A NEW ERA IN ADVANCED HEART FAILURE THERAPY

LEFT VENTRICULAR ASSIST DEVICES

Rahatullah Muslem

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Left ventricular assist devices

“Een nieuw tijdperk in eindstadium hartfalen therapie”

Mechanische steunharten

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by

Rahatullah Muslem
born in Peshawar, Pakistan

Erasmus University Rotterdam

DOCTORAL COMMITTEE

Promotor:	Prof.dr. A.J.J.C. Bogers
Other Members:	Prof.dr. F. Zijlstra Prof.dr. W.J.L. Suyker Prof.dr. R.J.M. Klautz
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For my family

"Try not to become a man of success, but rather try to become a man of value."

– Albert Einstein.

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CHAPTER 1

Introduction, aims, and outline of the thesis

A small history of the Heart

The first written description of the heart was probably produced by Imhotep, an Egyptian Half God, who wrote 5000 years ago The Ebers Papyrus, a twenty meter long medical encyclopedia. He described for the first time the heart and the rivers that flow from it (the vascular system) as one organ, known today as the cardiovascular system.(1,2)

Then, 2300 years after Imhotep, the science of the human heart flourished again in Alexandria. In this city, ruled by Ptolomeus I (Ptolemy I Soter 367-283 BC) and full of philosophers and scientists,(3,4) for the first time in history human dissections were allowed. Aristotle (384-322 b.Chr.) had often looked at the heart and recognized multiple parts of it.(5) He believed that the heart consisted of three chambers; the left ventricle, the left atrium, and the right ventricle. In addition, Aristotle thought that the heart was the most important organ in human beings, and that it housed the soul and the mind.

The heart was for the first time described as a pump by Erasistratus of Iulis on Ceos (about 315–240 BCE) in Alexandria.(1) Claudius Galenus, born around 131 after Chr., build on this idea and saw the cardiovascular system as a mechanical system.(6) Galenus contributed greatly to the knowledge about the heart. However, after the fall of the Roman Empire, science came to a standstill. Large parts or even complete works of great scientists got lost in this period, also referred to as the dark ages. Luckily, thanks to Islamic scholars, part of the knowledge gained until that time had been preserved and translated from Latin to Arabic and passed on to the next generations, eventually finding its way back to Europe. Finally, it was in the renaissance that science was reinvented by art, with Leanardo da Vinci leading this revolution.

Though the most groundbreaking discoveries regarding the heart and development in treatments have only been done in the past two-hundred years, including treatments like heart transplantation, and even being able to replace the heart with a mechanical pump, the mysteries of the heart are by far not unraveled and the biggest challenges arise when the heart starts to fail.

The failing Heart

Heart failure is a complex clinical syndrome, most often defined as the inability of the heart to adequately supply the peripheral tissues with oxygenated blood to meet their metabolic demands as a consequence of structural or functional impairment of

ventricular filling or ejection of blood.(7) Worldwide there are more than 23 million people with heart failure and it is projected that the prevalence will only increase.(8,9) In the Rotterdam Heart Study, the lifetime risk of heart failure at the age of 55 years was 33% for men and 29% for women.(10) In addition, heart failure is associated with high morbidity and mortality to such an extent, that it has been mentioned as the leading cause of death worldwide by the World Health Organization.

The etiologiy of heart failure is diverse and includes ischemic heart disease often associated with hypertension, and diabetes mellitus. Ischemic heart disease, often a consequence of atherosclerosis or a myocardial infarction, leads to damage of the myocardial tissue which subsequently weakens the heart's ability to contract or to pump blood sufficiently. (7,11) Other causes of heart failure are cardiomyopathies (e.g. dilated or hypertrophic), infections (e.g. viral myocarditis), congenital heart disease, and valvular heart disease. (7,11) These conditions result in symptoms of dyspnea, peripheral edema, fatigue, and palpitations. In addition, heart failure is commonly classified using the New York Heart Association (NYHA) classification system.(12)

Although some of these conditions can be treated, patients with refractory heart failure can have deterioration of their condition and develop end-stage heart failure. These patients are characterized by advanced structural heart disease and severe heart failure symptoms at rest (NYHA class IV). Furthermore, end-stage heart failure is a life threatening condition with a 1-year mortality rate of up to 50% (13). Until recently, the gold standard treatment option for these patients was heart transplantation.(14) However shortage of donor supply and ineligibility of patients has limited the possibility of heart transplantation to a selected group of patients. Subsequently, scientists and doctors were forced in developing novel treatment options for end-stage heart failure patients. Years of development have resulted in mechanical devices that are able to support the failing heart.

Assisting the failing heart - Mechanical circulatory support.

The concept of mechanically supporting the circulatory system dates back as far as 1812 to the concept of mechanical oxygenation and perfusion of Julien-Jean Cesar Le Gallois. (15) In the 20th century, following the success of the cardiopulmonary bypass system, the first pneumatically driven left ventricular assist device (LVAD) was introduced.(16) Initially mechanical circulatory devices were large paracorporeal pneumatic devices and used for short-term support as a bridge to recovery post-cardiotomy failure. The current LVADs used for the treatment of heart failure are relatively small, provide continuous

flow, are placed intra-pericardial, and are more hematological compatible. An LVAD exist of basically 5 parts; (I) an inflow cannula which is inserted in the left ventricle, (II) the pump device (LVAD), (III) an outflow graft inserted into the ascending aorta, (IV) a driveline which provides the LVAD with electricity, and (V) external batteries and controller connected through the driveline with the LVAD (Figure 1). Normally blood flows from the left atria in the left ventricle. Next the left ventricle contracts and pumps the blood through the aortic valve into the body circulation. However in patients with end-stage heart failure, the left ventricle is not able to adequately pump the blood into the body circulation. Therefore, these patients receive an LVAD, which pumps the blood from the left ventricle through the LVAD and outflow graft into the aorta and subsequently the circulatory system. The most common LVAD implantation indications include bridge-to-transplantation; intended for patients on the active waiting list for a heart transplantation who are anticipated to have a long waitlist time, increased risk of mortality or an impaired quality of life. Destination therapy; the last resort for patients with end-stage heart failure ineligible for a heart transplantation, and bridge-to-recovery; temporarily support for patients with acute heart failure and with the expectation of left ventricle recovery.

Current challenges

The mortality as well as the morbidity awaiting heart transplantation have been reduced due to the advancements made in mechanical circulatory support devices, better understanding of biocompatibility, and the development and refinement of the LVADs. In addition, the landmark clinical trial (REMATCH) has shown that the survival rate was superior in patients with end-stage heart failure supported with an LVAD compared to optimal medical therapy.(17) The survival has improved greatly over time with the third generation device reaching a 1-year survival of 80%.(18) All these changes have led to the new era in advanced heart failure therapy, in which LVAD therapy has become a cornerstone in the treatment of patients with advanced heart failure.

Although the survival rate of LVAD patients has improved greatly over time, complications following LVAD implantation remain very common. In addition, these complications are significantly higher in LVAD patients than in patients treated with optimal medical therapy.(19) These complication include bleeding, infection, pump thrombosis, cardiac arrhythmia, stroke, renal dysfunction and right heart failure.(20) With right heart failure being mentioned as the Achilles heel of LVAD therapy.(21) Due to the recent increase in the use of LVADs, the shift from LVAD therapy as bridge-to-transplantation to destination therapy, and the introduction of novel devices, the

published experience regarding LVADs and long-term support is limited. Previous studies have focused primarily on survival, using second generation devices, small populations, and short-term follow-up. However, the new third generation devices are currently implanted in older patients for a longer period of time. Research addressing the long-term outcomes following LVAD implantation, complications, and the impact of prolonged LVAD support on organ function is needed in order to improve current practice and adequately inform the patient about the benefits and the risks of LVAD therapy, and the quality of life following LVAD implantation.

Aims and outline of this thesis

As Immanuel Kant mentioned in *The Critique of Pure Reason* and Albert Einstein restated: *"The only source of knowledge is experience"*. In line with this saying, this thesis aims to assess the current body of evidence and experiences with continuous flow-LVADs in the new era of advanced heart failure therapy. Furthermore, we investigate clinical outcomes, complications, and the impact of LVAD on end-organ function. In addition, an effort was made to predict these end-points in order to improve the selection criteria for LVAD therapy and current clinical practice.

To depict the journey of a heart failure patient selected for LVAD therapy, a chronological order of clinical events is kept throughout this thesis. We start in **Chapter 2** with presenting a general overview of the history and evolution of LVADs over time. Previously used devices, current devices, and future devices not yet approved for clinical use, are discussed here. Furthermore, we touch upon patient selection and indications for LVAD therapy. In addition, the published literature regarding mortality and morbidity following LVAD implantation is reviewed here.

In **Chapter 3** and **4** we focused on the Achilles heel of LVAD therapy, early right-sided heart failure (RHF). Using the largest LVAD cohort of Europe, we aimed to derive and validate a novel risk score for early RHF after LVAD implantation. In addition, we determine the impact of RHF on mortality after LVAD implantation. Early recognition of RHF could help the clinician to timely intervene and prevent multi-organ failure.

Severe tricuspid regurgitation is associated with an impaired right ventricle function. However, controversy remains whether concomitant tricuspid valve surgery (TVS) during LVAD implantation is beneficial. In **Chapter 5** we systematically review the literature and pool the results of the impact of tricuspid valve surgery during LVAD implantation on, among others things, survival, RHF, and acute kidney injury.

Patients with an LVAD are challenging to evaluate using conventional imaging techniques. In **Chapter 6** and **7** we examine novel use of conventional imaging technics in LVAD patients. In **Chapter 6** we describe our pilot study where we evaluated the potential use of contrast echocardiography for the evaluation of the left ventricle. Furthermore, despite a decade of experience in using ^{18}F-FDG PET/CT to diagnose various infections, its use in LVAD patients remains scarce. Therefore, we reviewed the current evidence in the literature and described our single center experience using ^{18}F-FDG PET/CT for the diagnosis and management of LVAD infections in **Chapter 7**.

Prior to LVAD implantation, many heart failure patients have an impaired renal function. In **Chapter 8, 9** and **10** we investigate the impact of renal function on LVAD therapy, and vice versa, in the first year after LVAD implantation. In **Chapter 8** we studied the incidence, predictors and the impact of acute kidney injury on mortality and renal function. Thereafter, in **Chapter 9,** we determined the association of pre-operative proteinuria with mortality and the need for renal replacement therapy. In addition, in **Chapter 10,** we examined the effect of age on renal function and mortality after LVAD implantation.

Complications related to the hemocompatibility of the devices remain a significant problem, with bleeding being the most common complication following LVAD implantation (14). Because patients are at risk of both thromboembolic events and bleeding, a coagulopathy paradigm arises with the LVAD functioning as a double-edged sword. In **Chapter 11, 12,** and **13** we focus on hematological complications and outcomes. In **Chapter 11** we investigate the incidence, predictors, and clinical outcome of early bleeding events in patients after LVAD implantation. Furthermore, we present a case-report of an unusual cause of pump thrombosis (**Chapter 12)** and, we summarize the literature focusing on acquired coagulopathies, describing the incidence, impact and underlying mechanism of acquired coagulopathy disorders in patients supported by LVADs. In addition, we will discuss diagnostic and management strategies for these acquired coagulopathies (**Chapter 13)**. Thereafter, in **Chapter 14,** and **15,** we determine the differences in hemocompatibillity between second and third generation LVADs. Lastly, in **Chapter 16** we present an innovative assisting device for a hemiplegic LVAD patient who was impaired by a stroke and unable to operate his LVAD.

