplantation, BTC; bridge-to-candidacy, ICD; implantable cardioverter defibrillator, INTERMACS; Interagency Registry for Mechanically Assisted Circulatory Support, MCS; Mechanical circulatory support, RA; right atrial, PA; pulmonary arterial

Figure 2. A bar graph depicting the percentages of echocardiograms showing moderate-to-severe aortic regurgitation in each individual year following the implantation of an LVAD.

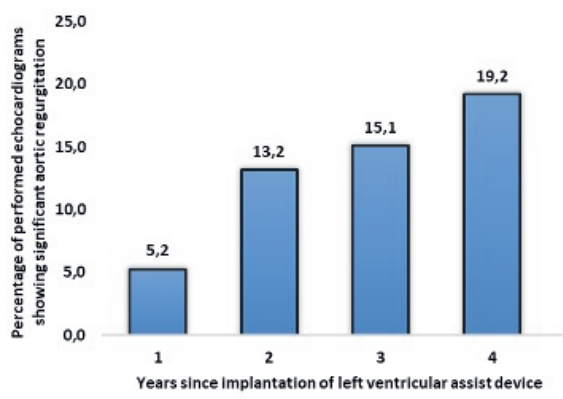

Figure 2a shows the percentage of echocardiograms which show significant aortic regurgitation in the years following LVAD implantation. At the end of year 1, the cohort contained 14% severe aortic regurgitation with 9248 patients at risk. At the end of year 2 the cohort contained 6% severe aortic regurgitation with 3503 patients at risk. At the end of year 3 the cohort contained 8% severe aortic regurgitation with 1034 patients at risk and at the end of year 4, the cohort contained 11% severe aortic regurgitation with 117 patients at risk.

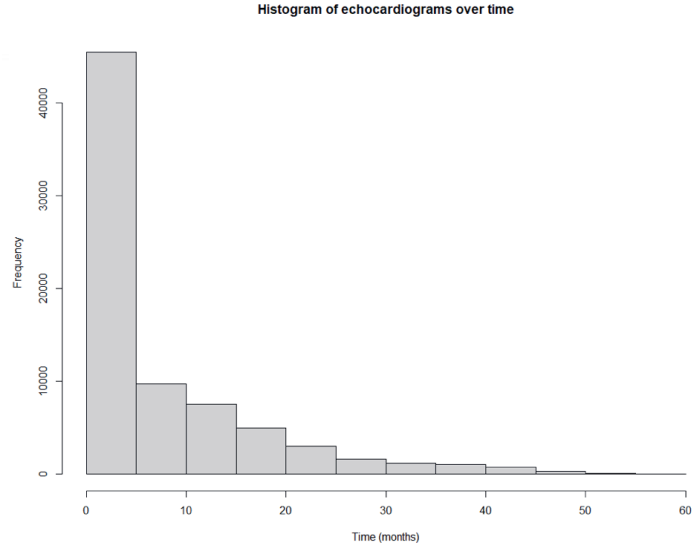

Figure 2b shows a histogram showing the number of individual echocardiograms performed for each year.

Post-LVAD AR and mortality

All clinically relevant covariates were analyzed with a joint model analysis, with AR incorporated as a time-varying variable (**Table 2**), yielding several independently associated baseline predictors for subsequent overall mortality. It was noted that older age (hazard ratio (HR) 1.02, 95% confidence interval (CI) 1.02 – 1.02), higher body mass index (kg/m^2)

(HR 1.02, 95% CI 1.01 – 1.02)), concomitant AVR surgery (HR 1.36, 95% CI 1.12 – 1.65)), destination therapy (HR 1.25, 95% CI 1.17 – 1.34), ICD therapy (HR 1.32, 95% CI 1.22 – 1.43), INTERMACS profiles 1 (HR1.54, 95% CI 1.37 – 1.76), profile 2 (HR 1.4, 95% CI 1.27 – 1.55) and profile 3 (HR 1.25, 95% CI 1.14 – 1.38), the need for temporary mechanical circulatory support (HR 1.19, 95% CI 1.11 – 1.29), an increase in creatinine (mg/dl) (HR 1.30, 95% CI 1.19 – 1.42)), a moderate (HR 1.83, 95% CI 1.47 – 2.24) and moderate-to-severe impaired (HR 2.00, 95% CI 1.62 – 2.41) left ventricular ejection fraction, severe tricuspid valve regurgitation (HR 1.17, 95% CI 1.00 – 1.34), and mild (HR 1.18, 95% CI 1.09 – 1.28), moderate (HR 1.97, 95% CI 1.04 – 1.50) and severe (HR 1.97, 95% CI 1.07 – 4.34) AR at baseline are independent predictors for mortality. Furthermore, we found that male sex (HR 0.89, 95% CI 0.82 – 0.96), mild (HR 0.85, 95% CI 0.74 – 0.95), moderate (HR 0.77, 95% CI 0.68 – 0.87) and severe (HR 0.75, 95% CI 0.65 – 0.85) mitral regurgitation were associated with a lower rate of mortality following the development of AR. Moreover, we found that the development of significant AR (HR 1.07, 95% CI 1.05 – 1.09) and the slope of the development of AR (HR 3.34, 95% CI 1.87 – 6.48) were independent predictors for overall mortality. The units for the slope of AR is in log(odds) per months, hence if log(odds) changes by 1 per month this translates to a 3.34 times increased hazard of death. In the setting of two echocardiograms a log(odds) change of 1 occurs if the echocardiograms are 1.4 month apart and on the first echocardiogram none-to-mild AR is noted and moderate-to-severe AR on the second echocardiogram. Lastly, we analyzed the change of the hazard ratio of moderate-to-severe AR, however, this did not change significantly over time (**Supplemental figure 5**), suggesting that developing AR early or late during follow-up had the same association with mortality.

Table 2. Predictors of mortality following the development of aortic regurgitation post left ventricular assist device implantation derived from a joint model analysis.

Baseline characteristic	Hazard ratio	95% CI	P-value
Age	1.02	(1.02 to 1.02)	<0.001
Male sex	0.89	(0.82 to 0.96)	0.006
Body mass index (kg/m^2)	1.02	(1.01 to 1.02)	<0.001
Ischemic etiology	1.08	(0.95 to 1.22)	0.208
Concomitant AVR surgery	1.36	(1.12 to 1.65)	0.002
Concomitant AoV repair surgery	1.02	(0.82 to 1.26)	0.836
Destination therapy	1.25	(1.17 to 1.34)	<0.001
Current ICD therapy	1.32	(1.22 to 1.43)	<0.001
Atrial arrhythmia	1.09	(1.01 to 1.18)	0.032
INTERMACS profile			
• Profile 1	1.54	(1.37 to 1.76)	<0.001
• Profile 2	1.40	(1.27 to 1.55)	<0.001
• Profile 3	1.25	(1.14 to 1.38)	<0.001
• Profile 4 – 7	Ref		
Temporary MCS	1.19	(1.11 to 1.29)	<0.001
Creatinine, mg/dl	1.30	(1.19 to 1.42)	<0.001
Total bilirubin, mg/dl	1.02	(0.98 to 1.06)	0.408
RA pressure, mmHg	1.00	(1.00 to 1.00)	0.904
Mean PA pressure, mmHg	1.00	(0.99 to 1.00)	0.086

Baseline characteristic	Hazard ratio	95% CI	P-value
Left ventricular ejection fraction			
• Mild (≥40%)	Ref		
• Moderate (30-39%)	1.83	(1.47 to 2.24)	<0.001
• Moderate/severe (<30%)	2.00	(1.62 to 2.41)	<0.001
Right ventricular ejection fraction			
• Normal	Ref		
• Mild	1.06	(0.98 to 1.16)	0.124
• Moderate	1.05	(0.97 to 1.15)	0.286
• Severe	1.11	(0.99 to 1.23)	0.066
Baseline mitral valve regurgitation			
• None	Ref		
• Mild	0.85	(0.74 to 0.95)	0.004
• Moderate	0.77	(0.68 to 0.87)	<0.001
• Severe	0.75	(0.65 to 0.85)	<0.001
Baseline tricuspid valve regurgitation			
• None	Ref		
• Mild	1.01	(0.89 to 1.13)	0.922
• Moderate	1.07	(0.94 to 1.20)	0.316
• Severe	1.17	(1.00 to 1.34)	0.040
Baseline aortic valve regurgitation			
• None	Ref		
• Mild	1.18	(1.09 to 1.28)	<0.001
• Moderate	1.25	(1.04 to 1.50)	0.020
• Severe	1.97	(1.07 to 4.34)	0.028
Moderate to severe AR during follow-up[1]	1.07	(1.05 to 1.09)	<0.001
Moderate to severe AR slope [1]	3.34	(1.87 to 6.48)	<0.001

AVR denotes aortic valve replacement, AoV; aortic valve, LVAD; left ventricular assist device, BTT; bridge-to-transplantation, BTC; bridge-to-candidacy, ICD; implantable cardioverter defibrillator, INTERMACS; Interagency Registry for Mechanically Assisted Circulatory Support, MCS; Mechanical circulatory support, RA; right atrial, PA; pulmonary arterial

[1]endogenous time-varying covariate

To illustrate the effect of significant AR on mortality, two identical hypothetical LVAD patients are modeled and presented in dynamic survival plots, with the only differences between them being the development of significant AR at 7 months of follow up. At the 20 months follow-up checkpoint, the survival probability is substantially reduced compared to the identical patient who did not develop significant AR at 7 months (60% vs 80%, p<0.001) (**Figure 3A & 3B**). Therefore, the estimated effect of significant AR following LVAD implantation is 20%. The predictive power of the model over the course of the follow-up period is showcased in **Supplemental Figure 6**.

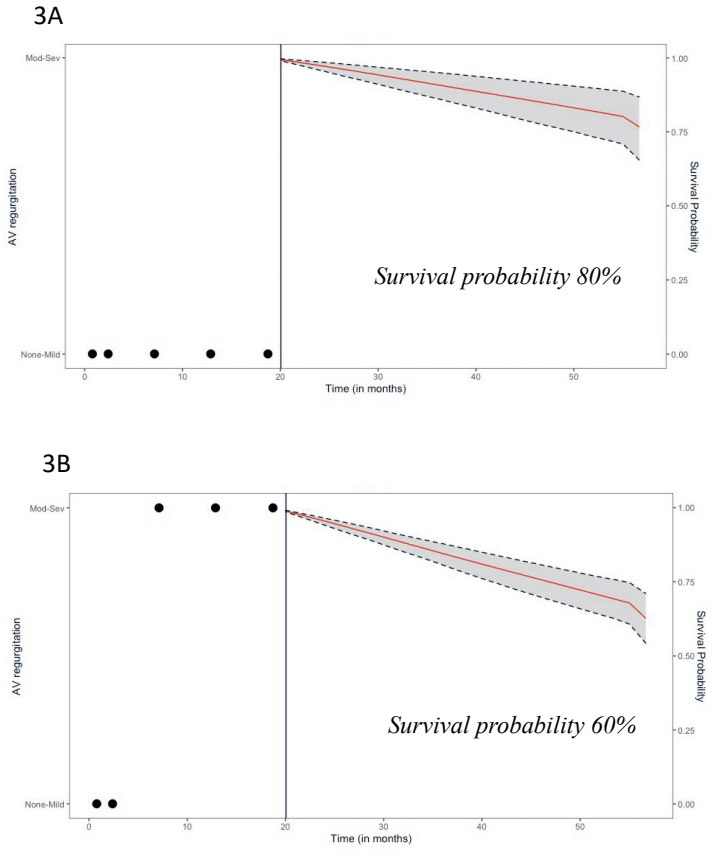

Figure 3a and Figure 3b show the same patient with the same baseline variables. At t = 20 months the patient in **Figure 3a**, the patient has 5 consecutive echocardiograms, all showing no significant aortic regurgitation. The estimated survival at t = 20 months is 80%. **Figure 3b** shows the same patient, however, this time the patient develops significant aortic regurgitation at t = 7 months with consecutive echocardiograms showing significant aortic regurgitation. The estimated survival at t = 20 months is 60%, showing a reduction of 20% (80% vs 60%, p<0.001).

Predictors of AR following LVAD implantations

The logistic mixed-effect regression analysis revealed that the age (odds ratio (OR) 1.05, 95% CI 1.04 – 1.07), INTERMACS profile 1 (OR 2.18, 95% CI 1.23 – 3.60) and mild AR (OR 6.13, 95% CI 4.44 – 8.50) are predictors of the development of significant AR following LVAD implantation. Moreover, the time of follow-up was an independent predictor for the development of significant AR, with longer LVAD support duration being associated with a higher probability of AR development. However, male sex (OR 0.29, 95% CI 0.20 – 0.41), a higher body mass index (OR 0.92, 95% CI 0.90 – 0.95), concomitant AVR surgery (OR 0.04, 95% CI 0.01 – 0.11) and mild mitral regurgitation (OR 0.47, 95% CI 0.26 – 0.83) were associated with a lower rate of significant AR following LVAD implantation. See **Table 3** for an overview of the multivariable model.

Table 3. Predictors of development of significant aortic regurgitation following left ventricular assist device implantation derived from a multivariable logistic regression.