The increase in patients receiving an LVAD as destination therapy, has made the long-term device durability extremely important. On the long-term, LVAD support can be hampered by factors including pump thrombosis, ventricular arrhythmias, or mechanical device failure. However, there is limited data on the long-term durability

of current LVADs and the distribution of complications over time. In **Chapter 17** we examined the incidence, predictors, and clinical outcomes of ventricle arrhythmias. In addition, in **Chapter 18** we investigated the long-term mechanical durability of LVADs, and identified the incidence and predictors of mechanical device failure.

Finally**,** in **Chapter 19**, we provide a general overview and discuss the most important findings of this thesis. In addition, the clinical implications and future perspectives will be discussed.

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CHAPTER 2

"The new era in advanced heart failure therapy", Left ventricular assist devices.

Muslem, R. Caliskan, K. Bogers, A.J.J.C.

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Abstract

The widespread acceptance of left ventricular assist devices (LVADs) has introduced a new era in the treatment of advanced heart failure therapy. Technological advances in this area have improved overall survival and reduced morbidity of patients awaiting heart transplantation. In addition, the successful use of LVADs has resulted in an expanded population eligible for this therapy. Patient as well as device selection remains the current challenge for clinicians. This chapter will discuss the historical developments, current indications, outcomes and the main limitations of long-term LVAD therapy.

INTRODUCTION

Heart failure is a major public health problem. Approximately 6 million Americans are affected by heart failure, with an incidence of over 800.000 per year, according to the American Heart Association(1) Heart transplantation (HTX) in this population remains the gold standard.(2) However, this treatment option is limited by the paucity of donor organs.(3) On the other hand, LVADs have become an accepted treatment option for these patients as bridge to transplant (BTT) and as destination therapy (DT) in whom ineligible for HTX.(4) Technological advances and improvements in patient selection have reduced the mortality and morbidity in this high risk population. Therefore, there is little doubt that LVADs will evolve to a corner stone of the treatment for advanced heart failure.

Advanced heart failure

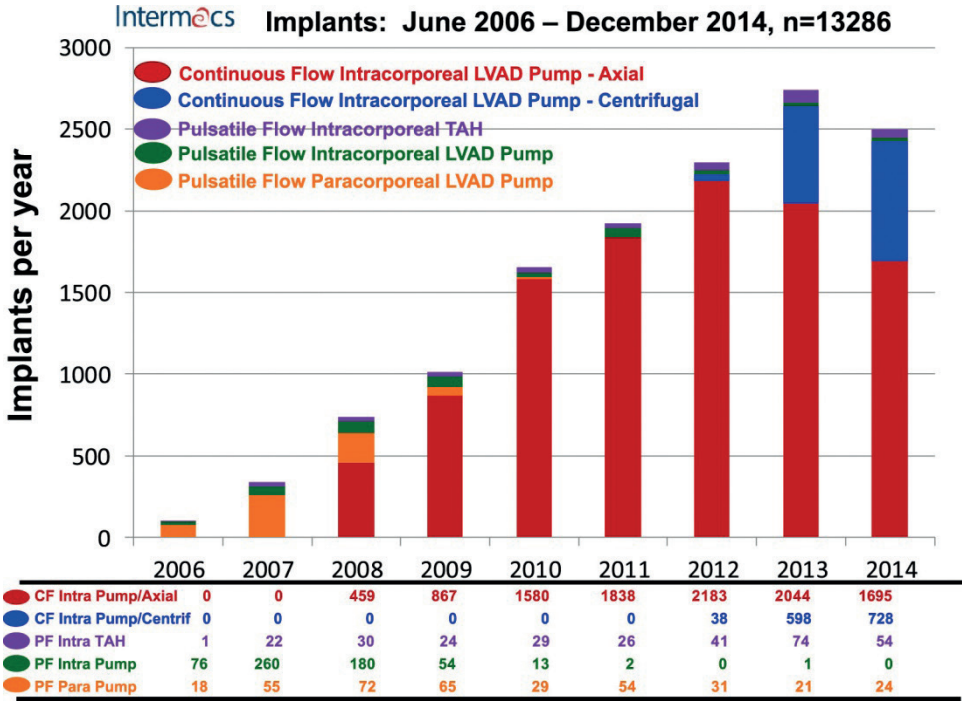
Heading for destination

Heart failure (HF) is depicted as a global epidemic, with over 30 million patients affected. (5) Despite the ongoing technical and medical improvements, the HF prevalence is still increasing,(5) as a result of improved survival after cardiovascular events and aging of the general population.(6) It is projected that the prevalence of HF will increase by approximately 25% in the upcoming two decades.(7)

The American college of Cardiology foundation and the American Heart Association both define HF as "a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood".(8) This structural and functional impairment has been associated with significant mortality and morbidity.(9) To such an extent, that HF previously has been described as a much more 'malignant' disorder than cancer.(10) HF imposes a huge economic burden, estimations of 2012 are reported to be US$108 billion spent on HF globally.(11) With the majority (86%) spent in high-income countries. The introduction and expanded use of evidence-based medical therapies have shown remarkably beneficial effects on the survival of HF patients in both The United States and Europe.(12, 13) The middle-aged individual have the most advantage.(13) Despite medical improvements, HF has a progressive course, whereby approximately 5-10% of HF patients develop end-stage heart failure. (9, 14, 15) Heart transplantation is the golden standard for those patients, however shortage of donor supply limits this option to a selected group of patients.
The mortality as well as the morbidity awaiting HTx have been reduced due to advancements in mechanical support, better understanding of biocompatibility and

the development and refinement of the LVADs. The REMATCH trial,(16) the first trial comparing first generation of implantable LVADs to optimal medical therapy reports a significant improvement in survival of 52% in the device group and 25% in the medical therapy group. Hereafter, an exponential growth of LVAD implantations has been noted (**Figure 1**).(4) The International Society for Heart Transplantation reports an increase in percentage of mechanically supported transplant recipients.(17) In addition, the number of patients implanted with a LVAD as DT has surpassed the number of BTT implants in the United States.(4)

Figure 1. Distribution of device type by year of implant



LVAD, left ventricular assist device; TAH, total artificial heart; CF, continuous flow; PF, pulsatile flow. Reprinted with permission from "Seventh INTERMACS annual report: 15,000 patients and counting" by James K. Kirklin et al., J Heart Lung Transplant. 2015 Dec; 34(12): 1495–1504. Elsevier Inc. 2017

The evolution of left ventricular assist devices

Failing towards success

The concept of mechanically supporting the circulatory system dates back as far as 1812 to Julien-Jean Cesar Le Gallois' concept of mechanical oxygenation and perfusion.(18) Although Le Gallois failed in his attempts, the objective to artificially oxygenate and perfuse organs became a prominent goal for later in the 19th century physiologist. This exploration has resulted in the first successful use of the cardiopulmonary bypass system in the year 1953.(19) Ten years later, the first clinical use of a pneumatically driven implantable LVAD was reported by Dr. Crawford.(20) Unfortunately, the patient died within a short period of time after the surgery. De-Bakey reported the first successful use of an LVAD as a bridge-to-recovery (BTR), using a paracorporeal pneumatic LVAD. (21) Initially, mechanical circulatory support devices were used for short-term support post-cardiotomy failure. However, with the increase in the availability of HTX over the following years, LVADs emerged as long-term devices used as bridge-to-transplantation (BTT).(22) The BTT strategy is intended for patients on the active waitlist for HTX who are anticipated to have a long waitlist time, increased risk of mortality or impaired quality of life. The first device introduced as BTT therapy for advanced heart failure patients was the Novacor LVAD (WorldHeart, Salt Lake City, UT, USA), in the year 1984.(23) The approval of the Novacor LVAD was soon followed by the introduction of multiple ventricular assist devices (VADs), e.g. Thoratec's HeartMate XVE, HeartMate IP, IVAD/PVAD (Thoratec Corporation, Pleasanton, CA, USA).

Despite high complication rates, the success of these devices led to the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial in 2001, which altered the course of HF treatment. The REMATCH trial reports survival of patients with advanced HF being superior in patients implanted with the first generation, pulsatile, permanent LVAD (HeartMate XVE) compared to optimal medical therapy. (16) Hereafter, the HeartMate XVE was approved for destination therapy (DT) for patients with advanced heart failure. (24) The DT strategy is intended for patients who are not eligible for HTX, though they will benefit in terms of survival or quality of life through LVAD support. The first generation devices had several limitations. These large, loud and heavy pumps were implanted in a pocket below the diaphragm, limiting it to those of larger size. (25) Furthermore, these were pneumatically driven pulsatile flow pumps with multiple moving parts, resulting in reduced device durability and an increased frequency of device replacement.(26) Finally, these devices were associated with high risk of bleeding, infections, thrombo-embolic events and device malfunction.(27)

Current devices

The second generation LVADs consisted of axial pumps, which were smaller, more silent, durable and able to provide continuous blood flow.(28) The first HeartMate II was introduced in 2007, followed by the HeartWare HVAD (HeartWare Inc., Framingham, MA, USA) in 2010. The HeartMate II is the most successful LVAD, with over 10,000 patients implanted worldwide.(4, 29) It consists of a rotary continuous axial flow pump. The inflow cannula is inserted in the left ventricle apex and the outflow graft in the ascending aorta. The HeartMate II and HeartWare HVAD are both approved for BTT in America and Europe.(30) Although, both the HeartMate II and the HeartWare HVAD are used for DT in Europe, the Heartmate II is, so far, the only device approved for DT in the USA.(30) The HeartWare HVAD, also known as left ventricular assist system (LVAS), is an advanced continuous flow device. In order to eliminate contact between the impeller and the pump, the HVAD pump utilizes a combination of passive magnetic levitation and hydrodynamic suspension.(31) The inflow and outflow graft of the HeartWare HVAD are similarly inserted as the HeartMate II and both device can provide up to 10 L/min flow. Furthermore, due to the smaller size of the second generation devices, they offer the possibility of fully intrathoracic implantation and, therefore, implantation in the smaller patients. In addition, due to its small size, the HeartWare HVAD, like the third generation devices, can be implanted through a minimally invasive approach as well as intrapericardial.(32)

The miniaturization and improvements of LVADs has continued over the past years to such an extent that one of the third generation devices, the HeartWare MVAD, is approximately one-third of the size of the HVAD pump. The MVAD and HVAD share the same properties; a continuous axial flow pump which rotates the impeller through a passive magnetic and hydrodynamic force. The MVAD is currently only available for investigational purposes. The HeartMate III, a fully magnetically levitated centrifugal continuous-flow circulatory pump, is the successor of the HeartMate II.(33) The device has a “bearingless” design and the internal surface has a specific texture in order to reduce anticoagulation requirements and thrombo-embolic events. Furthermore, the HeartMate III is incorporated with an induced pulse mode for achieving a level of pulsatility with continuous flow assistance. The HeartMate III has demonstrated the exceptional progress that is being made in the world of ventricular assist devices, with 74% of the patients being on support at 1-year follow-up without any mechanical failure or pump thrombosis.(34) LVAD therapy has now evolved from an exclusive treatment towards a solid clinical option for a large group of patients. Current challenges for clinicians are patient selection, optimal timing of implantation and management of complications.

Patient selection

Historically, LVADs were used for shorter periods of time in patients with cardiogenic shock or post-cardiotomy syndrome. A number of short-term devices, which can provide univentricular or biventricular support, have been approved for this purpose. We will focus on LVADs indicated for long-term support in patients with acute or chronic advanced HF.

Indications

An increasing number of patients are bridged to transplantation with a LVAD. The International Society for Heart Transplantation (ISHLT) reported in 2000 that 19.1% of transplant recipients were mechanically supported, increasing to 41.0% in 2012. (17) Despite these increasing numbers, there are no universally accepted criteria for LVAD implantation.(35, 36) LVAD support is often offered to patients accepted for HTX or candidates with an expected long waitlist time, developing end-organ damage or deteriorating clinically, despite optimal medical therapy. The guidelines utilize the outlined inclusion criteria in the clinical trials,(37) including the REMATCH and HeartMate II DT trial.(28, 38) In summary, these include the DT criteria in the USA, as described: patients with NYHA Class IV for at least 90 days who failed to respond to optimal medical therapy, with a left ventricular ejection fraction (LVEF) of <25%, with inotrope dependence, and a peak oxygen consumption of <14mL/kg/min, unless on an intra-aortic balloon pump, or physically unable to perform the exercise test. These criteria are similar to the ones the European Society of Cardiology (ESC) utilizes.(35) In addition, the ESC guidelines mention more concrete criteria as follows: patients with >2 months of severe symptoms despite receiving optimal medical and device therapy, and with more than one of the following criteria: (I) LVEF <25%, peak VO_2 <12 mL/kg/min, (II) ≥3 HF hospitalizations in previous 12 months without an obvious precipitating cause, (III) dependence on intravenous inotropic therapy, (IV) progressive end-organ dysfunction (worsening renal and/or hepatic function) due to reduced perfusion and not to inadequate ventricular filling pressure (PCWP ≥20 mmHg and systolic blood pressure ≤80-90 mmHg or Cardiac index ≤2 L/min/m^2), (V) absence of severe right ventricular dysfunction together with severe tricuspid regurgitation.(35) In addition to the BTT, DT and the BTR strategy, there is also a Bridge to Candidacy (BTC) strategy. Patients who are currently not eligible for HTX due to a contraindication (such as end-organ dysfunction, elevated pulmonary vascular resistance, cancer), though they might be in the future, can now be treated with a LVAD as BTC patients.

Comorbidities

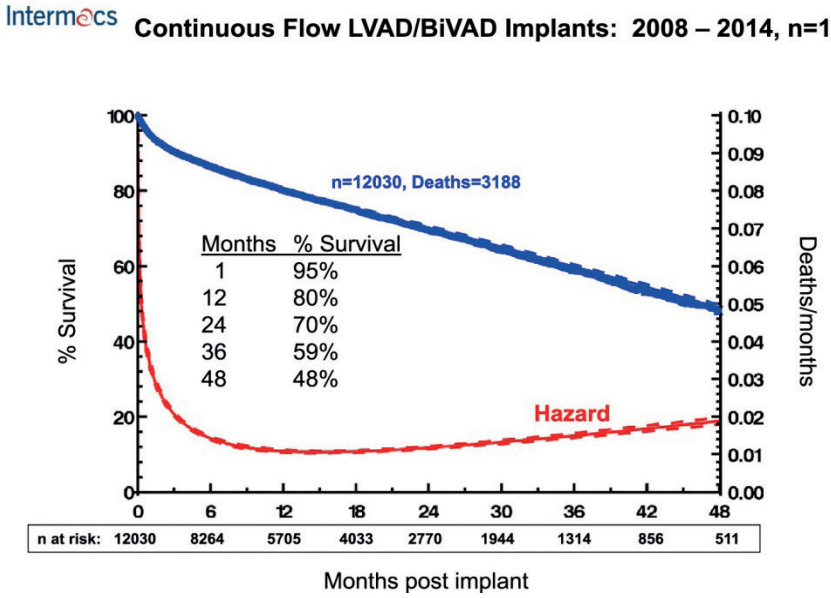
The presence of certain comorbidities can impact the outcomes post-implantation. Although advanced age is not a contraindication to LVAD therapy per se, many elderly have multiple comorbidities, frailty, or suffer from multi-organ dysfunction, which may impair their survival.(4) Selected patients age >70 years have been reported to have equal 3-years survival compared to patients age <70 years.(39) Contradicting larger studies which report older age being an independent predictor for mortality.(4) Therefore, LVAD implantation is feasible, though, in carefully selected elderly patients. Extreme body mass indices are considered relative contraindications to LVAD implantation, however, LVAD patients with obesity show similar survival rates compared to non-obese patients.(40) Renal dysfunction is highly prevalent in HF patients.(41) Although renal dysfunction is a risk factor for post-operative right heart failure and lower survival, it is not an absolute contraindication for LVAD implantation. Several studies have reported that renal function improves after LVAD implantation.(42, 43) Therefore, due to lack of discriminative ability between the cardiorenal syndrome or intrinsic kidney disease, pre-implantation renal dysfunction should be interpreted with caution. Ventricular arrhythmias (VAs) are generally tolerated by LVAD patients and it does not impact survival.(44) However, patients with left ventricle dysfunction due to refractory VAs may experience haemodynamic instability and recurrent VA post-implantation.(44, 45) Therefore, VAs should be treated before LVAD implantation. Patients with left and right heart failure (RHF) may not be eligible for solely LVAD therapy and may require biventricular mechanical support. However, no device has been approved for long-term right ventricle support and survival after biventricular support is severely impaired compared to LVAD.(4) Screening for RHF is therefore of paramount importance. Although there are no absolute post-implantation RHF prediction models, certain risk factors have been associated with the development of severe RHF post-implantation. These include elevated right atrial pressure, severe renal dysfunction (higher creatinine), liver dysfunction (higher AST, higher bilirubin), vasopressor requirement, tricuspid regurgitation and prior right ventricle dysfunction on echo.(46) An important tool for patient selection has been developed by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERAMCS). The INTERMACS score classifies patients in to a strata (level 1- critical cardiogenic shock to level 7- advanced NYHA class III), which is proportionally associated with higher hazard for mortality.(4) Although LVAD support has significantly improved survival for advanced HF patients, the use of LVADs is accompanied with a high risk for complications. These complications can prolong the waiting time for BTT patients to find a suitable organ or even preclude transplantation and result in death. Pre-operative optimization of end-organ function and appropriate patient selection are essential in order to minimize the risk for complications post-implantation.

Outcome

Survival

The REMATCH trial reports superior survival of patients with advanced HF treated with LVAD therapy compared to optimal medical treatment. The recent Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients (ROADMAP) study reports superior survival also in INTERMCAS level 4-7 patients treated with LVAD compared to patients treated with optimal medical treatment.(47) This suggest that in ambulatory HF patients LVAD therapy might be also superior compared to optimal medical treatment. The survival of LVAD patients has improved from 53% and 25% in the REMATCH trial to a rate of nearly 80% at one year and 70% at two year post-implantation (**Figure 2**) in the largest American LVAD registry (INTERMACS).(4) Lower rates have been reported by the largest European registry (EUROMACS) (73% and 63% at 1 and 2 years post-implantation).(29) The most recent results from the third generation device (HeartMate III) revealed a 1-year survival of 80%.(33) With respect to device strategy, DT patients have significant lower survival over time compared to BTT patients.(4) This is also true of lower INTERMACS classes, irrespective of device strategy.(31) Long-term outcome are scarce and remain, due to censoring of BTT patients, mainly relevant for DT patients. The post-market analysis of the HeartWare HVAD reports a 5-year survival of 59% for BTT and DT LVAD patients combined.(48) As outcomes improve with the development of new LVADs, the focus shifts towards reducing adverse events and improving quality of life during LVAD support.

Figure 2. Parametric survival curve and associated hazard function with the 95% confidence limit for survival after implantation of a continuous-flow left ventricular assist device or biventricular assist device



The number of patients at risk during each time interval is indicated below.
Reprinted with permission from "Seventh INTERMACS annual report: 15,000 patients and counting" by James K. Kirklin et al., J Heart Lung Transplant. 2015 Dec; 34(12): 1495–1504. Elsevier Inc. 2017

Morbidity

Adverse events are not uncommon in LVAD patients. Although the studies comparing LVAD with optimal medical treatment favour the initial in terms of survival, is has to be noted that the LVAD group experiences significant more adverse events.(16, 47) Re-hospitalization has also been shown to be higher in LVAD patients, ranging between 1.3 to 2.6 hospitalizations per patient-year.(28, 47) The most common complication following LVAD implantation is (i) bleeding, followed by (ii) infection, (iii) cardiac arrhythmia, (iv) respiratory failure, (v) stroke, (vi) renal dysfunction and (vii) RHF.(4) Pump thrombosis and mechanical device failure needing pump exchange are a substantial problem in LVAD devices, increasing mortality, morbidity and health care cost.(49, 50) The overall incidence of adverse events is decreasing,(4) however adverse events remain a huge burden for the patient and the caregiver. Routine clinical follow-up is necessary for early recognition and subsequent treatment. The predominant causes or modes of early and late mortality after LVAD implantation are to be neurologic events, RHF and multisystem organ failure.(4) In addition, the risk of death due to

infection rises over time.(4) Several survival models and risk scores have been developed to predict the outcome in LVAD patients. The Model for End Stage Liver Disease (MELD),(51) the DT risk score and the HeartMate II risk score are such models.(52, 53) The seventh INTERMACS reports 15000 patients, wherein age, creatinine, blood type not O and NYHA IV were identified as risk factors for late mortality.(4) Although risk scores can be useful in identifying high risk LVAD patients, they should not be relied upon as sole instruments for patient selection. Mainly because these risk scores do not provide guidance on whether the individual HF patient may benefit from LVAD therapy. Despite the high risk for adverse events, there is a linear increase in the use of LVADs. Further clinical research and innovation in device designs ought to improve patient care and prognosis over the next decades.

Myocardial recovery

Several studies have reported on the use of LVAD as bridge to recovery.(54-56) Mechanical unloading of the left ventricle leads to structural changes and reverse remodelling of the ventricle. This in turn leads to myocardial recovery, improved cardiac function and the possibility to explant the LVAD. Myocardial recovery is related to the aetiology and duration of heart failure, with higher rates of recovery being observed in patients with acute myocarditis, post-partum cardiomyopathy and post-cardiotomy heart failure.(57, 58) Although the incidence of recovery is low in large cohort studies. (4, 29) Recent studies have reported higher rates of myocardial recovery when LVAD therapy is combined with high dose neurohormonal blockade and beta-2 agonist therapy.(54, 55, 59) In addition, the use of intramyocardial injections of mesenchymal stem cells at the time of LVAD implantation showed a promising trend toward improved tolerability of weaning from LVAD.(60) LVAD therapy as bridge to recovery seems a feasible option for specific HF patients with reversible aetiologies. Models to identify BTR patients and standardized validated protocols to achieve myocardial recovery have yet to be elucidated.

CONCLUSIONS

HF is a leading cause of morbidity and mortality worldwide. LVAD therapy has become an accepted treatment option for advanced HF and is competing with HTX. The survival of LVAD patients improved over time, despite the occurrence of complications. Higher expectations are being set for the further generation of devices. It is hoped that these advancements will improve the outcomes in LVAD patients.

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CHAPTER 3

Derivation and Validation of a Novel Right-Sided Heart Failure Model After Implantation of Continuous Flow Left Ventricular Assist Devices The EUROMACS (European Registry for Patients with Mechanical Circulatory Support) Right-Sided Heart Failure Risk Score

Soliman, O. Akin, S. Muslem, R. Boersma E. Manintveld, O.C. Krabatch, T. Gummert, J.F. De By, T.M.M.H. Bogers, A.J.J.C. Zijlstra, F. Mohacsi, P. Caliskan, K. On behalf of the EUROMACS Investigators.

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Abstract

BACKGROUND: The aim of the study was to derive and validate a novel risk score for early right-sided heart failure (RHF) after left ventricular assist device implantation.