Baseline characteristic	Odds ratio	95% CI	P-value
Age	1.05	(1.04 to 1.07)	**<0.001**
Male sex	0.29	(0.20 to 0.41)	**<0.001**
Body mass index (kg/m^2)	0.92	(0.90 to 0.95)	**<0.001**
Ischemic etiology	0.73	(0.46 to 1.16)	0.202
Concomitant AVR surgery	0.04	(0.01 to 0.11)	**<0.001**
Concomitant AoV repair surgery	0.70	(0.31 to 1.58)	0.410
Destination therapy	0.87	(0.64 to 1.18)	0.322
Current ICD therapy	1.29	(0.93 to 1.86)	0.144
Atrial arrhythmia	0.82	(0.57 to 1.14)	0.292
INTERMACS profile			
• Profile 1	2.18	(1.23 to 3.60)	**0.004**
• Profile 2	1.53	(0.95 to 2.40)	0.088
• Profile 3	1.49	(0.96 to 2.26)	0.078
• Profile 4 – 7	ref		
Temporary MCS	0.97	(0.71 to 1.36)	0.824
Creatinine, mg/dl	1.18	(0.81 to 1.72)	0.382
Total bilirubin, mg/dl	1.19	(0.99 to 1.41)	0.076
RA pressure, mmHg	1.00	(0.99 to 1.02)	0.688
Mean PA pressure, mmHg	1.00	(0.98 to 1.01)	0.918
Left ventricular ejection fraction			
• Mild (≥40%)	1.48	(0.39 to 5.69)	0.570
• Moderate (30-39%)	1.14	(0.37 to 3.57)	0.830
• Moderate/severe (<30%)	1.29	(0.42 to 4.05)	0.670
Right ventricular ejection fraction			
• Normal	Ref		
• Mild	1.13	(0.78 to 1.65)	0.496
• Moderate	1.31	(0.93 to 1.89)	0.142
• Severe	1.11	(0.72 to 1.82)	0.716
Baseline mitral valve regurgitation			
• None	ref		
• Mild	0.47	(0.26 to 0.83)	**0.010**
• Moderate	0.70	(0.40 to 1.21)	0.214
• Severe	1.01	(0.54 to 1.82)	0.996
Baseline tricuspid valve regurgitation			
• None	ref		
• Mild	1.03	(0.61 to 1.78)	0.934
• Moderate	1.08	(0.63 to 1.89)	0.822
• Severe	1.15	(0.61 to 2.32)	0.674
Baseline aortic valve regurgitation			
• None	ref		
• Mild	6.13	(4.44 to 8.50)	**<0.001**

Baseline characteristic	Odds ratio	95% CI	P-value
Follow-up time			
• First 33% of follow-up (first month)	1.22	(1.19 to 1.24)	**<0.001**
• 33% to 66% of follow-up (1ST to 6TH month)	1.49	(1.45 to 1.53)	**<0.001**
• Last 33% of follow-up (6TH to 56TH month)	1.40	(1.36 to 1.45)	**<0.001**

AVR denotes aortic valve replacement, AoV; aortic valve, LVAD; left ventricular assist device, BTT; bridge-to-transplantation, BTC; bridge-to-candidacy, ICD; implantable cardioverter defibrillator, INTERMACS; Interagency Registry for Mechanically Assisted Circulatory Support, MCS; Mechanical circulatory support, RA; right atrial, PA; pulmonary arterial

Discussion

This large-scale analysis in the IMACS LVAD registry shows that significant AR occurs frequently and causes a significant excess in mortality in LVAD patients. Additionally, this analysis shows for the first time that the onset and the speed of development of a significant AR after LVAD implantation is an important predictor for worse outcome and mortality.

In more detail, firstly, a multivariable joint-model analysis in the IMACS registry reveals that two parametrizations of post-LVAD AR are associated with mortality. These novel statistical methods which we used in this study can uncover associations that are not easily investigated, but translation to clinical practice remains challenging. The developing AR at time point t, and the slope of AR development (e.g., at which rate the probability of AR is changing), with the slope being the strongest independent predictor for subsequent mortality in patients supported with LVAD therapy. This finding suggests that if the time between a normal echocardiogram and an echocardiogram with AR is small, this is highly associated with impaired survival. Second, predictors for the development of significant AR following LVAD implantation included mild severity of preoperative AR, and prolonged LVAD support. The longer on LVAD support, the higher the chance of developing significant AR. Moreover, the scheduling of a concomitant AVR surgery, as opposed to concomitant AoV repair surgery, was the strongest associated covariate against the development of significant AR following LVAD implantation. Our findings need to elucidate a discussion on what to do and when to intervene with preoperative and postoperative AR in LVAD patients.

In the current literature, the development of significant AR following LVAD implantation is treated as an endpoint while it has considerable negative clinical effects. The latest study with a considerable number of patients is the study by Truby et al., in which they found that significant AR has a negative impact on hemodynamics, hospitalization and survival.[4] They found several predictors for the development of significant AR following LVAD implantation. Our study, which contains the INTERMACS database, confirmed that older age, female sex, a lower preoperative BMI, and mild AR prior to implantation are all independent predictors of significant AR following LVAD implantation. Most likely a possible mismatch between implanted LVAD and patient body size, already degenerative valves due to older age and underlying prior conditions explain these predictors for AR.[16] Further research is needed to fully elucidate the mechanisms involved in the development of AR following LVAD implantation.

Furthermore, whereas Truby and colleagues admitted patients to the significant AR arm in their study, our patients had a dynamic AR status during follow-up which is essential novel information. This revealed that the time between the last normal-to-mild AR echocardiogram and first echocardiogram showing significant AR is clinically more relevant than the actual diagnosis of significant AR. This may reflect the phenomena that these patients need medical intervention earlier than scheduled, due to symptomatic AR or decrease in functional status. Hence the speed of AR occurrence in our models may be a marker for clinical deteriotiation and the need for a early intervention.

In case of symptomatic AR, recent novel investigations have shown promising results in treating LVAD with trans-catheter modalities.[17, 18]. In terms of treatment indications; less time between last "normal" echocardiogram and the echocardiogram with AR may be an excellent selection criterion for these patients, especially considering the associated risks for worse outcomes.

Of note, this study included patients with concomitant AVR and AoV repair surgery. This was deliberately done to investigate the impact of both procedures on the development of significant AR following LVAD procedure. We found in our cohort that, while concomitant AVR decreased the chances of developing significant AR substantially, the AoV repair surgery did not. A previous study did show benefit form AoV repair surgery in patient with mild AR.[19] They stated however that mild AR does not automatically translate to symptomatic AR and underline the importance of identifying patients with borderline aortic valve lesions needing repair. We believe caution is advised when scheduling concomitantly AVR since it was associated with an increased mortality rate in our cohort. [20]

Clinical implications

The current study underlines the importance of vigilance when significant AR develops quickly following a normal echocardiogram. While the development of significant AR is independently associated with mortality overall, the short time between normal-to-mild AR and significant AR should be considered as an extra harbinger of unfavorable outcomes which can trigger earlier intervention. Furthermore, we have shown that dynamic prediction models, such as joint modeling, are needed to derive more accurate estimates of outcomes, which may aid in clinical decision making for eventual (transcatheter) intervention. Lastly, while concomitant AVR is associated with a significant reduction of AR rate during LVAD support, caution is warranted when scheduling patients for a concomitant AVR procedure. The inherent risks of concomitant aortic valve surgery, longer cardiopulmonary bypass time, and the increased risk of right-sided heart failure should be weighed against the potential benefits.20, 21 However, when observing the available data, it seems that patients who are expected to receive prolonged (more than 12-months) of LVAD support are more likely to develop AR. Furthermore, patient with associated risk factors for the development of AR (e.g. lower BMI/BSA, female patients and patients with mild AR prior to implantation) are potential candidates for concomitant AVR surgery. However, every individual case should be reviewed and thoroughly discussed by the heart team prior to implantation to evaluate the benefit of concomitant AVR surgery for this specific patient.

Limitations

It is important to note that the merit of the current study should be considered following these limitations. First, the current study was performed using the IMACS database which is sensitive to missing data. Secondly, while this constitutes the largest study to date, some patients of the IMACS database were lacking preoperative and/or postoperative echocardiograms. Furhtermore, the average number of echocardiograms per patient is relatively low, potentially leading to inaccurate estimation of AI evolution over time. Moreover, no data regarding the quality and/or opening of the native aortic valve, possible closing through suturing of the valve and aortic root dilation were available, which are known contributors to the development of AR. Thirdly, no data was available on the device types/manufacturers in different patients, so no device specific analyses could be conducted. Furthermore, clinicians were not blinded to changes in their patient's status and therefore have acted accordingly which could have altered the AR trajectory of some patients. Lastly, the lack of physiologic data, i.e. the intermittend opening of the aortic valve, pump speeds at various times during LVAD support is regretful. These factors can play a role in the development of AR following LVAD implantation.

Conclusion

The development of significant AR occurs approximately in 1 in 8 patients following LVAD implantation with pre-operative AR and prolonged LVAD support being important predictors. Subsequent mortality in these patients seems substantially dictated by the development of significant AR, and, especially, by the time elapsed between a normal and a significant AR echocardiogram. Therefore, time elapsed between these echocardiograms may be an appropriate selection criterion for subsequent (transcatheter) therapy.

Disclosures: The data herein were independently analyzed, and conclusions are those of the authors alone and not those of the IMACS Steering Committee. We thank the IMACS Steering Committee for the opportunity to work with these data.

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Legend

Supplementary Figure 1. an overview of the selected covariates and their respective percentage of missing data, both in bar graph and pattern analysis.

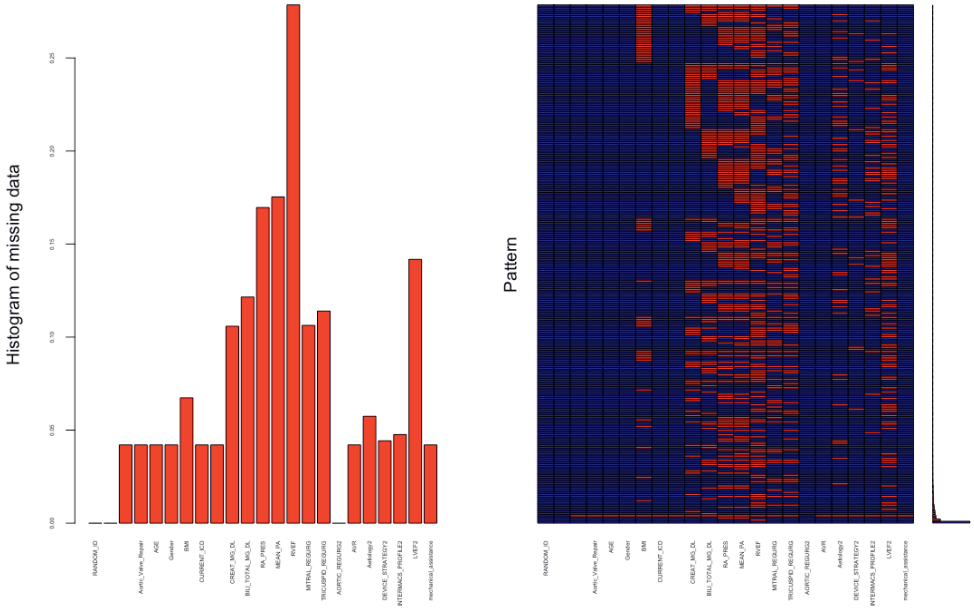
Supplementary Figure 2. Strip plot and density plot to check for major deviations between the imputed and the original data

Supplementary Figure 3. A figure showing the speed at which AR is changing at a certain timepoint is defined as the change in probability of AR expressed as log (odd of moderate to severe aortic regurgitation per month

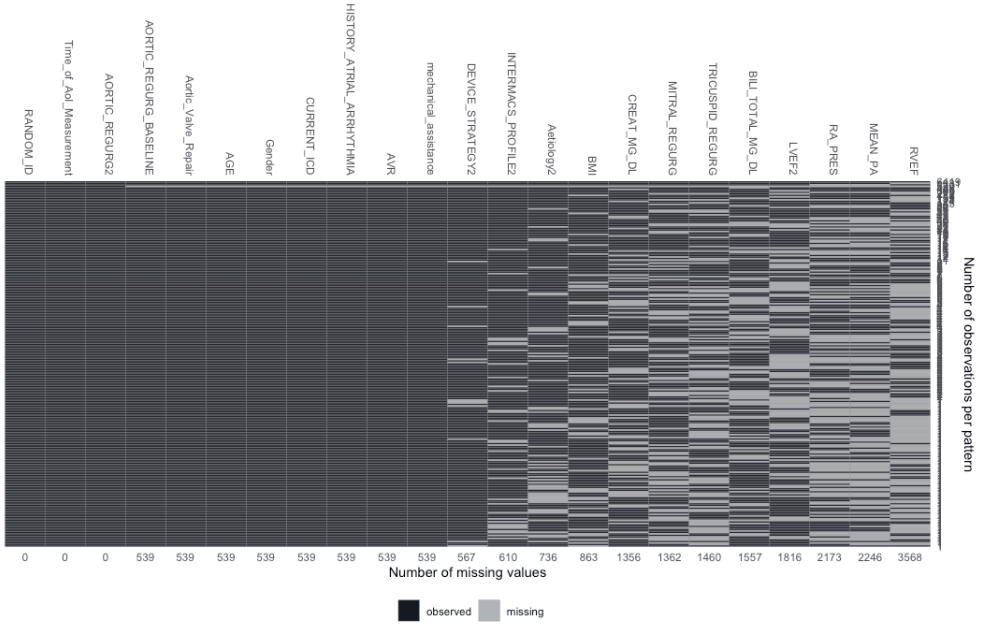
Supplementary Figure 4. A visual explanation for joint modeling and parametrizations

Supplementary Figure 5. A time dependent graph showing no significant changes to the hazard ratio within the elapsed follow-up time

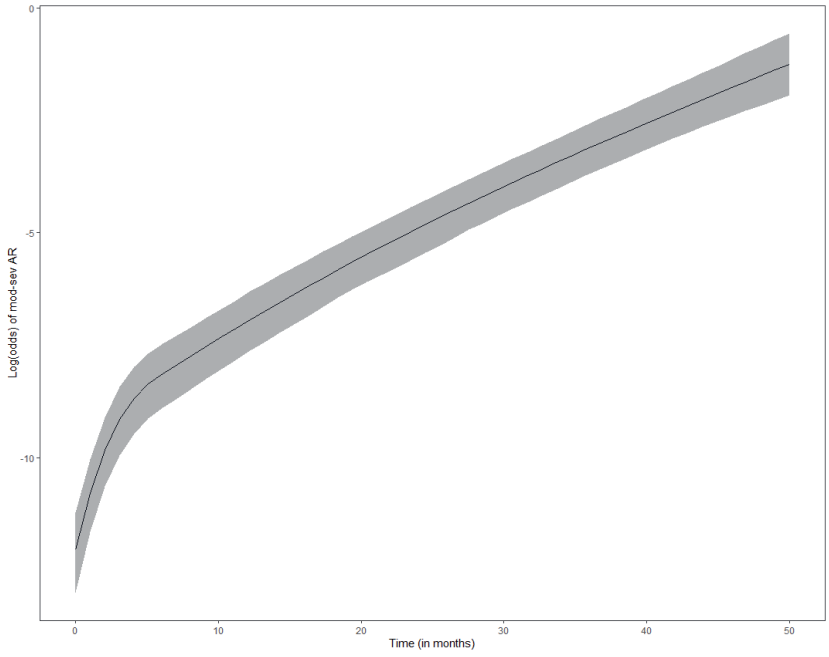
Supplementary Figure 6. A visual representation of the predictive power of the survival model over the course of the follow-up period



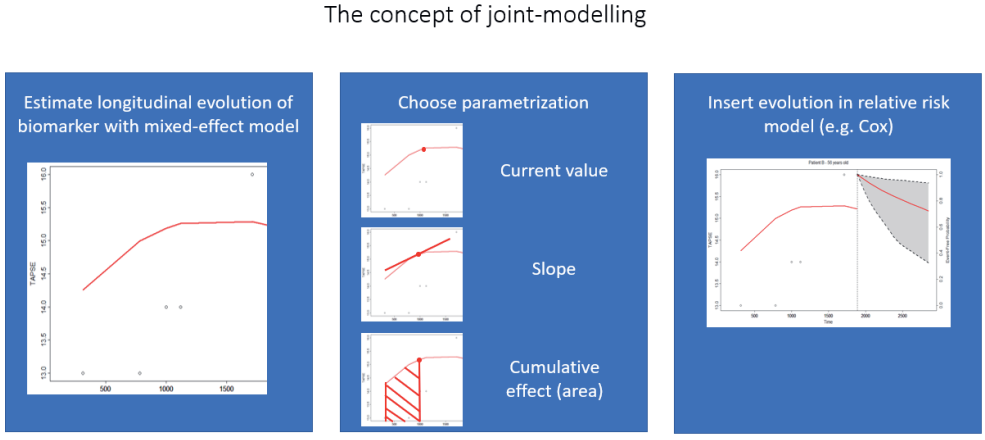
Supplementary figure 1



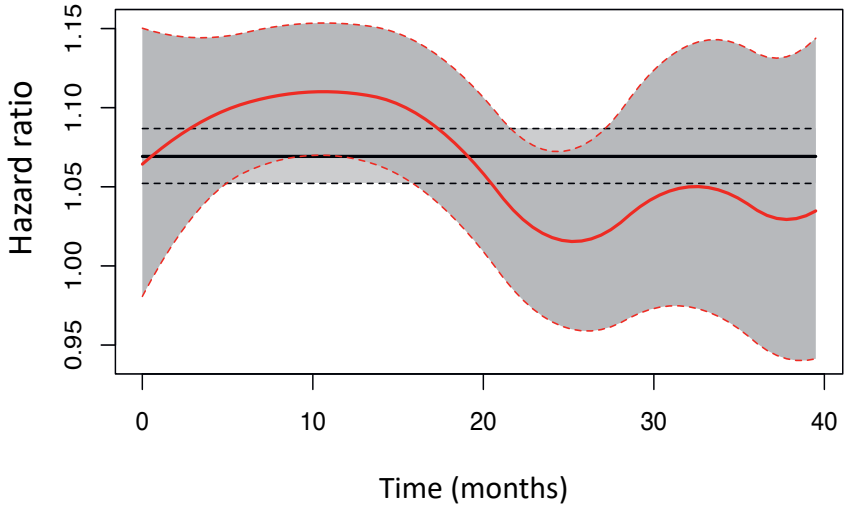
Supplemental Figure 2



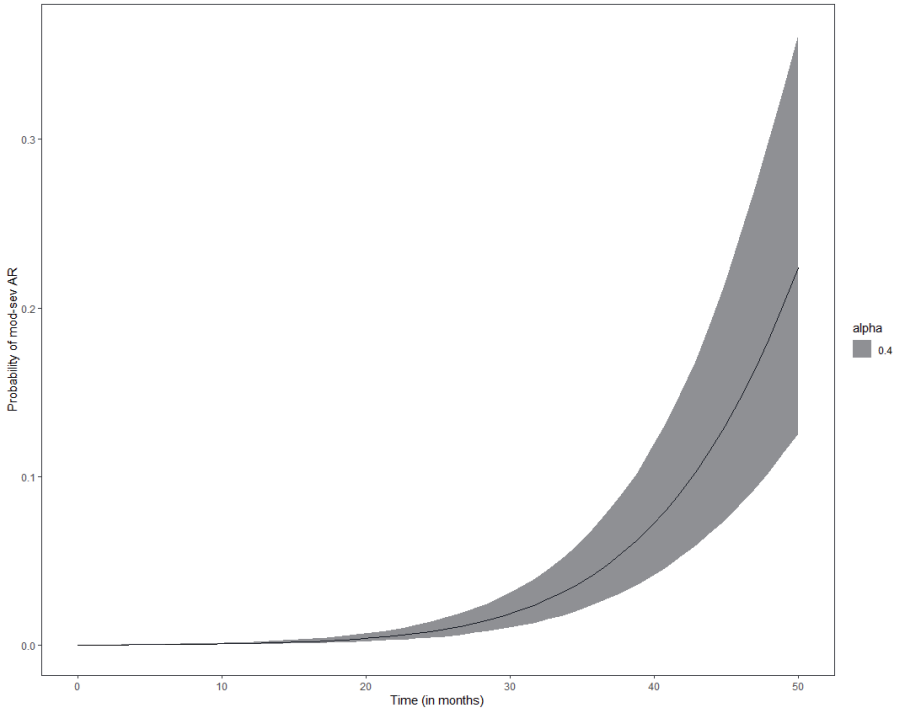
Supplemental figure 3



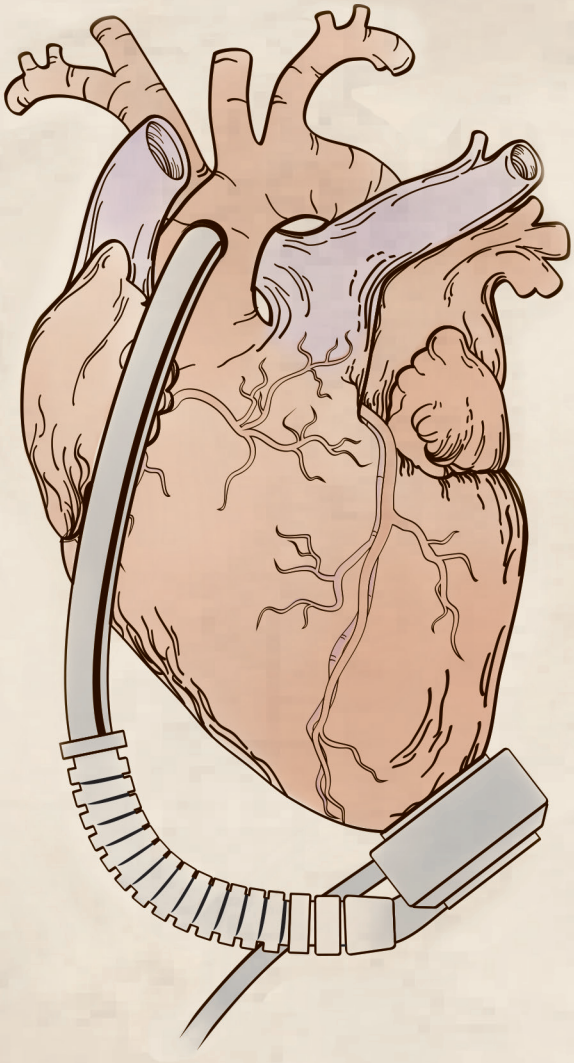
Supplemental figure 4



Supplemental figure 5



Supplemental figure 6



Chapter XIV

Outcomes following HeartMate II versus HeartMate 3 left ventricular assist device implantation. Over one and a half decade: The Rotterdam experience

Yalcin YC, Rasheed M, Muslem R, Brugts JJ, Constantinescu AA, Manintveld OC, Birim O, Bekkers J, Bogers AJJC, Caliskan K

Submitted

Abstract

Background: Continuous-flow left ventricular assist device (LVAD) therapy has become an indispensable treatment modality for patients with end-stage heart failure. Our aim was to evaluate our "real-word" experience with 2 generations of mainstream LVAD device types, the HeartMate II (HMII) and HeartMate 3 (HM3) for the treatment of patients suffering from end-stage heart failure within our tertiary referral center.

Methods: The analysis included all consecutive adult patients in whom an LVAD was implanted from December 2006 until December 2020. The primary outcome was early (<90 days) and late (until 3 years) survival.

Results: In total, 151 patients (median age 56 years [IQR 47 – 62], 76% male) underwent implantation of an LVAD: in 66 (44%) a HMII and in 85 (52%) received an HM3, with a median follow-up period of 768 days [IQR 221-1206] and 549 days [IQR 262 - 1010], respectively. The HM3 patients compared with the HM II patients were older, had a higher median body mass index, a worse baseline renal function, and had more often destination therapy (DT) strategy. However, despite the increased age and rate of DT, both early and late survival rates did not differ between both groups. Furthermore, adverse event rates are significantly lower in HM3 patients.

Conclusion: Despite older age, higher risk profile and increasing DT patients, survival remained favorable with lower adverse events in HM 3 patients compared with the HM II patients. Therefore, LVAD therapy remains an important modality to improve survival in selected patients with end-stage heart failure.

Introduction

Heart failure is a leading public health concern affecting millions of people all over the globe.[1] Even though heart transplantation is still considered the golden standard for treating end-stage heart failure, it use is severely restricted due to the shortage of donor hearts and the ineligibility of high risk candidates to undergo heart transplantation.[2] Mechanical circulatory support with durable continuous flow left ventricular assist devices (LVAD) has become a crucial and effective therapy to either bridge patients to a heart transplantation (BTT) [3, 4] or as a stand-alone modality, effectively being destination therapy (DT).[5, 6] Short-term survival of LVAD patients continues to improve with a current 30-day mortality rate of 5%.[6] Nevertheless, LVAD therapy still faces many challenges regarding morbidity including events of bleeding, strokes, infections, and pump thrombosis.[2, 3, 6] Previous studies reported a high incidence of pump thrombosis in HeartMate II devices (HMII, Abbott, MN, USA).[7, 8] This warranted the development of newer centrifugal devices with the aim to lower the incidence of morbidity and mortality. In recent years, the introduction of the HeartMate 3 (HM3, Abbott, MN, USA), a fully magnetically levitated centrifugal-flow pump, yielded a significantly lower rate of pump thrombosis opposed to the previous axial model.[[9]] Recent randomized controlled trials have confirmed the superiority of HM3 over HM II in terms of survival, device durability, stroke, and device malfunction.[10, 11] This has enabled clinicians to treat a new population of patients with LVAD therapy who were previously at high risk for adverse events. While the initial randomized trials were promising, further real-world data is needed to reaffirm these findings. Therefore, this study aimed to evaluate and describe the experience of our tertiary academic referral center with the HeartMate II and the HeartMate 3 devices in the treatment of end-stage heart failure patients.

Methods

Study design

In the present single-center, retrospective cohort study, all consecutive adult patients (>17 years of age), undergoing LVAD implantation were included. Patients either received the HMII (from 2006 until 2016) or the HM3 (from 2016 until 2021) at the ErasmusMC University Medical Centre in Rotterdam, The Netherlands. Patients were grouped and evaluated based on the type of initially implanted LVAD device. All data were obtained from the electronic patient records and the present study was approved by the institutional ethics review board of the ErasmusMC University Medical Center (MEC-2017-1013).

Study Outcomes and definitions

The primary outcome of the study was early (≤90 days) and late (until 3 years) survival following LVAD implantation. Patients were censored at the time of death, at the end of their respective follow-up or at the time of heart transplantation. Secondary outcomes included the length of intensive care unit stay, length of hospital stay, bleeding events, the need for redo thoracotomy, incidence of stroke, LVAD-related infections, acute kidney injury (AKI), confirmed cases of pump thrombosis, and the need for temporary right ventricular assist device (RVAD) therapy post-LVAD implantation. AKI was defined according to the kidney

disease improving global outcomes (KDIGO) criteria.[12] All the aforementioned adverse events were defined according to the updated definitions of adverse events for trials and registries of mechanical circulatory support.[[13]] Bleeding was defined as upper and lower gastro-intestinal bleeding, mediastinal bleeding (including cardiac tamponade) and heavy epistaxis. Left ventricular assist device related infections included driveline infection and pocket infection and pump infection, and were clinically defined as fever, with or without increased levels of C-reactive protein (CRP), and the culture and subsequent treatment of a pathogen. Events of stroke included both ischemic and hemorrhagic etiology. Lastly, a propensity score matching was performed to reduce the covariate imbalance between both groups (HMII vs HM3).

Statistical analysis

Patient' characteristics are presented as median with interquartile range and as frequency (*n*, %) for categorical data. Differences for continuous variables between the HM II and HM3 group were evaluated by student's *t*-test or Mann-Whitney U test according to distribution, and for categorical data by the Pearson χ^2 test or Fisher exact test, where appropriate. Kaplan-Meier curves for survival were constructed to estimate the difference in survival rate between both groups and compared by the log-rank test. Competing risk analysis was conducted in R with the package *'mstate'* to estimate the probability of mortality and heart transplantation overtime. For the propensity score matching analysis a logistic regression was performed on group indicators. The resulting propensity variable is then used to select controls for cases. A 1:1 matching without replacement using a calliper of 0.1 was applied. If a covariate remained unbalanced after matching, it was added to the propensity matched model to achieve satisfactory balance. A two-tailed *P*-value of <0.05 was considered as statistically significant. Analyses were performed using SPSS 26.0 software (SPSS, Inc., Chicago, IL, USA) and R (Version 3.6.1, Vienna, Austria).