METHODS: The European Registry for Patients with Mechanical Circulatory Support (EUROMACS) was used to identify adult patients undergoing continuous-flow left ventricular assist device implantation with mainstream devices. Eligible patients (n=2988) were randomly divided into derivation (n=2000) and validation (n=988) cohorts. The primary outcome was early (<30 days) severe postoperative RHF, defined as receiving short- or long-term right- sided circulatory support, continuous inotropic support for ≥14 days, or nitric oxide ventilation for ≥48 hours. The secondary outcome was all-cause mortality and length of stay in the intensive care unit. Covariates found to be associated with RHF (exploratory univariate P<0.10) were entered into a multivariable logistic regression model. A risk score was then generated using the relative magnitude of the exponential regression model coefficients of independent predictors at the last step after checking for collinearity, likelihood ratio test, c index, and clinical weight at each step.

RESULTS: A 9.5-point risk score incorporating 5 variables (Interagency Registry for Mechanically Assisted Circulatory Support class, use of multiple inotropes, severe right ventricular dysfunction on echocardiography, ratio of right atrial/ pulmonary capillary wedge pressure, hemoglobin) was created. The mean scores in the derivation and validation cohorts were 2.7±1.9 and 2.6±2.0, respectively (P=0.32). RHF in the derivation cohort occurred in 433 patients (21.7%) after left ventricular assist device implantation and was associated with a lower 1-year (53% versus 71%; P<0.001) and 2-year (45% versus 58%; P<0.001) survival compared with patients without RHF. RHF risk ranged from 11% (low risk score 0–2) to 43.1% (high risk score >4; P<0.0001). Median intensive care unit stay was 7 days (interquartile range, 4–15 days) versus 24 days (interquartile range, 14–38 days) in patients without versus with RHF, respectively (P<0.001). The c index of the composite score was 0.70 in the derivation and 0.67 in the validation cohort. The EUROMACS-RHF risk score outperformed (P<0.0001) previously published scores and known individual echocardiographic and hemodynamic markers of RHF.

CONCLUSIONS: This novel EUROMACS-RHF risk score outperformed currently known risk scores and clinical predictors of early postoperative RHF. This novel score may be useful for tailored risk-based clinical assessment and management of patients with advanced HF evaluated for ventricular assist device therapy.

INTRODUCTION

Continuous-flow left ventricular (LV) assist devices (LVADs) are increasingly used in patients with end- stage heart failure (HF) as a bridge to transplantation, a bridge to candidacy, or destination therapy (DT). The 1-year survival reported for patients treated with continuous-flow LVAD was ≈80% and 73% in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) and the European Registry for Patients with Mechanical Circulatory Support (EUROMACS), respectively.[1,2] Early post-LVAD mortality is due partly to the development of right-sided HF (RHF) in the early post-LVAD phase.[3] The pathophysiology of RHF, however, is not well known.[4,5] Post-LVAD RHF has been reported to be between 4% and 50%,[6–10] and RHF-associated 6-month mortality was seen in up to 29% of patients receiving an LVAD.[11] Moreover, RHF has a greater impact in patients who receive LVAD as DT, for whom there is no opportunity for bailout with heart transplantation.

Management of RHF depends primarily on the tim- ing and severity of the condition. Patients with severe preoperative RHF are usually considered for biventricular support. In primary LVAD operations, post-LVAD patients with RHF often require prolonged inotropic support, nitric oxide (NO) ventilation, prolonged intensive care unit (ICU) stay, or temporarily a right ventricular (RV) assist device.

Prediction and early recognition of RHF could help in timely intervention and thus improvement of patients' outcome. Several prediction scores of RHF in patients with LVAD have been proposed.[9,11–13] Those prediction scores have mostly been based on earlier-generation LVADs and were derived from rather small populations or heterogeneous LVADs.

The objective of this study was to develop and validate a new simple score to predict early post-LVAD RHF in a large population with continuous-flow LVADs from the EUROMACS Registry.

METHODS

The Euromacs Registry

The EUROMACS is a registry of the European Association for Cardio-Thoracic Surgery. The registry gathers data for scientific analyses, aimed at improving care of patients with end-stage HF who require mechanical circulatory support.[2] All

relevant clinical, echocardiographic, hemodynamic, and laboratory parameters were prospectively collected by partici- pating sites in the EUROMACS Registry and entered into an electronic database (see Appendix I in the online-only Data Supplement for the list of the EUROMACS sites and investigators [alphabetic according to country]). The EUROMACS Registry began officially in January 1, 2011, but sites were also allowed to collect data retrospectively from patients who were already implanted before that date. A protocol for data collection and data entry, including all relevant data for the registry, was provided to all participating centers before data entry was allowed. Details of the registry and data collection are described elsewhere.[2] This study was approved by the institutional review committee of all respective participating centers, and all subjects gave informed consent.

Study Design

The present study was approved by the EUROMACS Committee. All patients (n=3897) undergoing LVAD implan- tation between January 2006 and May 2017 were identified. We excluded patients <18 years of age (n=171) and patients with primary devices (total artificial heart, single-ventricle assist device) other than LVAD (n=97). Devices other than mainstream (n=641) were also excluded (Figure 1).

Study outcome

The primary outcome was early (<30 days) severe postoperative RHF, defined as receiving short- or long-term right-sided circulatory support, continuous inotropic support for ≥14 days, or NO ventilation for ≥48 hours.[14] The secondary outcome was all-cause mortality and length of stay in the ICU. We used a hierarchy selection of the components of RHF definition in which the need for RV assist device has the strongest weight, the prolonged use of inotropes comes next, and the use of inhaled NO comes last. Of note, only a small minority were defined on the basis of the last outcome component.

Potential Predictors of RHF

We examined 82 potential preoperative predictors and car- diopulmonary bypass (CPB) time for the association with RHF. Preoperative clinical data included age, sex, body surface area, body mass index, ethnic origin and blood group type, HF etiology, New York Heart Association functional class, and INTERMACS class.[15] Comorbidity factors included diabetes mellitus, history of neurological events, carotid artery dis- ease, history of cardiac arrest, use of mechanical ventilation, use of feeding tube, implantable cardioverter-defibrillator, history of major myocardial infarction, previous cardiac surgery, renal dialysis, ultrafiltration, and positive blood

culture. Furthermore, LVAD strategies such as DT, use of an intra- aortic balloon pump, and use of extracorporeal membrane oxygenator were also included.

The preoperative use of HF medication included individual medications such as milrinone, dobutamine, dopamine, levosimendan, vasopressors, norepinephrine, and epinephrine, as well as the use of ≥3 intravenous inotropes. Amiodarone, angiotensin-converting enzyme inhibitors, β-blockers, aldosterone antagonists, loop diuretics, and anticoagulants were also examined.

Preoperative echocardiographic parameters were recorded and analyzed in accordance with published guidelines,[16,17] including tricuspid annular plane systolic excursion, RV dysfunction on visual score, LV diastolic and systolic dimensions and volumes, LV ejection fraction, and mitral, aortic, and tricuspid valvular regurgitation. Median duration of echo- cardiographic data collection before LVAD surgery was 6 days. Severity of valvular regurgitation was graded as none, trivial, mild, moderate, or severe according to published guidelines.[18,19]

Hemodynamic predictors included cardiac rhythm, heart rate, systolic and diastolic blood pressures, and Swan-Ganz recordings. The Swan-Ganz recordings included systolic, diastolic, and mean pulmonary artery (PA) pressure; right atrial (RA) pressure; transpulmonary gradient; pulmonary vascular resistance; pulmonary capillary wedge pressure (PCWP); pulmonary and systemic vascular resistance; stroke index; and cardiac index. The transpulmonary gradient was calcu- lated as the difference between the PA mean pressure and PCWP, which has a normal value of ≤12 mm Hg. Pulmonary vascular resistance is calculated as transpulmonary gradient divided by cardiac output, which has a normal value of <3 Wood units (or 240 dynes·s·cm^{-5}). The ratio of RA to PCWP and the PA pulsatility index were also calculated. The RV systolic work index was calculated as follows: RV stroke volume index×(mean PA pressure−central venous pressure)×0.0136 expressed in grams per square meter per beat. The factor 0.0136 was used to covert pressure (millimeters of mercury) into work (grams per square meter). Normal values are 5 to 10 g/m^2 per beat.

Candidate laboratory variables included serum sodium and potassium levels; renal function parameters, including blood urea nitrogen; serum creatinine levels; and liver function parameters, including alanine transaminase, aspartate transaminase, lactate dehydrogenase, total bilirubin, and serum albumin levels. In addition, white blood count, plate- lets count, hemoglobin level, and serum C-reactive protein were evaluated.

Statistical Analysis

Patient characteristics are described as means (SD) or medians (interquartile range [IQR]) for continuous variables and frequency (percentage) for categorical variables. Differences between patient groups were evaluated for continuous variables by the Student *t* tests (gaussian distribution) or nonparametric Mann-Whitney-*U* tests (nongaussian distribution) and for categorical variables with the $\chi 2$ test.

Univariate logistic regression analysis was applied to relate a broad range of preoperative parameters to the study outcome, including demographics, clinical values, comorbidities, medications, and echocardiographic, hemodynamic, and laboratory parameters. Variables with a value of $P<0.10$ entered the multivariate stage, and a logistic regression model was constructed to predict early post-LVAD RHF, applying the stepwise forward method, with a value of $P=0.05$ a modelentry criterion. All variables were checked for multicollinearity assumption using correlations, tolerance, and variable inflation factor to avoid redundancy in the prediction model. Casewise diagnostics were done, as well as a check for the Mahalonobis and Cook distances for outliers. Outliers outside 3 SD were omitted.

Dichotomization of all relevant continuous variables was performed at the 25th percentile (systolic blood pressure, diastolic blood pressure, cardiac index, PA pulsatility index, RV stroke work index, serum albumin, serum hemoglobin, and platelets), at the 50th percentile (body surface area, tricuspid annular plane systolic excursion, LV end-diastolic diameter, LV end-diastolic volume, systolic PA pressure, diastolic PA pressure, transpulmonary gradient, RA pressure, systemic vascular resistance, and RA/PCWP ratio), or at the 75th percentile (heart rate, CPB time, serum creatinine, serum alanine transaminase, serum aspartate transaminase, lactate dehydrogenase, total bilirubin, white cell count, and serum C-reactive protein). Dichotomization was based mainly on clinical relevance such as using the 25th percentile for a variable with a known association of its lower value and worse outcome and vice versa. In some cases such as the RA/PCWP ratio, we used the receiver-operating characteristic (ROC) curve area under the curve (AUC) analysis to calculate the best cutoff point for its association with RHF.

The relative magnitude of the model regression coefficients from statistically significant variables in the final multivariable model was used to calculate an individual patient's risk score for the development of post-LVAD RHF. The model discrimination abilities were evaluated by the c index of the final multivariate model. ROC curve analysis of the EUROMACS-RHF risk score was compared with published risk scores and with individual known markers of RHF. Finally, we validated the risk model in the validation

cohort. The optimal cutoff value for the EUROMACS-RHF risk score was calculated through the ROC curve and the respective Youden index.

We handled the missing data by performing multiple imputations of all relevant parameters in the entire popu lation. SPSS version 24 was used for multiple imputations using the automated function. After analyzing the patterns of missing values in the data set, we used the built-in automatic method that perform imputations based on data scanning. The automatic method scans the data and uses the monotone method if the data show a monotone pattern of missing values; otherwise, fully conditional specification is used. A 50% limit for the missing data was set to exclude variables with excessive missing data. No relevant parameter had >10% missing data. Furthermore, the vast majority of variables that were included in the final multivariable regression model had <5% missing data.