Results

Baseline characteristics

In total, 151 patients (median age 56 years [IQR 47 – 62], 76% male) were included in this analysis; 66 in the HMII group and 85 in the HM3 group with a median follow-up period of 768 days [IQR 221-1206] and 549 days [IQR 262 - 1010], respectively. The baseline characteristics are displayed in **Table 1**. Patients with a HM3 compared with those with a HM II had a higher mean age, a higher median body mass index (BMI), a higher prevalence of pacemaker/ICD implantation, were more frequent destination therapy patients and had higher creatinine levels. However, the need for preoperative intra-aortic balloon pump (IABP) support and extra-corporeal membrane oxygenation was significantly lower in the HM3 group compared with the HMII group. Furthermore, Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles were higher (where low values indicate unstable patients) in the HM3 group. All other covariates were comparable between both groups.

Table 1. Baseline characteristics of implanted patients, dichotomized and compared according to left ventricular assist device type

	HeartMate II (n=66)	HeartMate 3 (n=85)	p-value
Age at implantation	52 [43-58]	58 [52-63]	0.001
Male gender	48 (73%)	67 (79%)	0.383
BMI, kg/m2	23 [21-25]	25 [23-28]	**<0.001**
Bridge/Candidacy-to-transplant	63 (93%)	50 (63%)	**<0.001**
Ischemic cardiomyopathy	26 (39%)	39 (48%)	0.366
Diabetes	6 (9%)	16 (20%)	0.084
Atrial fibrillation	14 (22%)	21 (26%)	0.571
History of CVA	6 (9%)	11 (14%)	0.434
History of pacemaker/ICD	40 (63%)	66 (82%)	**0.010**
IABP	27 (42%)	18 (22%)	**0.010**
ECMO	13 (21%)	5 (6%)	**0.009**
INTERMACS			0.001
• Profile I	18 (28%)	13 (16%)	
• Profile II	25 (39%)	16 (20%)	
• Profile III	14 (22%)	21 (26%)	
• Profile ≥ IV	7 (11%)	31 (38%)	
Laboratory values			
Platelets, x10^9/L	202 [157-268]	210 [150-260]	0.831
INR	1.7 [1.3-2.0]	1.5 [1.3-2.0]	0.629
Creatinin, umol/L	122 [91-149]	140 [106-178]	**0.027**
Total billirubin, umol/L	28 [17-48]	14 [9-20]	0.189
AST, U/L	41 [29-87]	37 [27-59]	0.221
ALT, U/L	44 [24-108]	37 [21-71]	0.382

BMI denotes body mass index; CVA, Cerebrovascular accident; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; INTERMACS, interagency registry for mechanically assisted circulatory support; INR, International normalized ratio; AST, aspartate aminotransferase; ALT, Alanine aminotransferase

Early and late clinical outcomes

The overall mortality for the total cohort at 90-days and 3-year was 17 (11%), and 26 (17%), respectively. Following stratification for initial device type, both early and late survival did not differ significantly between the HMII and HM3 groups (**Table 2**). Patient survival curves are illustrated in **Figure 1** and shows a survival rate of 84.8% vs 77.7%, p=0.567 for the HMII and HM3, respectively. The median follow-up time, median intensive care unit stay, and median total hospital stay were not different between HM II and HM3 patients. The early outcomes show similar rates for RVAD need following LVAD implantation and similar redo thoracotomy rates. However, the rate of AKI, 44 (66%) in the HMII patients and 38 (45%) in the HM3 patients, was significantly lower in the HM3 group.

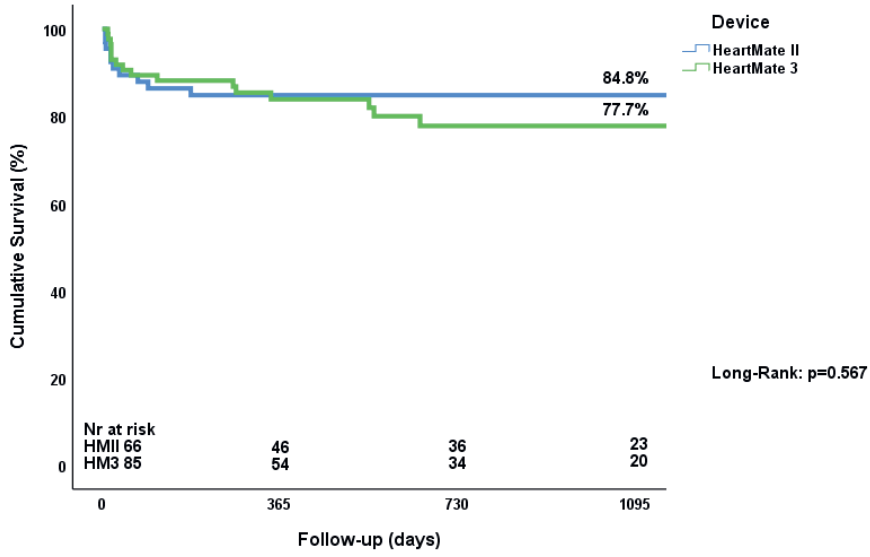


Figure 1. A Kaplan Meier curve depicting and comparing the survival for patients with either a HeartMate II or a HeartMate 3

Table 2. Patient outcomes following implantation, comparing the HeartMate II with the HeartMate 3 left ventricular assist device

	HeartMate II (n=66)	HeartMate 3 (n=85)	p-value
Median total follow-up time (days)	768 [221-1206]	549 [262-1010]	0.19
Intensive care unit stay (days)	6 [5-17]	8 [4-17]	0.429
Total hospital stay (days)	36 [26-49]	30 [23-49]	0.995
Early clinical outcomes (≤90 days)			
Mortality	8 (12%)	9 (11%)	0.750
Need of right ventricular assist device	5 (8%)	4 (5%)	0.64
Redo thoracotomy	31 (48%)	27 (32%)	0.279
Acute kidney injury	44 (66%)	38 (45%)	**0.04**
Late clinical outcomes (>90 days)			
Mortality	10 (15%)	16 (19%)	0.567
Transplantation	29 (44%)	7 (8%)	**<0.001**
Explantation due to recovery	3 (5%)	0	**0.047**
Bleeding	40 (63%)	41 (59%)	0.716
• Gastrointestinal bleeding	7 (11%)	12 (14%)	0.519
Stroke	13 (20%)	9 (11%)	0.264
• Ischemic	7 (9%)	4 (5%)	
• Hemorrhagic	6 (15%)	5 (6%)	
Left ventricular assist device related infection	24 (38%)	18 (22%)	**0.035**
Confirmed pump thrombosis	3 (5%)	1 (1%)	**0.001**

The late outcomes shows the rate of transplantation (29 (44%) HMII vs 7 (8%) HM3) significantly higher in the HMII group. Moreover, strokes rates were comparable between both groups (13 (20%) HMII vs 9 (11%) HM3) However, the rates of LVAD related infections (24 (38%) HMII vs 18 (22%) HM 3), and the rate for confirmed pump thrombosis (3 (5%) HMII vs 1 (1%) HM3) were significantly lower in the HM3 group. Lastly, comparing the competing risks of mortality and heart transplantation between HMII and HM3 at 3 years, the cumulative incidence of heart transplantation was lower in the HM 3 group compared with the HM II group, whilst the mortality between both groups is similar (**Figures 2** and **3**).

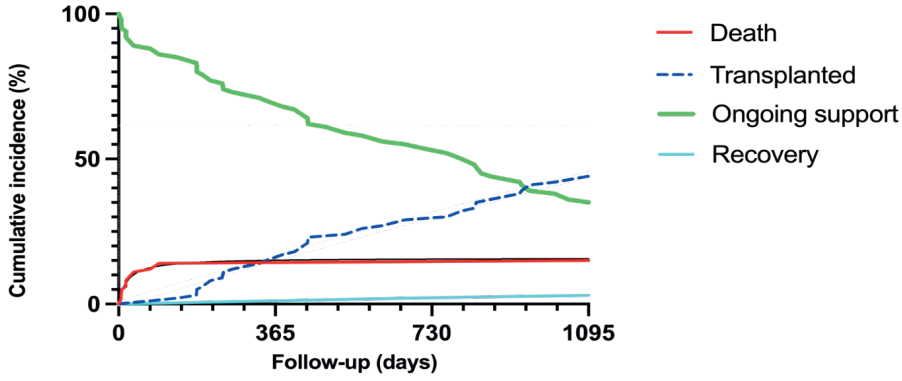


Figure 2. A competing outcomes analysis showing the rates of mortality, heart transplantation and ongoing support for the HeartMate II cohort (n=66)

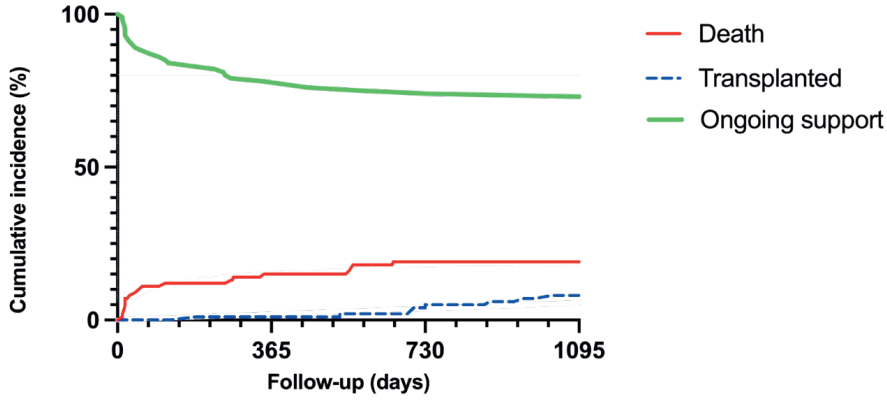


Figure 3. A competing outcomes analysis showing the rates of mortality, heart transplantation and ongoing support for the HeartMate 3 cohort (n=85)

Propensity matched cohort

Following the matching of individual cases, a 1:1 matched cohort was derived. In total, 76 patients (38 HMII and 36 HM3) were included. See **Table 3** for their patient characteristics. Following propensity score matching, only the characteristics bridge-to-transplantation and baseline INR were significantly different between both groups. When comparing outcomes between both groups, we found that in the early period (≤90days) the rate of acute kidney injury was higher in the HMII group. Furthermore, in the late period, we found that the infection rate and the pump thrombosis rate were both higher in the HMII group. See **Table 4** for the overview of the outcomes. Lastly, we looked at the survival rates between both groups. We found that, with propensity score matching, there was significant difference in the survival rate between the HMII and the HM3 patients (**Figure 4**).

Table 3. Baseline characteristics of propensity score matched patients, dichotomized, and compared according to left ventricular assist device type

	HeartMate II (n=38)	HeartMate 3 (n=38)	p-value
Age at implantation	54 [46-60]	54 [48-62]	0.602
Male gender	26 (68%)	31 (82%)	0.185
BMI, kg/m2	23 [21-27]	24 [22-27]	0.757
Bridge/Candidacy-to-transplant	37 (97%)	27 (71%)	**<0.001**
Ischemic cardiomyopathy	14 (37%)	18 (47%)	0.353
Diabetes	4 (11%)	8 (21%)	0.208
Atrial fibrillation	10 (26%)	8 (21%)	0.589
History of CVA	5 (13%)	7 (18%)	0.529
History of pacemaker/ICD	29 (76%)	28 (74%)	0.791
IABP	14 (37%)	13 (34%)	0.811
ECMO	6 (16%)	5 (13%)	0.744
INTERMACS			0.120
• Profile I	6 (16%)	12 (32%)	
• Profile II	16 (42%)	7 (18%)	
• Profile III	9 (24%)	10 (26%)	
• Profile ≥ IV	7 (18%)	9 (24%)	
Laboratory values			
Platelets, x10^9/L	208 [157-285]	205 [125-272]	0.358
INR	1.7 [1.3-2.7]	1.5 [1.3-2.0]	**0.005**
Creatinin, umol/L	135 [108-165]	122 [104-172]	0.352
Total billirubin, umol/L	13 [10-25]	15 [10-26]	0.226
AST, U/L	33 [23-55]	42 [20-62]	0.110
ALT, U/L	33 [20-52]	34 [20-76]	0.060

BMI denotes body mass index; CVA, Cerebrovascular accident; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; INTERMACS, interagency registry for mechanically assisted circulatory support; INR, International normalized ratio; AST, aspartate aminotransferase; ALT, Alanine aminotransferase

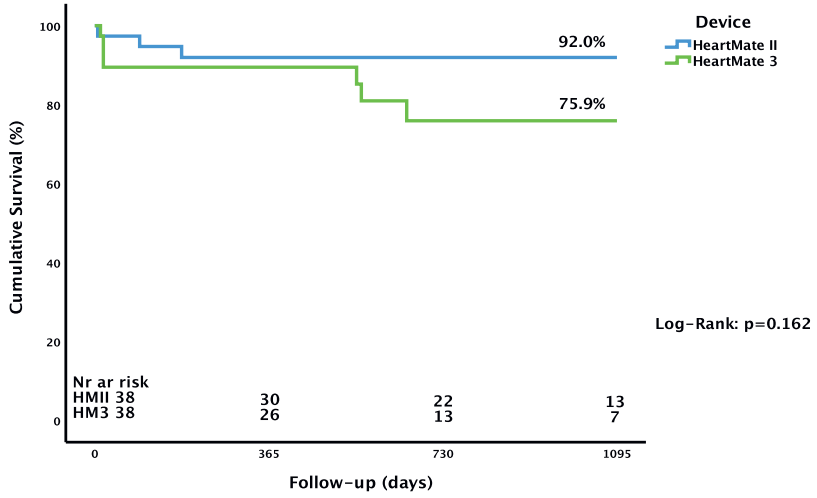


Figure 4. A Kaplan Meier curve depicting and comparing the survival for patients with either a HeartMate II or a HeartMate 3 who are propensity score matched.