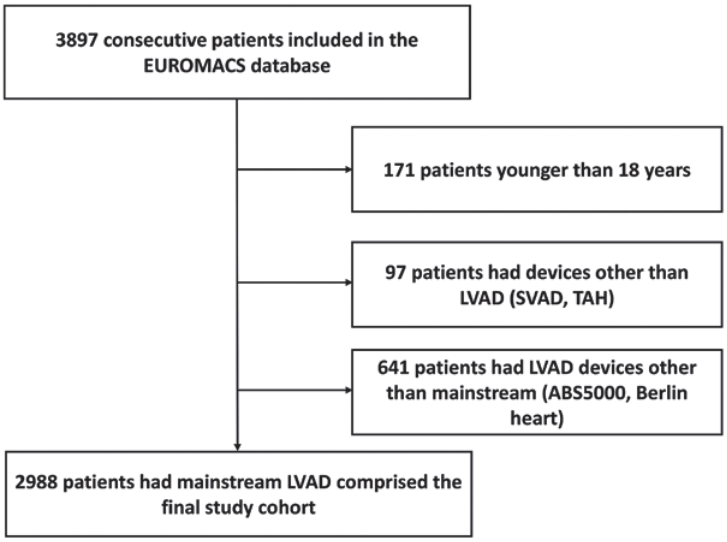
The incidence rate of post-LVAD RHF was calculated over the follow-up period. We plotted Kaplan-Meier curves for the occurrence of up to 2-year all-cause mortality according to the presence or absence of post-LVAD RHF and stratified by the EUROMACS-RHF risk score categories. The log-rank test was used to examine time to mortality differences in the Kaplan-Meier analyses. A 2-tailed value of $P<0.05$ was considered statistically significant, and all statistics were under- taken with SPSS statistics version 24 (IBM Corp, Armonk, NY) and the R-statistical package.

RESULTS

Patient Population

The final study population comprised 2988 patients with a mean age of 53±13 years and 523 women (18%). The majority were white (68%, n=2022). The main type of HF was nonischemic (66%, n=1985). The main indication for LVAD was bridge to candidacy (37%, n=1102), followed by bridge to transplantation (24.5%, n=731). HeartWare HVAD was the most used LVAD brand (50.5%, n=1509), followed by HeartMate II (40.3%, n=1204), and the minority received Heart- Mate 3 (8%, n=240).

Figure 1. Flowchart of the study population.



EUROMACS indicates European Registry for Patients With Mechanical Circulatory Support; LVAD, left ventricular assist device; SVAD, single-ventricle assist device; and TAH, total artificial heart.

Table 1. Baseline Characteristics of Patients Undergoing Left Ventricular Assist Device Implantation

Variables	Derivation Cohort (n=2000)	Validation Cohort (n=988)	*P* Value
Demographics			
Age, y	53±13	53±12	0.71
Female sex, n (%)	344 (17)	179 (18)	0.54
Body surface area, m^2	1.96±0.23	1.97±0.23	0.11
Body mass index, kg/m^2	26.0±5.1	26.3±4.9	0.18
White race, n (%)	1347 (67)	675 (68)	0.36
Nonischemic origin, n (%)	1335 (67)	650 (66)	0.60
Blood type O, n (%)	733 (37)	359 (36)	0.60
NYHA functional class, n (%)			0.93
III	635 (32)	299 (30)	
IV	805 (40)	404 (41)	
INTERMACS class, n (%)			0.57
1	222 (11)	111 (11)	
2	630 (32)	297 (30)	
3	513 (26)	263 (27)	
≥4	559 (28)	275 (28)	
IABP, n (%)	198 (10)	76 (8)	0.06
VA-ECMO, n (%)	178 (9)	95 (10)	0.52
Intravenous medication, n (%)			
Use of vasopressors	410 (21)	208 (21)	0.71
Use of ≥3 inotropes	239 (12)	119 (12)	0.93
Laboratory values			
Serum creatinine, mg/dL	1.20 (0.95–1.60)	1.20 (0.92–1.60)	0.69
AST, U/L	32 (22–63)	32 (22–77)	0.54
Total bilirubin, mg/dL	1.30 (0.82–2.09)	1.30 (0.79–2.10)	0.46
Albumin, g/dL	3.6 (3.0–4.2)	3.6 (2.9–4.2)	0.75
Hemoglobin, g/dL	12.2 (10.5–13.9)	11.7 (10.1–13.6)	0.78
Hemodynamic			
RA pressure, mm Hg	11 (7–15)	9 (6–15)	0.11
PCWP, mm Hg	25 (16–30)	22 (17–28)	0.91
PAPI	2.55 (1.50–3.75)	2.88 (1.65–4.25)	0.29
PAP, mean, mm Hg	35 (29–43)	34 (27–44)	0.58
RVSWI, g/m^2 per beat	6.7 (4.1–10.2)	6.8 (4.5–9.6)	0.91
RA/PCWP	0.48 (0.31–0.78)	0.42 (0.29–0.67)	0.12
Echocardiographic			
Severe RV dysfunction, n (%)	192 (10)	91 (9)	0.83
TAPSE, mm	14 (12–16)	15 (13–17)	0.59
Severe tricuspid regurgitation, n (%)	278 (14)	113 (11)	0.29
Severe mitral regurgitation, n (%)	218 (11)	134 (14)	0.97
LVEF grade <20%, n (%)	718 (36)	405 (41)	0.80

All continuous values are presented in mean±SD unless stated otherwise or presented as median (IQR).AST indicates serum aspartate transaminase; IABP, intra-aortic balloon pump; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support (for INTERMACS classes, see text for details); LV, left ventricular; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PAPI, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial; RV, right ventricular; RVSWI, right ventricular stroke work index; TAPSE, tricuspid annular plane systolic excursion; and VA-ECMO, veno-arterial extracorporeal membrane oxygenator.

Derivation and Validation Cohorts

The final study patients were randomly divided into derivation (67%, n=2000) and validation (33%, n=988) cohorts. Both cohorts were well matched in key base- line and operative characteristics (Tables 1 and 2). Mainstream device brands were HeartMate II (40% [n=800] versus 41% [n=404]), HeartMate 3 (9% [n=169] versus 7% [n=71]) (both manufactured by Thoratec Corp, now Abbott Laboratory, Pleasanton, CA), and HeartWare HVAD System (50% [n=1007] versus 51% [n=502]) (manufactured by HeartWare Corp, now Medtronic, Framingham, MA) in the derivation and validation co- horts, respectively (P=NS). The 3 main indications for LVAD were as bridge to transplantation (25% [n=490] versus 24% [n=241]), bridge to candidacy (38% [n=754] versus 35% [n=348]), and DT (17% [n=333] versus 17% [n=170]) in the derivation and validation cohorts, respectively (P=NS; Table 2).

Early Post-LVAD RHF

LVAD implantation was complicated by RHF in 433 patients (21.7%) in the early 30-day post-LVAD period. Diagnosis of RHF was based on the need for postoperative mechanical RV support in 141 patients (7.1%), the need for prolonged postoperative inotropic support in 327 (16.4%), and the need for prolonged NO ventilation in 17 (1%). Median time to RV assist device implantation was 1 day (IQR, 0–5 days). Components of RHF definition are shown on Figure I in the online-only Data Supplement.

Logistic Regression Analysis for Early Post-LVAD RHF

Exploratory univariate logistic regression analysis for early post-LVAD RHF yielded 58 potential covariates (P<10) of 83 tested variables, which are listed in Tables 3 and 4, as clinical, medication, laboratory, echocardiographic, hemodynamic, and operative co- variates (Table 5). Covariates were eliminated because of reasons mentioned above such as collinearity, resulting in 21 variables in the multivariable model. Significant predictors of early post-LVAD RHF in the derivation cohort included INTERMACS class, need for multiple intravenous inotropes, severe RV dysfunction, RA/PCWP ratio, and hemoglobin. The final model has a c index of 0.70 in the derivation cohort.

Table 2. Operative Characteristics of Patients Undergoing Left Ventricular Assist Device Implantation

Operative characteristics	Derivation Cohort (n=2000)	Validation Cohort (n=988)	*P* Value
Main LVAD strategy, n (%)			0.20
BTT (on the list)	490 (25)	241 (24)	
BTC (possible BTT)	754 (38)	348 (35)	
DT	333 (17)	170 (17)	
LVAD device brand, n (%)			0.68
HeartMate II	800 (40)	404 (41)	
HeartMate 3	169 (9)	71 (7)	
Heart Ware HVAD	1007 (50)	502 (51)	
Surgical duration			
CPB time, min	85 (65–115)	85 (63–115)	0.89
Surgery time, min	212 (175–298)	220 (180–286)	0.55

BTC indicates bridge to candidacy; BTT, bridge to transplantation; CPB, cardiopulmonary bypass; DT, destination therapy; and LVAD, left ventricular assist device.

Patients in INTERMACS class 1 through 3 had a 27% risk of RHF versus 12% risk for those in INTERMACS class 4 through 7 (P<0.001). Additionally, patients on ≥3 inotropic agents in the preoperative period had 42% risk of RHF versus 22% risk for those on ≤2 inotropic agents (P<0.001). In terms of semi-quantitative echocardiographic assessment, patients with severe RV dysfunction on visual score had 50% risk of RHF versus 23% for those with better RV function. Furthermore, patients with an RA/PCWP ratio >0.54 had 27.1% risk of RHF versus 16.1% for those with lower ratio (P<0.001). Finally, patients with hemoglobin ≤10 g/dL had 35% risk of RHF versus 23% risk for those with hemoglobin >10 g/dL (P<0.001).

EUROMACS-RHF Risk Score

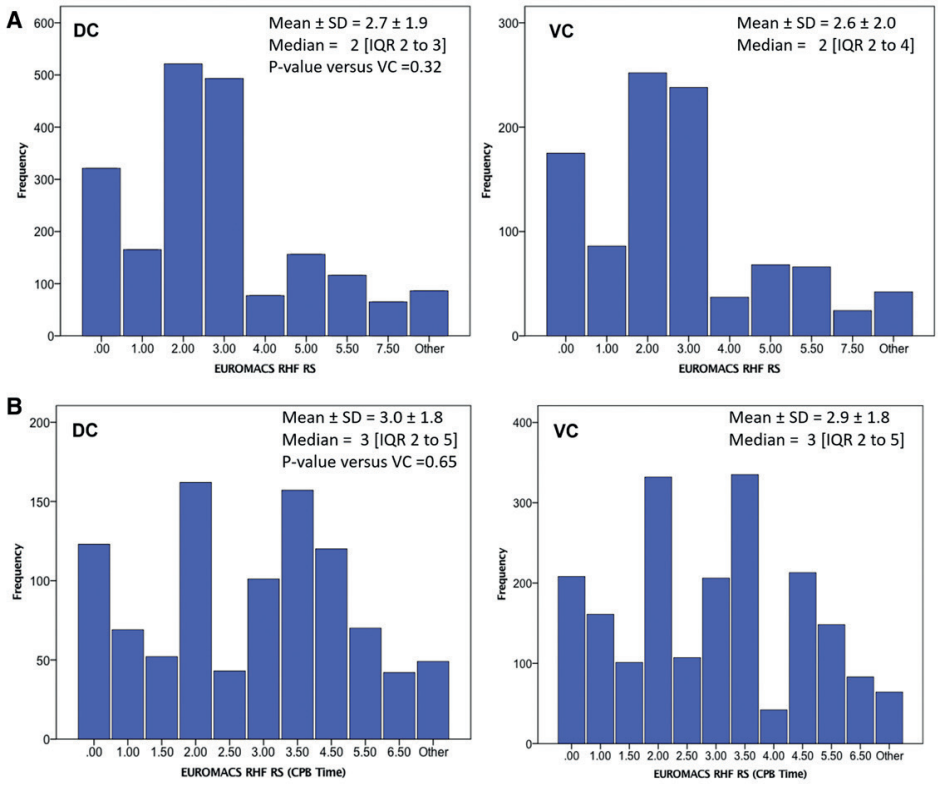
With the use of the relative magnitude of the coefficient of regression in the multivariable model in the derivation cohort, points were assigned to the 5 covariates (Table 6). Values were rounded to the nearest integer to simplify the calculation of the composite risk score in routine clinical practice. A total 9.5-point score was generated.