Table 4. Patient outcomes following propensity score matching, comparing the HeartMate II with the HeartMate 3 left ventricular assist device

	HeartMate II (n=38)	HeartMate 3 (n=38)	p-value
Median total follow-up time (days)	831 [403-1095]	567 [243-987]	0.738
Intensive care unit stay (days)	7 [5-17]	8 [5-21]	0.782
Total hospital stay (days)	30 [27-48]	36 [28-53]	0.461
Early clinical outcomes (≤90 days)			
Mortality	1 (3%)	4 (11%)	0.165
Need of right ventricular assist device	0	0	n.a.
Redo thoracotomy	15 (40%)	13 (43%)	0.748
Acute kidney injury	20 (53%)	5 (13%)	<0.001
Late clinical outcomes (>90 days)			
Outcome			
• Mortality	3 (8%)	7 (18.4%)	0.162
• Transplantation	21 (55%)	6 (16%)	**<0.001**
• Explantation due to recovery	0	0	n.a.
Bleeding	20 (53%)	14 (37%)	0.166
• Gastrointestinal bleeding	4 (11%)	5 (13%)	0.723
Stroke	11 (29%)	5 (16%)	0.204
• Ischemic	5 (13%)	1 (3%)	
• Hemorrhagic	6 (16%)	5 (13%)	
Left ventricular assist device related infection	16 (42%)	8 (21%)	**0.048**
Confirmed pump thrombosis	2 (5%)	0	**0.011**

Discussion

This single-center study was aimed to describe and evaluate the "real-world" experience of our tertiary academic referral center with the HeartMate II and the HeartMate 3 devices in the treatment of end-stage heart failure patients. Even though the HM3 patients had, compared with the HMII group, a higher mean age, higher BMI, and worse renal function, their rate of survival and the adverse event rates was similar in both groups. Importantly, the majority of patients receiving HM3 support were designated as destination therapy, mostly due to older age and their higher rate of co-morbidities, which were not all chaptered in this retrospective study. Of note, the additional propensity score matched analysis revealed that despite a higher rate of DT indications, outcomes remained favorable for HM 3 patients. This study highlights both the advances of the newer generation of LVAD device therapy, as well as the increasing experience of the overall multidisciplinary team including our surgeons, heart failure cardiologists, anesthesiologists, and intensive care team.

Previous studies evaluating the clinical experience of continuous-flow LVAD's have reported a long-term survival (1 to 3 years) ranging from 75%-85% [14-17], depending on the proportion of HM3 and HMII, and have reported a short-term survival ranging from 85%-89%. [15, 16] The Society of Thoracic Surgeons INTERMACS 2020 annual report stated a 3-year survival of 61%. [18] Our clinical experience compares well with these survival rates, with exceeding long-term survival rates of 81% at 3-years of follow-up.

The HeartMate 3, a fully magnetically levitated centrifugal continuous flow left ventricle assist device, has proven to reduce the hemocompatibility related complications by reducing the absolute rates of stroke, GI bleedings, and pump-thrombosis.[9, 10] Mehra et al. reported a significant difference between HM II and HM3 regarding freedom form disabling stroke and malfunctioning device replacement/removal free survival.[10] However, our data showed no significant difference in stroke rates between device types. Nonetheless, we did notice a significant difference in the rate of confirmed pump thrombosis, favoring the HM 3 device. Confirmed by autopsy, the HMII group had 3 cases (5%) of confirmed cases and the HM3 had 1 (1%) case of confirmed pump thrombosis during device exchange. The reason for the exclusion of suspected cases was the nature of pump thrombosis detection. The current standard for detecting imminent pump thrombosis is through spikes in levels of hemolysis. However, due to the inherent lower rate of hemolysis in the HM3, we opted to only include the confirmed cases of pump thrombosis.

In the Netherlands, the incidence of heart failure in the increasingly aging population will only rise over time.[19] As heart donation has not been increasing with the demand, end-stage heart failure patients are continuously confronted with limited therapy modalities. This cumbersome situation has been partly alleviated by the introduction of durable continuous-flow LVAD's. The new generation of LVADs has proven to be a true innovation and an excellent modality to improve survival and, maybe even more important, regain quality of life.[20, 21] As the survival following LVAD implantation has been ever increasing over the past decade, it has allowed us to treat more destination therapy patients with increasingly favorable outcomes. The shift from younger patients who were almost exclusively bridge-to-transplant/candidacy to destination therapy (i.e. older patients with a less than optimal

preoperative condition) has allowed us to improve our selection criteria. This is noticeable in the difference in INTERMACS profiles and in the need for preoperative circulatory support (i.e. IBAP or ECMO). This resulted in similar survival rates for patients who historically were worse off when scheduled for LVAD implantation.[6]

The focus of LVAD research has partly been shifting toward the reduction of LVAD therapy related morbidity. However, there is still room for improvement, especially regarding post-implantation right ventricular failure, infection management and optimal LVAD therapy timing. Nonetheless, LVAD therapy has proven a great success in the treatment of end-stage heart failure.

Limitations

Some limitations of this present study merit consideration. First, this study is retrospective in nature and can therefore not establish causation. Second, the current study is a single-center study which represents the clinical expertise of our multidisciplinary team. Third, the number of HM II and HM 3 patients were limited. Moreover, the inclusion of HM3 patients without the completed follow-up may have influenced the outcomes. Fourth, the number of patients matched via the propensity score analysis was fairly small and therefore this analysis could be prone to a type 2 error. Finally, limited data were available to properly investigate the role of HMII and HM3 on the incidence of early and late right heart failure (RHF).

Conclusion

Despite the older age and higher DT strategy of the second era, outcomes are more favorable in the HM3 as compared with HMII. Importantly, the survival rate following LVAD implantation remains exemplary regardless of a lower transplantation rate and higher destination therapy strategy in the HM3 group. Therefore, LVAD therapy with the HeartMate 3 remains an important modality to improve the morbidity and mortality of end-stage heart failure patients.

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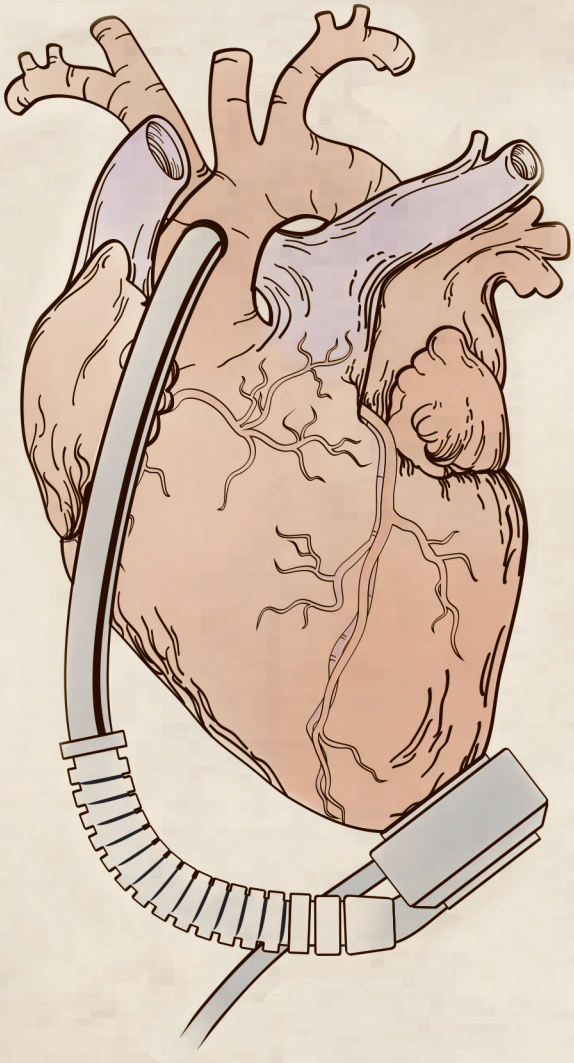

Chapter XV

Discussion, future perspectives, and conclusions

The aim of this thesis was to identify, quantify and predict clinical adverse events in patients treated with left ventricular assist device (LVAD) therapy. These data can in turn be used to optimize patient selection criteria for LVAD therapy. With the latest early survival rates (<6 months) as high as 80-88%, the question whether we can improve upon early survival becomes increasingly more focused towards patient selection [1,2]. The remaining early mortality most likely stems from the relatively larger number of patients who are confronted with more advanced stages of heart failure or who are in full blown cardiogenic shock [3,4]. This results in a focus on late survival and quality of life, including the onset of disabling adverse events during LVAD support. This thesis aimed to investigate these events with the goal to assess and thereafter predict subsequent events.

Left ventricular assist device therapy and end organ dysfunction

The goal of LVAD therapy is to improve the quality of life, long-term survival and secondary organ failure caused by the severe acute or chronic heart failure. By restoring the decreased output and resolving right sided congestion, in theory, all secondary compromised organs, should resume their normal function following implantation. However, this remains clinically very challenging in many patients including the elderly and patients with clinically significant co-morbidity. Both in the older and in the newer generation LVAD's, secondary organ dysfunction can either exacerbate, improve, or continue to persist. Acute kidney injury (AKI), which can occur acutely and can be present chronically in the context of the cardiorenal syndrome, is a frequent and deleterious complication following LVAD implantation [5,6] Therefore, **Chapter II** contains a state-of-the-art review on AKI following LVAD support. Herein we discussed many topics, including definitions and prevalence, novel biomarkers, pathophysiology, and associated risk factors. These include the risk factors during the preoperative, intraoperative, and post-operative period. By reviewing the current literature, we aimed to give an accurate overview of the current clinical evidence and insights for the management and prevention of AKI. The incidence of AKI following LVAD implantation is reportedly between 11% and 45% [5,7-9]. These studies rely on creatinine measurements or on urine production to quantify the degree of AKI. These patients could have benefitted from muscle independent kidney function markers, such as neutrophil gelatinase associated lipocalin and plasma cystatin C.[10-12] The use of these relatively novel biomarkers have however only sporadically been studied in LVAD patients and needs yet to be clinically elucidated and adopted. Furthermore, more stringent selection criteria for LVAD therapy seem to be urgently needed since risk factors associated with AKI following LVAD implantation are present in relatively old patients, worse baseline renal function, and/or lower Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles.[13] Perhaps some of these patients could benefit from earlier interventions such as preoperatively optimizing renal function with the aim to reach euvolemia as close as possible. Moreover, monitoring of (chronic) right-sided congestion and overall hemodynamic profile via an implantable hemodynamic sensor or invasive right heart catheterization prior to LVAD candidacy should be considered. While these options are viable, the definitive answer to preventing AKI, a devastating complication in LVAD patients, remains yet to be elucidated.

Following this review, In **Chapter III**, we conducted a larger multicenter study including 400 patients who had received LVAD therapy. We aimed to quantify the evolution of renal function postoperatively, and to determine the factors associated with sustained renal function improvement. Albeit the temporal trend of renal function had been described in earlier studies, a major limitation of these studies resides in their methodology.[7,14,15] The use of means over time is heavily reliant on availability of data at certain time points and can potentially be heavily skewed by outliers. In our study, we used a longitudinal approach which analyzed all the available data, and subsequently adjusted for measurement between several time points from the same patients and between patients. This approach yields a more realistic evolution of renal function over time. Our study showed that the evolution of renal function can be divided into 3 phases: (1) the marked early improvement phase, (2) the relatively steady state phase in which renal function improvement stops and lastly (3) the deterioration phase. The first phase is experienced by almost 60% of the cohort while only 13% of the cohort experiences sustained renal function improvement. This indicates that there is room for improvement. The proposed more stringent criteria are confirmed by our study, showing that renal function improvement occurs less frequent in older and sicker patients. It is important to note that the use of serum creatinine can partly mask true renal function recovery. A recent study, which included a prospective cohort with cystatin c measurements follow LVAD implantation found that initial improvement in serum creatinine could most likely be attributed to muscle wasting prior to implantation.[16] They concluded that while creatinine derived estimated glomerular filtration rate (eGFR) rises and subsequently declines, cystatin c derived renal function remains relatively stable over time and more accurately predicted kidney related adverse events. This highlights the need for more research, preferably prospective studies, to further crystalize the post-implantation care.

Hepatic dysfunction prior to LVAD therapy has been reported previously and is a known risk factor for mortality prior to LVAD implantation.[17-19] Hepatic dysfunction, defined by the model for end-stage liver disease (MELD) score, has previously been used to investigate its predictive value in the LVAD cohort. However, the evolution of hepatic function following LVAD implantation has been poorly studied. Therefore, in **Chapter IV** we studied the effect of hepatic dysfunction on outcomes following LVAD implantation. In our cohort a MELD score ≥12.6 was associated with an increased risk for mortality. Furthermore, neurologic events, and surgical re-exploration following LVAD implantation happened significantly more often in patients with a MELD score of ≥12.6. Recent studies confirm these findings and offer new insight into risk factors such as prolonged cardiopulmonary bypass time and right heart failure.[20,21] Moreover, our study showed that despite initial hepatic dysfunction, liver function (as defined by serum total bilirubin and serum albumin) improves with LVAD support over time. The hepatic dysfunction was even reversible in those with a MELD score of ≥12.6. This study further highlights the need of concomitant evaluation of the liver function in the timing and selection of the patients for LVAD therapy.