Predictive Power of the EUROMACS-RHF Risk Score in the Derivation Cohort

The mean score in the derivation cohort was 2.7±1.9, ranging from 0 to 9.5 (Figure 2A). Likewise, data on the operative EUROMACS-RHF risk score are shown in Figure 2B. The predicted rate of RHF was significant (P for linear trend <0.001) increased from 11% for a score of 0 to 2 to 43.1% for a score of >4 (Figure 3A). Sensitivity, specificity , positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative

predictive value according to the EUROMACS-RHF risk score are presented in Table I in the online only Data Supplement, and those of the operative EUROMACS-RHF risk score are presented in Table II in the online-only Data Supplement.

Figure 2. Distribution of the European Registry for Patients With Mechanical Circulatory Support



(EUROMACS) right-sided heart failure (RHF) risk score (A) and the postoperative EUROMACS-RHF risk score (B) in the derivation cohort (DC) and the validation cohort (VC). CPB indicates cardiopulmonary bypass; IQR, interquartile range; and RS, risk score.

Table 3. Exploratory Unadjusted Univariable Analysis for Outcome of Early Postoperative Right-Sided Heart Failure After Left Ventricular Assist Device Implantation in the Derivation Cohort

Covariate	Univariable Analysis OR (95% CI)	*P* Value
Demographic and clinical characteristics		
Age (per 1-y increase)	1.005 (0.996–1.013)	0.27
Female sex	1.032 (0.780–1.366)	0.83
Body surface area (per 1-m^2 unit increase)	1.501 (0.933–2.414)	0.09
Body mass index (per 1-kg/m^2 unit increase)	1.018 (0.997–1.039)	0.10
Race (white vs others)	3.785 (2.829- 5.064)	<0.001
Heart failure origin (non-ischemic vs ischemic)	0.986 (0.787–1.236)	0.91
NYHA functional class (IV vs III)	1.677 (1.354–2.078)	<0.001
INTERMACS (1–3 vs 4–7)	2.969 (2.218–3.974)	<0.001
Blood type O (yes vs no)	1.153 (0.926–1.435)	0.20
Diabetes mellitus (yes vs no)	1.142 (0.505–3.055)	0.64
History of CVA (yes vs no)	0.966 (0.665–1.404)	0.86
Symptomatic PVD (yes vs no)	1.173 (0.742–1.856)	0.50
History of cardiac arrest (yes vs no)	2.240 (1.494–3.357)	<0.001
Use of mechanical ventilation (yes vs no)	2.457 (1.803–3.348)	<0.001
Use of feeding tube (yes vs no)	3.485 (2.382–5.099)	<0.001
ICD implantation (yes vs no)	1.054 (0.848–1.310)	0.63
COPD (yes vs no)	0.757 (0.529–1.083)	0.13
Prior major MI (yes vs no)	1.536 (1.536- 2.076)	0.005
Prior cardiac surgery (yes vs no)	1.501 (1.102- 2.045)	0.01
Renal replacement therapy (yes vs no)	4.191 (2.427–7.237)	<0.001
Ultrafiltration (yes vs no)	2.332 (1.497–3.635)	<0.001
Intra-aortic balloon pump (yes vs no)	1.983 (1.450–2.712)	<0.001
VA-ECMO (yes vs no)	3.565 (2.596–4.896)	<0.001
Medication use		
Use of vasopressors	3.026 (2.373–3.858)	<0.001
≥3 Intravenous inotropes	2.601 (1.953–3.466)	<0.001
Amiodarone	1.787 (1.415–2.257)	<0.001
ACE inhibitors	0.772 (0.611–0.975)	0.03
β-Blockers	0.521 (0.410–0.662)	<0.001
Aldosterone antagonists	0.611 (0.477–0.783)	<0.001
Loop diuretics	1.529 (1.067–2.193)	0.02
Anticoagulant therapy	3.040 (2.284–4.045)	<0.001

ACE indicates angiotensin-converting enzyme; CI, confident interval; COPD, chronic obstructive pulmonary disease; CVA, cerebral vascular accident; ICD, implantable cardioverter-defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; MI, myocardial infarction; NYHA, New York Heart Association; OR, odds ratio; PVD, peripheral vascular disease; and VA-ECMO, veno-arterial extracorporeal membrane oxygenator

Validation of the EUROMACS-RHF Risk Sore

The mean score in the validation cohort was 2.6±2.0, ranging from 0 to 8.5 (Figure 2A). The predicted rate of RHF was similar and significant (P<0.001 for linear trend) increased from 12.5% for a score of 0 to 2 to a 42.4% for a score of >4 (Figure 3B). The c index was 0.70 in the derivation versus 0.67 in the validation cohort (Figure II in the online-only Data Supplement). The Hosmer-Lemeshow goodness-of fit P value was 0.61 in the validation cohort, which reflects an appropriate fit for the data in this cohort. A comparison of the ROC curve of the EUROMACSRHF risk score with a modified score that includes CPB time >100 minutes and 2 previously published RHF scores derived from continuous-flow LVAD populations demonstrated higher AUC for the EUROMACS-RHF risk score compared with the Kormos et al[11] (P<0.001) score and the Central Venous Pressure >15 mmHg, Severe RV Dysfunction, Preoperative Intubation, Severe Tricuspid Tegurgitation, Tachycardia[21] (P<0.001) score (Table 7). AUC was similar for the EUROMACS-RHF and modified postoperative EUROMACS-RHF scores (P=0.41). ROC curve comparison with other individual known hemodynamic and echocardiographic markers of RV failure demonstrated the highest AUC for the EUROMACS-RHF score (all P<0.001).

Table 4. Exploratory Unadjusted Univariable Analysis for Outcome of Early Postoperative Right- Sided Heart Failure After Left Ventricular Assist Device Implantation in the Derivation Cohort Using Laboratory, Echocardiographic, and Hemodynamic Characteristics

Covariate	Univariable Analysis OR (95%CI)	*P* value
Laboratory characteristics		
Sodium	1.010 (1.002–1.018)	0.01
Potassium	1.237 (1.075–1.425)	0.003
BUN	1.004 (1.002–1.007)	0.001
Creatinine (per 1-unit increase)	1.407 (1.213–1.632)	<0.001
Creatinine >2.3 mg/dL (75%)	2.373 (1.662–3.389)	<0.001
AST >37 U/L	2.091 (1.661–2.633)	<0.001
ALT >72 IU/L	2.400 (1.736–3.319)	<0.001
LDH (>445 vs ≤445 U/L)	1.554 (1.173–2.058)	0.002
Total bilirubin >2 mg/dL	1.620 (1.260–2.082)	<0.001
Albumin (<3.3 vs ≥3.3 g/dL)	1.107 (0.809–1.515)	0.52
WBCs	1.050 (1.026–1.074)	<0.001
Hemoglobin ≤10 g/dL	1.628 (1.281–2.070)	<0.001
Platelets	0.996 (0.996–0.998)	<0.001
HCO_3 (per 1-mEq/dL increase)	0.996 (0.963–1.030)	0.80
Echocardiographic characteristics		
Severe RV dysfunction	3.535 (2.578–4.848)	<0.001
LV end-diastolic diameter (per 1-mm increase)	1.003 (1.000–1.006)	0.04
LV end-systolic diameter (per 1-mm increase)	1.004 (1.000–1.009)	0.05

LV end-diastolic volume (per 1-mL increase)	0.998 (0.995–1.001)	0.11
LV end-systolic volume (per 1-mL increase)	0.998 (0.994–1.002)	0.36
TAPSE (≤14 vs >14 mm)	1.241 (0.847–1.817)	0.27
LV ejection fraction (<20% vs >20%)	1.780 (1.391–2.278)	<0.001
Severe vs less severe mitral regurgitation	0.550 (0.389–0.777)	0.001
Severe vs less severe tricuspid regurgitation	0.917 (0.666–1.262)	0.59
Severe vs less severe aortic regurgitation	4.888 (1.483–16.114)	0.009
Hemodynamic characteristics		
Non-sinus vs sinus rhythm	1.202 (0.957–1.508)	0.11
Heart rate (≥96 vs <96 bpm)	1.445 (1.141–1.832)	0.002
Systolic blood pressure (≤85 vs >85 mm Hg)	1.623 (1.202–2.190)	0.002
Diastolic blood pressure (≤52 vs >52 mm Hg)	1.629 (1.199–2.213)	0.002
Cardiac index (≤1.2 vs >1.2 L/min)	0.817 (0.482–1.387)	0.46
PAP, systolic (≥53 vs <53 mm Hg)	1.220 (0.919–1.620)	0.17
PAP, diastolic (≥27 vs <27 mm Hg)	0.818 (0.617–1.085)	0.16
PAP, mean (≥35 vs <35 mm Hg)	0.967 (0.730–1.282)	0.82
RA pressure (≥11 vs <11 mm Hg)	1.729 (1.279–2.338)	0.001
PCWP (≥12 vs <12 mm Hg)	1.086 (0.649–1.819)	0.75
SVR (≥1488 vs <1488 mm Hg)	0.712 (0.479–1.059)	0.09
TPG (≥12 vs <12 mm Hg)	1.043 (0.758–1.436)	0.80
PVR (≥3.3 vs <3.3 mm Hg)	0.163 (0.027–0.983)	0.05
PAPI (≤1.6 vs >1.6)	2.175 (1.584–2.988)	<0.001
RVSWI (≤4.6 vs >4.6 g/m^2 per beat)	1.481 (1.051–2.086)	0.03
RA/PCWP (>0.54 vs ≤0.54)	2.075 (1.383–3.112)	<0.001

ALT indicates alanine transaminase; AST, serum aspartate transaminase; BUN, blood urea nitrogen; CI, confidence interval; HCO, bicarbonates; LDH, lactate dehydrogenase; LV, left ventricular; OR, odds ratio; PAP, pulmonary artery pressure; PAPI, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial; RV, right ventricular; RVSWI, right ventricular stroke work index; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TPG, transpulmonary gradient; and WBC, white blood cell.

EUROMACS-RHF Risk Score and All-Cause Mortality

Cumulative survival in the postoperative 24 months was higher in patients without RHF at the 6-month (79% versus 61%), 12-month (71% versus 53%), 18-month (65% versus 49%), and 24-month (58% versus 45%) follow-up compared with patients with RHF (log-rank test, P<0.001; Figure 4A). Likewise, cumulative survival in the postoperative 24 months was at the 6-month (80% versus 66% versus 56%), 12-month (73% versus 60% versus 48%), 18-month (66% versus 54% versus 46%), and 24-month (61% versus 46% versus 43%) follow-up patients with low, intermediate, and high EUROMACS-RHF risk score, respectively (log-rank test, P<0.001; Figure 4B). Multiorgan failure and sepsis were the most frequent primary causes of death, in particular in patients with RHF. Other common causes of death were cerebrovascular accidents, bleeding, and cardiopulmonary failure (Figure 5). Multiorgan failure was seen in 50% of patients who died with sepsis as
the primary cause of death.