In **Chapter V**, we conducted a single center cohort study after the occurrence of interference between an implantable cardioverter defibrillator (ICD) and a LVAD. Previously, interference between the HeartMate II and ICD's had been reported.[22] In our study we observed similar interference between the new HeartMate 3 LVAD and patients with an ICD, especially

from the firms Biotronik. Subsequently, we initiated a stepwise approach to connect and interrogate the ICD's. The stepwise approach has proven to be fairly successful and described also by others.[23]

Lastly, **Chapter VI** describes the setting in which the failing heart has an intrinsic cardiac rhythm morbidity, namely atrial fibrillation (AF). Previous studies were inconclusive on whether pre-operative AF causes an increased rate of morbidity and mortality following LVAD implantation.[24-26] Therefore, we aimed to investigate the impact of preoperative AF on hemocompatibility-related adverse events and long-term mortality following LVAD implantation. With the use of data provided by the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) we reported an overall increased mortality rate for patients suffering from preoperative AF. However, following a multivariable analysis, preoperative AF was not an independent risk factor associated with mortality. This indicates that other variables present at the pre-operative phase, such as older age, better predict the risk for mortality than preoperative AF. Furthermore, no difference in freedom from cerebrovascular accidents, pump thrombosis or bleeding events had been observed in the complete follow-up. We observed an increase in the rate of cerebrovascular accidents only in patients who were alive after 24 months. Nonetheless, these patients have a lower survival rate than those without preoperative AF. With the increasing age of potential LVAD recipients and potentially higher rate of preoperative AF, more research is needed into the impact of AF on LVAD outcomes.

Infections in the setting of LVAD therapy

Infections related to LVAD therapy occur frequently and increase the rate of hospitalization and increase the risk for multiple subsequent adverse events.[3,27-30] Even though LVAD related infections occur frequently, no uniform standardized treatment protocol has been proposed. This is due to differences in geographic location, with some microorganisms being less prevalent in some parts of the world. Moreover, differences between hospitals from the same country also hinder the ability to propose a standardized treatment protocol. Nonetheless, to evaluate the care of one of the most frequent LVAD related infections, the driveline infection, we reviewed the current literature in **Chapter VII**. We found several studies which reported on their current wound care protocol regarding driveline exists. While some studies shared some aspects of their wound care, currently no standardized wound care protocol exist. Furthermore, the included studies have small sample sizes and therefore are difficult to generalize to the entire LVAD population. The pillars of the current optimal driveline wound care should include the use of a dressing kit, sterile technique, the use of chlorhexidine gluconate as a cleaning agent, and the use of silver-based dressing as a covering material. Additionally, the use of an anchoring device, only 1 to 2 times per week dressing change after the driveline wound has completely healed and, lastly, to keep the driveline exit dry during showering. While evidence for these recommendations is limited, these are the only reported effective methods in care of driveline exit wounds.

When the right side of the heart fails

Right-sided heart failure (RHF) has been described by some as the Achilles' heel of LVAD therapy.[31] Moreover, since the introduction of the newer devices, the HeartWare ventricular assist device (HVAD) and the HeartMate 3, the incidence of RHF has increased.[32,33] While earlier studies focused on the onset of early (<90 days) RHF, more recent studies shifted their focus towards late (>90 days) RHF. Although the underlying mechanisms involved are far from being crystalized, the need for adequate management is paramount. In the setting of medically refractory RHF, an intervention like a durable right ventricular assist device (RVAD) is not currently available and the use of RVAD's is solely warranted in desperate settings.[34,35] Therefore, to treat these patients with severe, refractory RHF, we attempted to treat one of our patients with a novel pharmacological treatment, intermittent infusion with Levosimendan. The use of Levosimendan has been described successfully in the end-stage heart failure patients, albeit the studies remain rather small and heterogeneous.[36] While this approach requires a thorough and stringent patient selection, this novel treatment approach seems promising.

Aortic valve pathophysiology with altered hemodynamics

The aortic valve (AoV) is the one-way exit from the left ventricle to the ascending aorta. However, in patients with an LVAD, the AoV is bypassed, with blood flowing from the left ventricle straight to the ascending aorta through the outflow graft. This renders the intended function of AoV to be disturbed. Still, the AoV may open (to some extent) and close in concordance with the (minimal) contraction of the left ventricle. However, the AoV can be a cause for concern in the case of valvular insufficiency given the hemodynamic integrity by LVAD therapy are heavily reliant on the integrity of the AoV. Previously, studies have investigated whether surgical closure of the native AoV can be a viable treatment modality in case of (imminent) valve regurgitation.[37,38] Initially, this seemed a relatively easy and adequate solution to the previously mentioned conditions. However, further research found that closure of the native valve is associated with an increased rate of aortic regurgitation (AR) during prolonged LVAD support.[39] Therefore, in the case of echocardiographically confirmed moderate-to-severe AR, aortic stenosis or previous mechanical prosthesis implantation, the International Society for Heart and Lung Transplantation (ISHLT) and European Association for Cardiothoracic Surgery (EACTS) guidelines recommend concomitant aortic valve replacement (AVR) surgery with a biological prosthesis during LVAD surgery.[40,41] In **Chapter IX**, we evaluated our own single center experience with AVR surgery. In total, 11 patients received either concomitant AVR, trans-catheter AVR or AVR during LVAD support. We found 4 patients who had developed AoV thrombosis with one of these patients experiencing a subsequent ischemic stroke 24 days later. Additionally, CT-scans showed that in some of these patients' aortic root thrombosis had formed. These data, concerning only a small cohort of patients, were worrisome. Therefore, with the purpose of shedding light on a possible increased rate of thromboembolic events in these patients, we turned to the ISHLT Mechanical Circulatory Support (IMACS) database, a large international LVAD database containing data on patients treated in the US, Europe, Japan, the UK, and various individual hospitals worldwide. **Chapter X** focuses on the rate of thromboembolic and bleeding

events in LVAD patients who underwent concomitant AoV surgery (either AVR or AoV repair surgery). Overall, 785 (5.1%) out of a total of 15.267 LVAD patients had received a concomitant AoV surgery. When comparing outcomes for both patients with and without concomitant AoV surgery, we found no difference in ischemic or hemorrhagic strokes. Furthermore, in a separate competing outcome analysis, AoV surgery was not associated with increased rates of stroke, despite the increase in mortality. However, a significant difference was observed in the bleeding rates between both groups. We found that patients with concomitant AoV surgery had higher administrations of dual antithrombotic medical therapy, both an oral anticoagulation and a platelet aggregation inhibitors. Probably, in an effort to prevent thromboembolic events, patients who underwent AoV surgery had higher rates of bleeding, both surgical bleedings, as well as nonsurgical bleedings. Interestingly, we found that concomitant aortic valve repair surgery was associated with an increased rate of pump thrombosis, with the underlying mechanism yet to be elucidated. Of note, most of the concomitant AoV surgeries were scheduled in patients with mild AR at the time of LVAD implantation, which seems probably superfluous in most patients. The increased bleeding rate, the amount of concomitant AoV surgeries not backed by current guidelines and the increased pump thrombosis rate with AoV repair surgery underlines the need for more data, preferably in the form of randomized clinical trials to further define the optimal selection criteria for concomitant AoV surgery.

In the letter to the editor, **Chapter XII**, we make a case for the use of repeated measurements in a longitudinal data form, as is proposed by the guidelines for cardiac valve interventions.[42] Thereafter, we advocate for the use of joint model analysis to investigate the impact of AR on survival. Therefore, with the use of the data from the IMACS database, we aimed to apply this method in the next chapter.

Chapter XIII includes data from 12.810 patients, with over 36.000 individual echocardiograms. Significant AR (defined as moderate-to-severe regurgitation) was observed on 2.660 echocardiograms. We confirmed that predictors for the development of significant AR include mild AR prior to LVAD implantation and prolonged LVAD support.[43] Moreover, we found that AVR surgery as opposed to AoV repair surgery, was associated with a significant reduction in the rate of post-operative significant AR. Mortality following the development of significant AR was illustrated with the use of simulated patients. Two identical patients were simulated, with one developing significant AR at month 7 and the other did not. At month 20, the excess mortality was 20%. Furthermore, the strongest independent predictor for mortality was the speed of the development of significant AR. This means that faster development of significant AR is accompanied by worse survival. This was the first study to our knowledge to incorporate the mixed models and joint model analysis to accurately depict the impact of significant AR following LVAD implantation.

The Erasmus MC experience

In **Chapter XIV**, we evaluated our experience with LVAD therapy since 2006. The introduction of the HeartMate II has been an indispensable addition in the treatment of end-stage heart failure. The initial use of the devices, to bridge patients to a heart transplantation has saved many patients who otherwise would not have survived. Our center opted for the use of the HeartMate 3 in 2016 and since then more patients have been implanted with a HeartMate 3 than a HeartMate II. Gradually we started implanting older patients with more comorbidities prior to implantation. The gained knowledge and experience over the years has been the key to achieving similar survival rates in these patients despite increasing ages, co-morbidities and the shift from only bridge-to-transplantation indication to destination therapy.

Future perspectives

The future looks a little bit brighter for patients with end-stage heart failure. Ongoing research and novel insights incrementally improve our understanding and subsequently improve patient outcomes. While LVAD therapy has been successful so far, there are many areas of concern which need to be addressed. These areas of improvement include infections, right heart failure, risk of thrombo-embolic events, bleeding, and last but not least the appropriate patient selection.

LVAD related infections

One of the most common adverse events during prolonged LVAD therapy is a driveline infection.[27,44-46] The driveline connects the implanted device with the extracorporeal world and is therefore a breeding ground for infections. Driveline infections often warrant hospitalization and prolonged antibiotic treatment, and thereby decreasing overall quality of life. While superficial infections can be treated with relative ease, deep tissue driveline infections are much harder to treat, and may lead to pump pocket and mediastinal infections. Hopefully, these infections diminish with fully implantable devices. These devices would need to be powered with a wireless technology akin to the novel chargers for contemporary phones. The implanted LVAD would need to consume less energy than it does now and charging the device would have to be efficient without heating or damaging the skin. The development of such devices, with all the recent progression in battery technology, seems only a matter of time.

Right heart failure

The novel LVAD devices, the HeartWare ventricular assist device (HVAD) and the HeartMate 3 both have witnessed an increased rate of late RHF.[32,44] The underlying mechanisms postulated include altered right ventricle geometry, interventricular interdependence, mechanical constraint due to the left to right crossing LVAD outflow graft, increased pre- and afterload following LVAD implantation, contemporary device design, and preoperatively underdiagnosed RV dysfunction. Our understanding of RHF has improved over time, however the appropriate prevention of RHF is yet to be elucidated. Patients who are at risk of RHF often suffer from pre-implant RHF.[47] This should serve as a starting point, with identifying those who suffer from right ventricular dysfunction. Second, LVAD therapy in

patients who appear to be prone to RHF should be supported by the use of novel minimal invasive diagnostic devices such as the Cardio MEMS, which can monitor pulmonary artery pressures in real time.[48] This allows for optimal timing in case of imminent increases of right ventricular afterload. Subsequent timely intervention with the use of pulmonary vasodilator and/or diuretics could prevent hospitalization and prevent the need for RVAD therapy.

Device characteristics

The latest addition to the LVAD therapy devices, the HeartMate 3, has impacted the care for LVAD patients in a major way. Pump thrombosis, a dreaded outcome in the HeartMate II and HVAD era, seems to be a problem of the past. Nonetheless, there are several other concerns which need to be addressed to elevate LVAD therapy to the next stage. First, the device needs to be smaller and fully implantable without need of a transcutaneous driveline exit. The risk of infection is a major drawback of the current devices. Furthermore, the latest devices still require major open-heart surgery. Less invasive strategies could possibly alleviate some clinical complications like bleedings and RHF.[49] The miniaturization of these devices could perhaps one day enable percutaneous or thoracoscopic implantation of these devices, markedly reducing the risk for early adverse events, as well as implantation primarily as a RVAD, LVAD, BIVAD or probably as a "total heart". Lastly, the device needs to be "smart" and incorporate feedback mechanisms in the design. The need for real time assessment of cardiac output, preload, afterload, and oxygen demand needs to be registered by the device, which subsequently changes its output accordingly. Although outside of the scope of this thesis, the recently introduced and temporarily withdrawn Aeson, the Carmat total artificial heart, included a feature which alters its cardiac output according to the physiological needs of the patient. In general, these features may further improve the perspectives of the patient with the failing heart.

Patient selection criteria

Last but not least, the final area of improvement includes patient selection. Due to the increasing age of the population and the myriad of medical advancements in the last 20 years, we live to be older and live to be sicker for longer. This begs the question, in an increasingly aging population, who is a suitable candidate for LVAD therapy?

The need for LVAD therapy has grown exponentially in the last decades, with heart transplantation rates stagnant for years.[3] However, the recent introduction of donation after circulatory death, as opposed to donation after brain death, has the potential to double the available donor hearts.[50] Nonetheless, despite this great progress, most patients waiting for a transplantation will most likely never receive a donor heart unless they bridge the time. Therefore, it is paramount to optimize the current patient selection criteria for LVAD therapy, as prolonged medical therapy increases the risk of complications. The recent changes to the United Network for Organ Sharing allocation of donor hearts has had tremendous impact on those supported with bridge-to-transplant LVAD therapy, reducing their urgency and therefore chances of ever being transplanted.[51,52] This prompted a study, using data from the latest MOMENTUM 3 trial, to successfully showcase that bridge-to-transplantation/candidacy and destination therapy are terms which belong to the past.[53] What now remains is to determine what the optimal selection criteria are, since LVAD therapy prior to a heart transplantation is associated with worse outcomes.[54] Furthermore, age of the LVAD recipient

is an important factor to consider, given that they are at risk for mortality but also have the most to gain.[55] Renal function, pulmonary hypertension, psychosocial factors and right ventricular function all seem to be important factors to include in the selection of LVAD eligibility. While the selection criteria are continuously being optimized, the current thesis contributed to the larger body of evidence on which these criteria are established.

Conclusion

The treatment of patients with end-stage heart failure in the last one and a half decade with continuous flow LVAD therapy has been a great success. The survival rates have increased to unprecedented heights, with increased quality of life and less debilitating adverse events. This thesis was an effort to improve patient selection criteria and has subsequently identified several areas for further improvement. The aim to improve outcomes remains paramount for the future success of this treatment modality.