Table 5. Exploratory Unadjusted Univariable Analysis of Operative Characteristics for Outcome of Early Postoperative Right-Sided Heart Failure After Left Ventricular Assist Device Implantation in the Derivation Cohort

Covariate	Univariable Analysis OR (95%CI)	*P* Value
LVAD strategy		
BTT vs other	0.441 (0.334–0.583)	<0.001
LVAD device brand		
HeartMate II	1 (Reference)	
HeartMate III	1.734 (1.364–2.204)	<0.001
HeartWare HVAD	1.803 (1.211–2.684)	0.004
Surgical duration		
CPB time (per 10-min increase)	1.041 (1.020–1.062)	<0.001
CPB time >100 min (yes vs no)	1.544 (1.235–1.929)	<0.001
Surgery time (per 10-min increase)	1.020 (1.010–1.030)	<0.001
Surgery time >215 min (yes vs no)	1.377 (1.098–1.726)	0.006

BTT indicates bridge to transplantation; CI, confidence interval; CPB, cardiopulmonary bypass; LVAD, left ventricular assist device; and OR, odds ratio. For manufacturers of the LVADs, see text.

EUROMACS-RHF Risk Score and ICU Stay Duration

Median ICU stay was 7 days (IQR, 4–15 days) versus 24 days (IQR, 14–38 days) in patients without versus with RHF (P<0.001). Likewise, the ICU stay was linearly increased from 6 days (IQR, 4–13 days) versus 13 days (IQR, 6–25 days) versus 19 days (IQR, 9–31 days) in the EU- ROMACS-RHF score low, intermediate, and high risk category, respectively (P<0.001 for trend; Figure 6A and 6B).

Subgroup Analysis

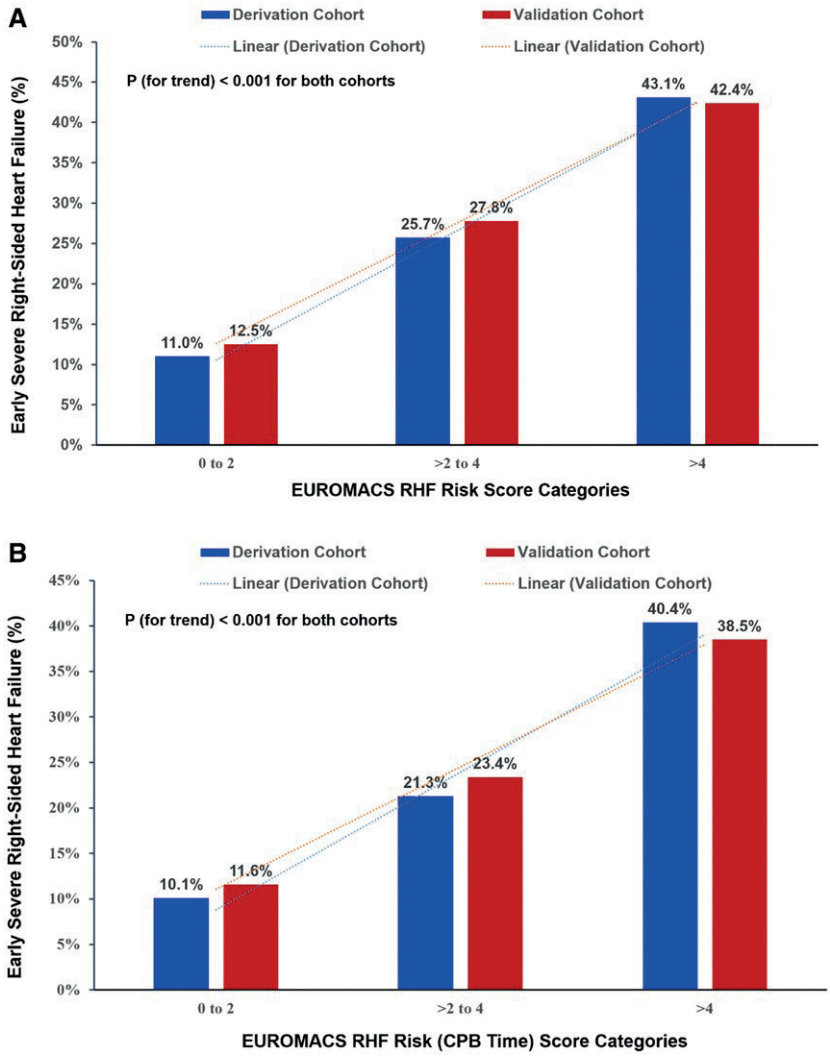
We performed subgroup analysis to test the predictive value of the EUROMACS-RHF risk score in patient populations treated with different LVADs. The incidence of RHF was 15.5% versus 24.1% versus 24.9% for patients treated with HeartMate II, HeartWare, and Heart- Mate 3, respectively (P<0.001 for trend; Table III in the online-only Data Supplement). In the derivation cohort, the AUC of the EUROMACS-RHF risk score was 0.75, 1.66 1.66, and 0.60 in the HeartMate II, HeartWare, and HeartMate 3 populations, respectively (Table IV in the online-only Data Supplement). Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value ac- cording to the EUROMACS-RHF risk score in the device brand subgroups are presented on Tables V–VII in the online-only Data Supplement.

Table 6. European Registry for Patients with Mechanical Circulatory Support Multivariable Model for Right- Sided Heart Failure Derived From the Derivation Cohort

Variables	OR	Lower 95% CI	Upper 95% CI	χ^2 Value (χ^2=56.9)	Coefficients	Score
Preoperative model						
RA/PCWP >0.54	2.075	1.383	3.112	12.441	0.730	2
Hemoglobin ≤10 g/dL	1.611	1.037	2.502	4.506	0.477	1
Multiple intravenous inotropes	3.197	1.851	5.524	17.355	1.162	2.5
INTERMACS class 1–3	2.903	1.723	4.893	16.014	1.066	2
Severe RV dysfunction*	2.055	1.183	3.57	6.534	0.720	2
Postoperative RHF model after adding CPB time						
RA/PCWP >0.54	2.151	1.412	3.278	12.699	0.766	1
Hemoglobin ≤10 g/dL	2.609	1.544	4.409	12.839	0.959	1.5
Multiple intravenous inotropes	3.013	1.712	5.302	14.635	1.103	2
INTERMACS Class 1–3	3.393	1.946	5.915	18.561	1.222	2
Severe RV dysfunction*	2.099	1.193	3.694	6.618	0.742	1
CPB time >100 min	2.032	1.296	3.184	9.562	0.709	1

CI indicates confidence interval; CPB, cardiopulmonary bypass; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; OR, odds ratio; PCWP, pulmonary capillary wedge pressure; RA, right atrial; RHF, right-sided heart failure; and RV, right ventricular.
See Appendix I in the online-only Data Supplement for an explanation of how to use this table to predict an individual patient's risk of RHF. Examples of risk score calculation using the model presented in Table 6.
The following example illustrates the use of Table 6 to calculate the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) RHF risk score of early postoperative RHF after LVAD implantation in individual patients: Consider a patient who was referred to left ventricular assist device implantation who has INTERMACS class 3, has severe RV dysfunction on echocardiography, has an RA/PCWP ratio of 0.55 on Swan-Ganz catheter, is on 3 inotropic support, and has a hemoglobin of 10 g/dL. Using the EUROMACS-RHF risk score of RHF model coefficients in Table 6, this patient's preoperative risk score for RHF is the highest because he scored all points (2+1+2.5+2+2=9.5) according to the prediction model. Furthermore, if this patient had CPB time >100 min, this patient's postoperative risk score for RHF with a similar formula will be 8.5 points.
*Semiquantitative assessment of RV systolic function on echocardiography.

Figure 3. Frequency of early right- sided heart failure (RHF) stratified by (A) the European Registry for Patients With Mechanical Circulatory Support (EUROMACS) RHF risk score and (B) the postoperative EUROMACS-RHF risk score categories.



CPB indicates cardiopulmonary bypass.

Discussion

This study is a multicenter study that includes the largest European population of patients who received currently used continuous-flow LVADs, evaluating the risk for RHF. Early severe RHF occurs in one fifth of patients with LVAD in this study and is associated with high mor tality, up to 29% in some series.11 We developed and validated a novel EUROMACS-RHF risk score using a simple 5-item scoring system for the prediction of early RHF after continuous-flow LVAD implantation.

RHF is an important and frequent complication in the early postoperative period after LVAD implantation.[3] In prior studies, rates of post-LVAD RHF have ranged between 4% and 50%.[6–10] This wide range of reported RHF incidence is due partly to the lack of a universal definition of post-LVAD RHF across the literature. In primary LVAD implantation, severe RHF requires either mechanical RV support via RV assist device or extracorporeal membrane oxygenator, pharmacological support via the use of continuous intravenous inotropic support, or pulmonary vasodilators such as inhaled NO. Those 3 components are used in the RHF definition in this study, which is in line with the INTERMACS definition of severe RHF.[14]

Risk stratification of patients undergoing LVAD implantation is important to identify candidates for RV support, to provide timely pharmacological intervention, and thus to improve patients' outcome. This could be important in the decision process, preoperative preparation, and timing of surgery. This should be reflected also in the in- formed consent of the patients and the family, especially in patients receiving DT in whom there is no opportunity for bailout with heart transplantation. Few risk-scoring systems have been described to predict post-LVAD RHF. However, those studies are limited by small sample size, single centers, and the heterogeneous nature of LVADs. Kormos et al11 and Atluri et al[21] investigated multivariate predictors of RHF in 484 and 167 patients, respectively, who received continuous-flow LVAD. However, the studies included only HeartMate II devices, disregarding other currently used mainstream LVADs such as HeartWare or the new HeartMate 3. In our study, the EUROMACS-RHF risk score was derived from a population of 2000 patients treated with mainstream LVADs.

Table 7. Performance Characteristics of Clinical Risk Prediction Scores and Individual Predictors for Right- Sided Heart Failure in the Derivation Cohort

	C Index (95% CI)	*P* Value
Risk scores		
EUROMACS-RHF risk score*	0.70 (0.67–0.73)	1 (Reference)
Postoperative EUROMACS-RHF risk score†	0.71 (0.68–0.74)	0.41
Kormos et al[11] score	0.58 (0.54–0.61)	<0.0001
CRITT score[21]	0.63 (0.60–0.66)	<0.0001
Individual hemodynamic parameters		
RA pressure, mm Hg	0.60 (0.55–0.65)	<0.0001
TPG, mm Hg	0.55 (0.50–0.61)	<0.0001
PVR, woods unit	0.56 (0.51–0.61)	<0.0001
RVSWI, g/m^2 per beat	0.52 (0.47–0.56)	<0.0001
Severe RV dysfunction	0.57 (0.52–0.61)	<0.0001

CI indicates confidence interval; EUROMACS, European Registry for Patients with Mechanical Circulatory Support; CI, confidence interval; CRITT, Central Venous Pressure >15 mmHg, Severe RV Dysfunction, Preoperative Intubation, Severe Tricuspid Tegurgitation, Tachycardia; PVR, pulmonary vascular resistance; RA, right atrial; RHF, right-sided heart failure; RV, right ventricular; RVSWI, right ventricular stroke work index; and TPG, transpulmonary gradient.

*P value is EUROMACS-RHF risk score versus other scores or individual parameters.

The preoperative score includes need of ≥3 inotropic agents, Interagency Registry for Mechanically Assisted Circulatory Support class 1 through 3, severe RV dysfunction on semiquantitative echocardiography, RA/pulmonary capillary wedge pressure ratio >0.54, and hemoglobin ≤10 g/dL.

†The modifi postoperative score includes cardiopulmonary bypass time >100 minutes and the 5 preoperative components of the EUROMACS-RHF risk score.