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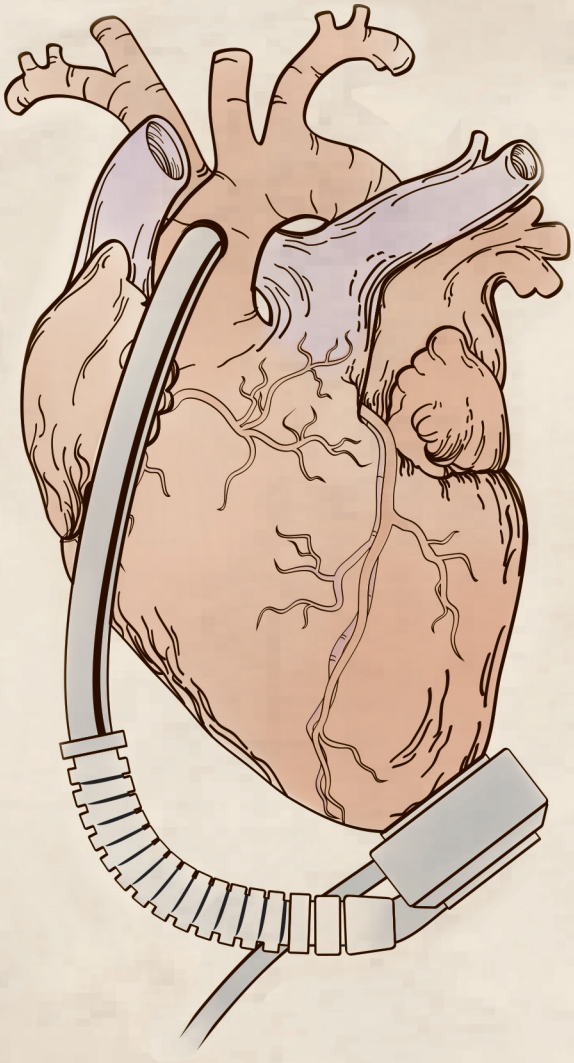


Chapter XVI

Summary/Samenvatting

Summary

This thesis has been an effort to improve the outcomes of patients suffering from end-stage heart failure treated with left ventricular assist device (LVAD) therapy. Moreover, this thesis aimed to assess and thereafter accurately predict the onset of adverse events to aid in future patient selection criteria. The following is a brief and concise summary of all the chapters of this thesis.

Chapter I begins with the general introduction, the aims and shows the outline of the current thesis.

Chapter II starts off with a state-of-the-art review on acute kidney injury following the implantation of a LVAD. This review focusses on all aspects of the pathophysiology, the current treatments, and the future perspectives of this debilitating outcome.

Chapter III is the first retrospective multicenter study conducted in this thesis, which looks at renal function following LVAD implantation. This study incorporates novel statistical methods to include all the longitudinal data available after implantation. This study highlights that renal function following LVAD implantation initially improves, which is followed by a steady state and thereafter deteriorate for the majority of patients. Only in a select group of patients does renal function improvement last after 1 year.

Chapter IV investigated the effect of preoperative liver dysfunction on outcomes following LVAD implantation. The Modified End-stage Liver Disease (MELD) score was used to define liver dysfunction in these patients. This study found that patients with preoperative liver dysfunction were less likely to survive the first year of follow-up. Nonetheless, liver function enzymes ameliorated in all patients who had survived the 1-year follow-up period, irrespective of prior liver dysfunction.

Chapter V includes a single center study investigating interference between several implantable cardioverter defibrillators (ICD) and LVADs. The study revealed interference between the latest LVAD, the HeartMate 3 and several ICD's from Biotronik and Medtronic. This interference made it hard or sometimes impossible to read the data on the ICD devices. Following these observations, a stepwise approach was formulated to prevent or bypass the interference, thereby effectively resolving this issue.

Chapter VI, which includes a study using data provided by the European registry for mechanical circulatory support (EUROMACS), investigated the effect of preoperative atrial fibrillation (AF) on outcomes following LVAD implantation. This study found an incidence of 1 in 4 patients suffering from AF prior to implantation. These patients had lower survival than those not suffering from preoperative AF. However, following a multivariable analysis, AF was not found to be an independent predictor of mortality following LVAD implantation. Furthermore, preoperative AF did not increase the rate of thromboembolic events (i.e.

ischemic stroke or pump thrombosis). Only after 2 years of follow-up did preoperative AF increase the rate of strokes.

Chapter VII contains a systematic review on the driveline exit-site wound care protocols in LVAD patients. While many patients suffer from driveline exit-site infections, to date no uniform, standardized protocol exist for the treatment. The main finding of this study was the vast differences in the treatment protocol, which made comparing these different protocols difficult. Following these findings, we suggest a treatment protocol comprised of all the possible treatment modalities, which include several cleaning agents, a clear weekly schedule, and the use an anchoring device and a cleaning kit.

Chapter VII, a case report, highlight our experience using intermittent monthly 24-hour Levosimendan infusions to treat a patient suffering from right sided heart failure while on prolonged LVAD support. This novel approach has proven to be successful and looks promising for future application.

Chapter IX, a case series, reviewed our LVAD patients who had received concomitant aortic valve replacement. We found that 4 out of the 11 patients total had suffered from aortic root thrombosis following this intervention. In order to investigate whether this phenomenon translates to increased rates of mortality and strokes ensued the following research in Chapters **X** and **XI**.

Chapter X found that the concomitant aortic valve surgery and LVAD implantation surgery decreased the survival rate. Furthermore, following a multivariable analysis, aortic valve replacement and not aortic valve repair was an independent predictor for mortality, both in the early and late follow-up period.

Chapter XI includes a study on the incidence of thromboembolic and bleeding events in LVAD patients who received concomitant aortic valve surgery. The study found no increase in the rate of stroke, both ischemic and hemorrhagic, following concomitant aortic valve surgery. In patients who received concomitant aortic valve repair, an increased rate of pump thrombosis was observed. Furthermore, surgical bleeding events, and nonsurgical bleeding events, both early and late, were more frequently observed in patients with concomitant aortic valve surgery. Lastly, the indication for concomitant aortic valve surgery was in almost 50% against the recommendation of the current guidelines.

Chapter XII, a letter to the editor, remarks on a study's methodology when analyzing the incidence and impact of aortic valve regurgitation during LVAD support. Therefore, in **Chapter XIII**, we apply the method most suited for analyzing the impact of aortic regurgitation. The application of advanced mixed models and joint models revealed an incidence of 1 in 8 LVAD patients developing aortic valve regurgitation. Furthermore, the impact of aortic valve regurgitation was an estimated excess mortality of 20%. Lastly, the strongest predictor for mortality after the development of aortic valve regurgitation was the duration of time until an echocardiogram confirming regurgitation.

The last study to be included, **Chapter XIV**, contains our own experience with LVAD therapy at the Erasmus MC university hospital. With over one and a half decade of experience, this study shows similar survival rates for HeartMate II and HeartMate 3 patients. This is despite the lower rate of bridge-to-transplant patients and higher rate of comorbidities in the HeartMate 3 group. This study highlights the importance of stringent selection criteria for LVAD therapy eligibility.

Finally, in **Chapter XV**, this thesis comes to an end. Herein the aforementioned chapters are discussed, future perspectives are philosophized, and the final conclusion follows.

Nederlandse samenvatting

Dit proefschrift is een poging geweest om de uitkomsten te verbeteren van patiënten die lijden aan eindstadium hartfalen welke zijn behandeld met left ventricular assist device (LVAD) therapie. Hoofdzakelijk was dit proefschrift gericht op het beoordelen en voorspellen van het optreden van ongewenste bijwerkingen. Deze informatie heeft als doel om te helpen bij het stellen van toekomstige selectiecriteria voor patiënten die mogelijk LVAD-therapie kunnen ontvangen. Hieronder volgt een korte en bondige samenvatting van alle hoofdstukken van dit proefschrift.

Hoofdstuk I begint met de algemene inleiding, de doelstellingen en toont de hoofdlijnen van het huidige proefschrift.

Hoofdstuk II begint met een state-of-the-art review over acute nier schade na implantatie van een LVAD. Deze review richt zich op alle aspecten van de pathofysiologie, de huidige behandelingen en de toekomstperspectieven van deze slopende ziekte.

Hoofdstuk III betreft een retrospectieve multicenter studie uit dit proefschrift die kijkt naar de functie van de nieren na LVAD-implantatie. Deze studie omvat moderne statistische methoden om alle longitudinale gegevens die beschikbaar zijn na implantatie te gebruiken. Hierin wordt benadrukt dat de nierfunctie na LVAD-implantatie aanvankelijk verbeterd. Hierna volgt een periode van stabilisatie waarbij de nierfunctie niet verder meer verbeterd en deze wordt gevolgd door aftakeling van nierfunctie voor de meerderheid van de patiënten. Slechts bij een selecte groep patiënten houdt de initiële verbetering van de nierfunctie na 1 jaar stand.

Hoofdstuk IV onderzocht het effect van preoperatieve leverdisfunctie op de uitkomsten na LVAD-implantatie. De Modified End-stage Liver Disease (MELD)-score werd gebruikt als surrogaat om leverdisfunctie bij deze patiënten te definiëren. Deze studie laat zien dat patiënten met preoperatieve leverdisfunctie minder kans hadden om het eerste jaar van follow-up te overleven. Desalniettemin verbeterden de leverfunctie-enzymen bij alle patiënten die de follow-up periode van 1 jaar hadden overleefd, ongeacht eerdere preoperatieve leverdisfunctie.

Hoofdstuk V omvat een studie in ons eigen centrum waarin de interferentie tussen verschillende implanteerbare cardioverter defibrillators (ICD's) en LVAD's werd onderzocht. De studie onthulde interferentie tussen de nieuwste LVAD, de HeartMate 3 en verschillende ICD's van Biotronik en Medtronic. Deze interferentie maakte het moeilijk of soms zelfs onmogelijk om de gegevens op de ICD-apparaten te lezen. Op basis van deze observaties is een stapsgewijze aanpak bedacht om deze interferentie te voorkomen of te omzeilen, waardoor dit probleem effectief wordt opgelost.

Hoofdstuk VI, bevat een studie welke met behulp van gegevens van het Europese register voor mechanische bloedsomlooponderstеuning (EUROMACS) onderzocht wat het effect is

van preoperatief atriumfibrilleren (AF) op de uitkomsten na LVAD-implantatie. Deze studie vond dat 1 op de 4 LVAD patiënten voor de operatie geleden heeft aan AF. Deze patiënten hadden na LVAD-implantatie een lagere overleving dan degenen die geen preoperatieve AF hadden. Echter, na een multivariabele analyse bleek AF geen onafhankelijke voorspeller te zijn van mortaliteit na LVAD-implantatie. Verder bleek dat AF het aantal trombo-embolische voorvallen (ischemische beroertes of pomptrombose) niet verhoogd. Wel blijkt dat als patiënten 2 jaar follow-up hebben overleefd, dat preoperatieve AF een toename van het aantal beroertes geeft.

Hoofdstuk VII is een systematische review welke kijkt naar de driveline-protocollen voor wondverzorging bij LVAD-patiënten. Hoewel veel patiënten last hebben van infecties bij de huiduitgang van hun driveline bestaat er tot op heden geen gestandaardiseerd protocol voor de behandeling hiervan. De belangrijkste bevinding van deze studie waren de enorme verschillen in het behandelprotocol, waardoor het moeilijk was om deze verschillende protocollen te vergelijken. Op basis van deze bevindingen hebben we een behandelprotocol voorgesteld met daarin alle mogelijke behandelmodaliteiten, waaronder meerdere reinigingsmiddelen, een duidelijk wekelijks schema en het gebruik van een verankeringshulpmiddel en een schoonmaak kit.

Hoofdstuk VIII, een casus rapport, belicht onze ervaring met het gebruik van intermitterende maandelijkse 24-uurs Levosimendan-infusies om een patiënt te behandelen die lijdt aan rechtszijdig hartfalen tijdens zijn LVAD-therapie. Deze nog ongebruikelijke aanpak is succesvol gebleken en ziet er veelbelovend uit voor toekomstige toepassing.

Hoofdstuk IX, ditmaal een casusreeks, beoordeelde onze patiënten die allen gelijktijdig een aortaklepvervanging hadden gekregen tijdens LVAD-implantatie. We ontdekten dat 4 van de 11 patiënten last hadden van aortawortelthrombose na deze interventie. Om te onderzoeken of dit fenomeen zich vertaalde in verhoogde sterftecijfers en beroertes zijn **Hoofdstukken X** en **XI** van dit proefschrift geïncludeerd.

Hoofdstuk X vond dat het gelijktijdig plaatsvinden van aortaklepchirurgie en LVAD-implantatie de overleving deed doen afnemen. Bovendien was na een multivariabele analyse aortaklepvervanging chirurgie en niet aortaklep reparatie chirurgie een onafhankelijke voorspeller voor mortaliteit, zowel in de vroege als in de late follow-up.

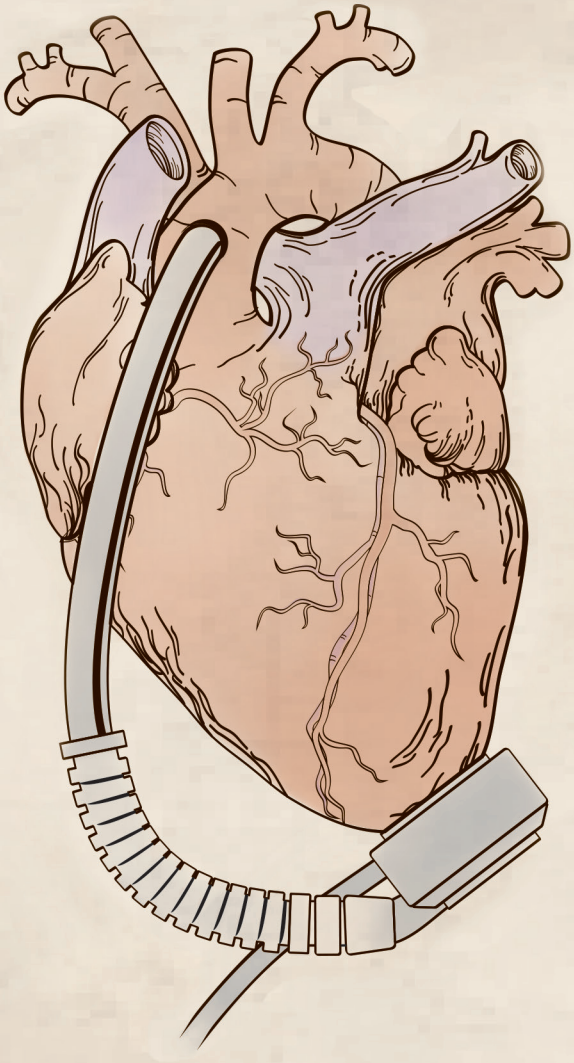
Hoofdstuk XI omvat een onderzoek naar de incidentie van trombo-embolische events en bloedingen bij LVAD-patiënten die gelijktijdig een aortaklep operatie ondergingen. De studie vond geen toename van het aantal beroertes, zowel ischemisch als hemorragisch, na het plaatsvinden van gelijktijdige aortaklep chirurgie. Bij patiënten die gelijktijdig aortaklep reparatie chirurgie ondergingen werd wel een verhoogde frequentie van pomptrombose waargenomen. Bovendien werden chirurgische bloedingen en niet-chirurgische bloedingen, zowel vroeg als laat, vaker waargenomen bij patiënten met gelijktijdige aortaklep chirurgie. Ten slotte was de indicatie voor gelijktijdige aortaklep chirurgie in bijna 50% van de gevallen niet volgens de aanbeveling van de huidige richtlijnen.

Hoofdstuk XII, een letter-to-the-editor, becommentarieert de gebruikte methodologie van een studie bij het analyseren van de incidentie en impact van aortaklep insufficiëntie tijdens LVAD-ondersteuning.

Als antwoord op deze studie passen we in **Hoofdstuk XIII** de methode toe die het meest geschikt is voor het analyseren van de impact van aortaklep insufficiëntie. De toepassing van geavanceerde mixed-modellen en joint modellen onthulde een incidentie van 1 op de 8 LVAD-patiënten die insufficiëntie van de aortaklep ontwikkelden. Bovendien was de impact van aortaklep insufficiëntie op overleving een geschatte oversterfte van 20%. Ten slotte was de sterkste voorspeller voor overlijden na de ontwikkeling van aortaklep insufficiëntie de tijdsduur tussen een normale en een echocardiogram die insufficiëntie bevestigde.

De laatste studie van dit proefschrift, **Hoofdstuk XIV**, bevat onze eigen ervaringen met LVAD-therapie in het academisch ziekenhuis Erasmus MC. Met meer dan anderhalf decennium aan ervaring laat deze studie een vergelijkbare overleving zien voor HeartMate II en HeartMate 3 patiënten. Dit ondanks het lagere aantal overbruggings-naar-transplantatie indicatie en de hogere frequentie van co-morbiditeit in de HeartMate 3 groep. Deze studie benadrukt het belang van strenge selectiecriteria om in aanmerking te komen voor LVAD-therapie.

In **Hoofdstuk XV**, komt dit proefschrift tot een einde. Hierin worden de eerdergenoemde hoofdstukken besproken, over toekomstperspectieven gefilosofeerd en volgt de eindconclusie.



Chapter XVII

Dankwoord/Acknowledgements

PhD Portfolio

List of publications

About the author

Dankwoord/Acknowdledgements

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PhD Portfolio

Name PhD student	Yunus Can Yalçin
Erasmus MC department	Cardiothoracic Surgery
Research school	Cardiovascular Research School (COEUR)
PhD period	February 2019 – February 2022
Title thesis	Durable left ventricular assist device therapy for end-stage heart failure ''optimizing selection criteria''
Promotor	Prof. Dr. Ad J.J.C. Bogers
Co-promotors	Dr. Kadir Caliskan & Dr. Rahatullah Muslem

Academic Education

Sep 2013 - Aug 2018	BSc in medicine, Erasmus MC, Rotterdam, the Netherlands
Feb 2019 - July 2022 (expected)	MSc in medicine, Erasmus MC, Rotterdam, the Netherlands

PhD Training

General courses	**Year**	**Workload**
Basic course Rules and Organization for Clinical researchers	2019	1.5
Research integrity	2019	0.3
Good clinical practice course	2021	0.6
In-depth courses	**Year**	**Workload**
Heart failure research	2018	0.5
The ''(un)paved road'' to heart transplantation, COEUR	2019	0.5
Vascular clinical Epidemiology, COEUR	2019	0.5
Ischemic heart disease, COEUR	2019	0.5
Sex and gender in cardiovascular research, COEUR	2019	0.5
Clinical courses/education	**Year**	**Workload**
Journal club cardiothoracic department	2018-2020	3.0
Biweekly LVAD therapy discussion	2017-2020	2.0
BLS course	2020	0.5
ALS course	2020	0.5
PBLS course	2020	0.5
International and national conferences	**Year**	**Workload**
International society of heart lung transplantation, Orlando, USA	2019	1.5
International society of heart lung transplantation, Online Virtual Experience	2020	1.5
International society of heart lung transplantation, Online Virtual Experience	2021	1.5
European society of cardiology, Paris, France	2019	1.5
Nederlandse verening voor thoraxchirurgie, voorjaarsvergadering, Online	2021	0.6

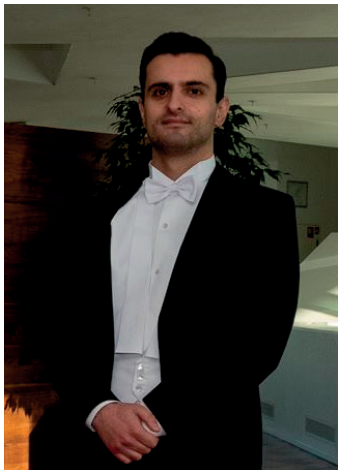
Oral presentations	**Year**	**Workload**
International society of heart lung transplantation, Orlando, USA	2019	0.6
International society of heart lung transplantation, Orlando, USA	2021	0.6
Nederlandse vereniging voor thoraxchirurgie, voorjaarsvergadering, Online	2021	0.6
Poster presentations	**Year**	**Workload**
International society of heart lung transplantation, Orlando, USA	2019	0.6
International society of heart lung transplantation, Online Virtual Experience	2021	1.5
European cociety of cardiology (2x)	2019	1.2
Teaching	**Year**	**Workload**
Clinical lesson for 2nd year medical students on LVAD therapy	2020	0.6
Supervising 2nd year medical students in writing a systematic review	2019 - 2020	2.0
Supervising master students during their master thesis	2019-2020	4.0
Supervising a last year cardiac device technician thesis	2019	0.6
Other	**Year**	**Workload**
Reviewer for the journal of the American college of cardiology: case reports	2020	0.6
Grants		
ISHLT Travel Grant 2019		
Total workload (ECTS)		**30.9**

List of publications

1. **Yalcin YC**, Bunge JJH, Guven G, Muslem R, Szymanski M, den Uil CA, Hesselink DA, Topkara VK, Manintveld OC, Colombo PC, Bogers AJJC, Caliskan K. Acute kidney injury following left ventricular assist device implantation; Contemporary insights and future perspectives. ***J Heart Lung Transplant. 2019;38(8):797-805.***
2. **Yalcin YC**, Muslem R, Veen KM, Soliman OI, Hesselink DA, Constantinescu AA, Brugts JJ, Manintveld OC, Fudim M, Russel SD, Tomashitis B, Houston BA, Hsu S, Tedford RJ, Bogers AJJC, Caliskan K. Impact of continuous flow left ventricular assist device therapy on chronic kidney disease: a longitudinal multicenter study. ***J Card Failure 2020 Apr;26(4):333-341.***
3. **Yalcin YC,** Muslem R, Veen KM, Soliman OI, Manintveld OC, Darwish Murad S, Kilic A, Constantinescu AA, Brugts JJ, Alkhunaizi F, Birim O, Tedford RJ, Bogers AJJC, Hsu S, Caliskan K. Impact of pre-operative liver dysfunction on outcomes in patients with left ventricular assist devices. ***Eur J Cardiothorac Surg 2020 May 1;57(5):920-928*.**
4. **Yalcin YC**, Kooij C, Theuns DAMJ, Constantinescu AA, Brugts JJ, Manintveld OC, Yap SC, Szili-Torok T, Bogers AJJC, Caliskan K. Emerging electromagnetic interference between implantable cardioverter defibrillators and left ventricular assist devices. ***Europace 2020 Apr 1;22(4):584-587.***
5. Antonides CFJ, **Yalcin YC**, Muslem R, De By TMMH, Bogers AJJC, Gustafson F, Caliskan K. Pre-operative atrial fibrillation and associated outcomes in patients receiving left ventricular assist device therapy: a EUROMACS study***. Eur J Cardiothorac Surg. Accepted for publication***
6. Ozdemir Z, **Yalcin YC**, de Bakker CC, van der Graaf M, Verkaik NJ, van Netten D, Caliskan K. Driveline Exit-Site Wound Care Protocols in Left Ventricular Assist Device Patients: A Systematic Review. ***Eur J Cardiothorac Surg. 2021 May 8;ezab195***
7. **Yalcin YC**, Caliskan K. Intermittent Levosimendan treatment for late onset right ventricular failure in a patient supported with a left ventricular assist device. ***Artif Organs. 2020 May;44(5):533-534.***
8. Veenis JF, Brugts JJ, **Yalcin YC**, Roest S, Bekkers JA, Manintveld OC, Constantinescu AA, Bogers AJJC, Zijlstra F, Caliskan K. Aortic root thrombus after left ventricular assist device implantation and aortic valve replacement. ***ESC Heart Fail. 2020 Oct;7(5):3208-3212.***
9. **Yalcin YC**, Veenis JF, Bekkers JA, Bogers AJJC, Brugts JJ, Caliskan K. Survival following concomitant aortic valve procedure and left ventricular assist device implantation: an ISHLT Mechanically Assisted Circulatory Support (IMACS) Registry. ***Eur J Heart Fail. 2020 Oct;22(10):1878-1887.***
10. Veen KM, **Yalcin YC**, Mokhles MM, Sufficient Methods for Monitoring Aortic Insufficiency. ***Ann Thorac Surg 2021;111:1098*.**
11. Schinkel AFL, Akin S, Strachinaru M, Muslem R, Bowen D, **Yalcin YC**, Brugts JJ, Constantinescu AA, Manintveld OC, Caliskan K. Evaluation of patients with a HeartMate 3 left ventricular assist device using echocardiographic particle image velocimetry. **J Ultrasound. 2021 Dec;24(4):499-503**
12. Antonides CFJ, Schoenrath F, de By TMMH, Muslem R, Veen K, **Yalcin YC**, Netuka I, Gummert J, Potapov EV, Meyns B, Özbaran M, Schibilsky D, Caliskan K; EUROMACS investigators. Outcomes of patients after successful left ventricular assist device explantation: a EUROMACS study. **ESC Heart Fail. 2020 Jun;7(3):1085-1094.**
13. Muslem R, **Yalcin YC**, Caliskan K, van der Heiden C, van Rhijn H, Bogers AJJC, Manintveld OC. Modification of a Ventricular Assistance Device for a Hemiplegic Left Ventricular Assist Device Patient. **ASAIO J. 2019 Jan;65(1):e12-e13.**

14. Bowen DJ, **Yalcin YC**, Strachinaru M, McGhie JS, van den Bosch AE, Soliman OI, Caliskan K. Right ventricular functional assessment by 2D multi-plane echocardiography prior to left ventricular assist device implantation. **Echocardiography. 2022 Jan;39(1):7-19.**
15. **Yalcin YC**, Veenis JF, Brugts JJ, Antonides CFJ, Veen KM, Muslem R, Bekkers JA, Gustafsson F, Tedford RJ, Bogers AJJC, Caliskan K. Rate of thromboembolic and bleeding events in patients undergoing concomitant aortic valve surgery with left ventricular assist device implantation. **Int J Cardiol. 2022 Apr 18:S0167-5273(22)00555-1.**

About the author



Yunus Can Yalçin was born on January 13th, 1994, in Zwolle, the Netherlands. After graduating from the Meander college in 2013, he started his medical training at the ErasmusMC. After obtaining his bachelor's degree in 2018 he was set to start his clinical rotation in 2019. However, during this time he worked on several research topics with his supervisors Prof. Dr. Ad Bogers, Dr. Kadir Caliskan and Dr. Rahatullah Muslem. This resulted in a fulltime position as a PhD student from the start of 2019 until the start of 2020. Following this period, he started with his clinical rotation which he expects to complete in July of 2022. During his clinical rotations he married with Sitara Yalçin-Zaidi, and she gave birth to their daughter Ayla Aslı on March 7th, 2022.

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This thesis has been an effort to improve the outcomes of patients suffering from end-stage heart failure treated with left ventricular assist device (LVAD) therapy. Moreover, this thesis aimed to assess and thereafter accurately predict the onset of adverse events to aid in future patient selection criteria. Although outcomes following LVAD implantation have greatly improved since its introduction, further research is paramount for the ongoing success of this treatment modality.

Dit proefschrift is een poging geweest om de resultaten van patiënten die lijden aan eindstadium hartfalen welke zijn behandeld middels left ventricular assist device (LVAD) therapie te verbeteren. Met name heeft dit proefschrift zich gericht op het beoordelen en daarna nauwkeurig proberen te voorspellen van ongewenste uitkomsten. Dit is gedaan om te helpen bij het aanscherpen van toekomstige selectiecriteria voor LVAD therapie. Hoewel de resultaten na LVAD-implantatie sterk zijn verbeterd sinds diens introductie blijft vervolg onderzoek van essentieel belang voor het succes van deze behandelingsmodaliteit.