Risk Score Components

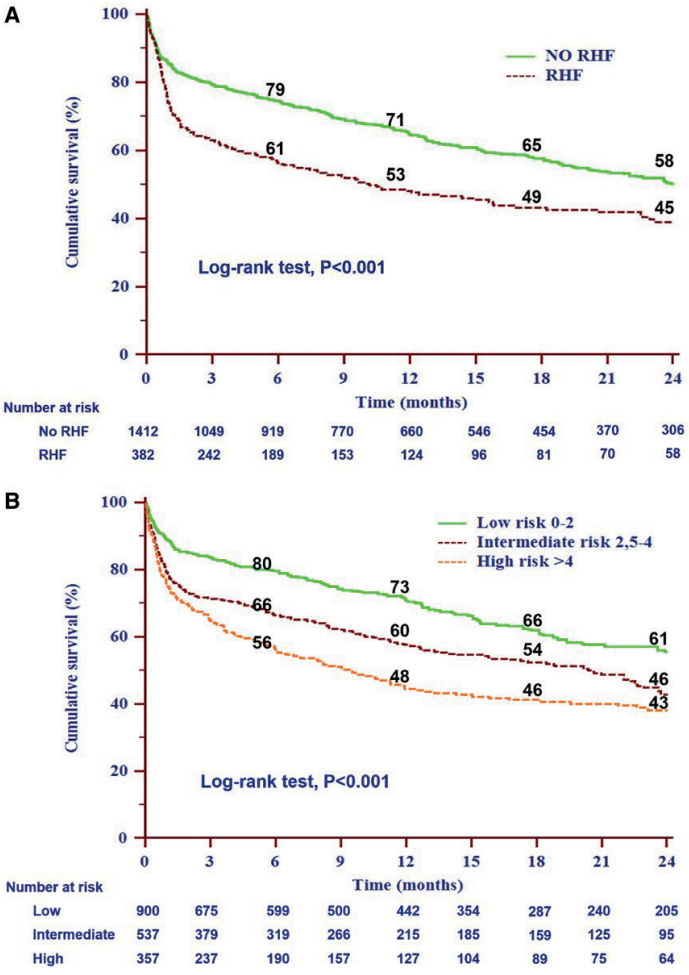
The EUROMACS-RHF risk score is composed of severe RV dysfunction (2 points), ratio of RA/PCWP ≥0.54 (2 points), advanced INTERMACS class 1 through 3 (2 points), need for ≥3 intravenous inotropes (2.5 points), and hemoglobin ≤10 g/dL (1 point).

Because of the multifactorial nature of RHF after LVAD,[4,5] 83 parameters of clinical relevance are examined in this study for possible association with early post-LVAD RHF.

Patients with preoperative severe RV dysfunction on echocardiography have an ≈2-fold increase in the incidence of evident RHF in the early post-LVAD period compared with those without severe RV dysfunction. Echocardiographic assessment of RV

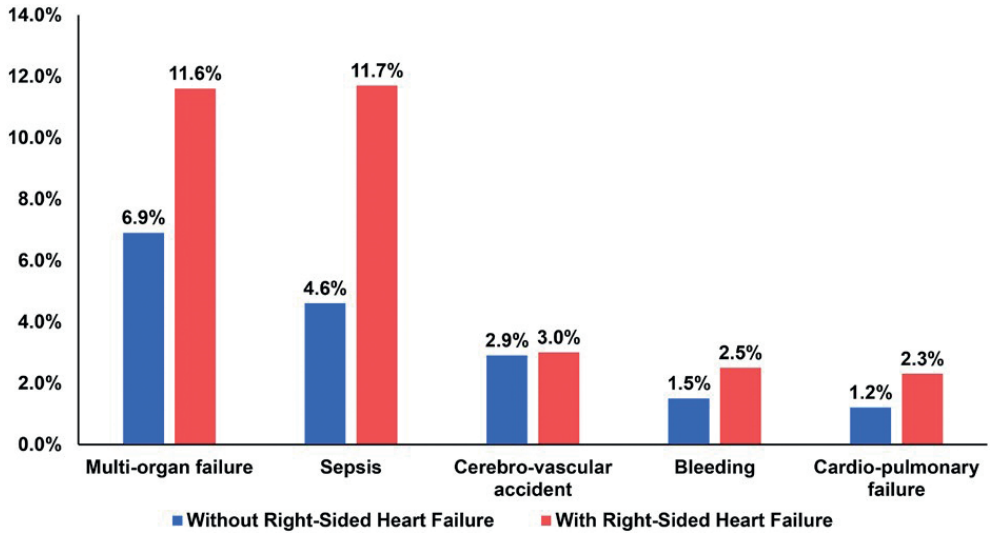
function is readily available to assess RV contractility at bedside. Of note, there is a potential high variability in visual scoring of RV function on a scale from normal to severe; therefore, a quantitative marker such as RV fractional area change or the recently introduced iRotate echocardiography[22] can accurately quantify RV function. Nevertheless, visual assessment of a severe RV dysfunction on echocardiography in daily practice is, in our expert opinion, simple but robust.

Figure 4. Two-year Kaplan-Meier estimates of death resulting from any cause stratified by (A) right-sided heart failure (RHF) and (B) the European Registry for Patients With Mechanical Circulatory Support (EUROMACS) RHF risk score strata.



Likewise, an elevated RA pressure in relation to pulmonary capillary wedge pressure shows a similar association with clinically evident early post-LVAD RHF. On the one hand, high RA pressure is a sign of RV failure; on the other hand, it could be a sign of volume overload. Aggressive diuresis, usually with inotropic support, and sometimes ultrafiltration, in case of ineffective diuresis, should be tried in patients with volume overload to achieve optimal euvolemic state.

Figure 5. Five main known causes of death in the derivation cohort.



In the EUROMACS database, as well as in other published data, most patients who are receiving an LVAD have some degree of RV dysfunction. In this study, 88% of patients have mild or more impairment of RV systolic function. However, RV dysfunction could remain silent as a result of a limited RV preload. RV preload has to increase immediately after LVAD to match increased LVAD workload. Furthermore, LV unloading tends to cause a leftward shift of the interventricular septum, therefore compromising effective RV contractility and aggravating the already impaired RV systolic function. The interventricular septum contributes to at least one third of the RV contractility.[23] Therefore, it is important to optimize LVAD flow to prevent excessive LV suction to avoid a vicious circle of RV function impairment.

The need for multiple inotropes in the preoperative period in this study was seen in 12% of patients and is associated with an ≈2-fold higher risk of RHF than in patients with ≤2 inotropes. The use of multiple inotropes has the greatest weight in predicting post-LVAD RHF among all 5 predictors. This might reflect in fact, the biventricular origin of hemodynamic instability. Despite the dire need for inotropic support in those patients, excess or prolonged use of intravenous inotropic agents could have a detrimental effect on the myocardial energetics and metabolism.[24] In this study, an average of 1.5 inotropes were used per patient. Moreover, dobutamine was the most (53%) used inotropic agent (Figure III in the online- only Data Supplement). On the other hand, 12% of patients received levosimendan. Levosimendan is currently available in the European Union and various countries but remains investigational in the United States.[25] Levosimendan could prevents the development of RHF and improves contractility in established pressure overload–induced RV failure in the preclinical setting.[26] However, the short- and long-term outcomes of those inotropic agents have not been demonstrated in randomized clinical trials. Further studies are needed to test their role in early intensive management of RHF. As a potential example, a randomized study could be designed to test a temporary RV circulatory support in patients who are on or require

>2 inotropes before LVAD implantation. In this proposed trial, patients could be randomized to an early temporary mechanical circulatory support or to escalating the number or doses of inotropic or vasopressor support.

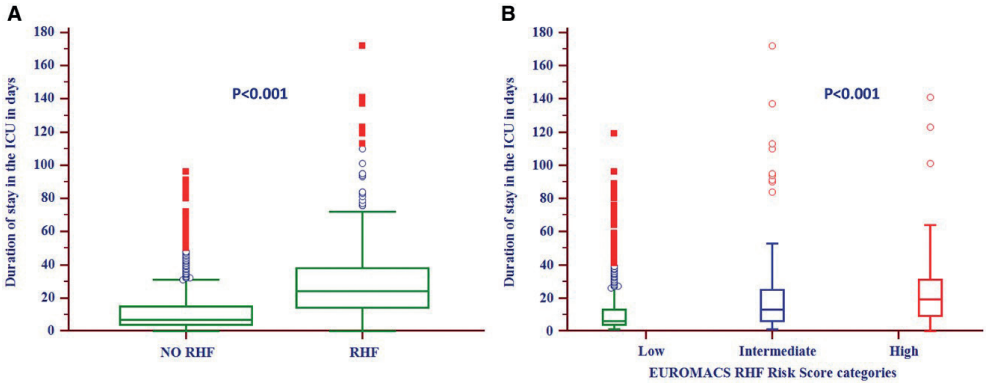
An advanced INTERMACS score is found in this study to be associated with an ≈5-fold increase in the incidence of evident RHF in the early post-LVAD period compared with those with less advanced INTERMACS class before LVAD. This finding is in line with published data from the INTERMACS database.[27] We categorized patients according to the modifiers of the INTERMACS profile definition into a group of hospitalized patients on intravenous inotropes or temporary circulatory support (class 1 through 3) and a second group including "frequent flyers" (class 4) and less sick (class 5 through 7) patients.[28] The fi group rep- resents sicker and decompensating patients who suffer severe hemodynamic derangement, threatening secondary organ (renal, hepatic) failure, compared with ambulatory, less sick, or relatively stable patients in the second group.

Finally, anemia as demonstrated with hemoglobin ≤10 g/dL was associated with 1.5-fold increase in post- LVAD RHF. Anemia is found in about one third of patients with chronic HF. The most common causes are chronic renal failure and iron deficiency. It could be speculated that anemia could play a role in triggering RHF in the setting of already vulnerable RV, and multiple blood transfusions in the early

postoperative period could play a role in the pathophysiology of RHF in those patients. Blood transfusion–associated circulatory overload has been associated with an increased risk of RHF.[29,30] Furthermore, the already vulnerable RV is very likely to be challenged by borderline perfusion and thus impaired oxygen delivery resulting from anemia. On the other hand, anemia might reflect the severity of the underlying multiorgan failure. Impaired nutrition, malabsorption (resulting from congestion and abnormal production of hepcidin), and reduced intracellular uptake of iron have been reported as causes of anemia in patients with HF.[31,32]

In this study, we examined CPB time and LVAD surgery time in the prediction model of early post-LVAD RHF. Both parameters are significantly associated with the incidence of early post-LVAD RHF; however, a CPB time >100 minutes remained significant in the final model. It is associated with a 2-fold increase in the incidence of early post-LVAD RHF, but it did not improve much the AUC of the composite score.

Figure 6. Median intensive care unit (ICU) stay in days stratified by (A) right-sided heart failure (RHF) and (B) the European Registry for Patients With Mechanical Circulatory Support (EUROMACS) RHF risk score strata.



Clinical Implications

In this study, RHF was associated with increased early and late mortality. Most common causes of death were multiorgan failure, sepsis and cerebrovascular accidents. Patients with RHF died more often as a result of multiorgan failure and sepsis. Those patients have severe systemic congestion and tissue hypoperfusion from under filling of the LVAD. Moreover, patients with RHF had a longer ICU stay. It has been reported that ≈50% of ICU patients had a nosocomial infection and are therefore at a high risk for sepsis.[33] Furthermore, intestinal source of infection is a known source of sepsis in patients with multiorgan failure in the ICU as a result of translocation of gut flora into bloodstream.

In this study, the composite 5-point score predicts early post-LVAD RHF, with graded risk for both RHF and death seen with higher scores. The score is simple, validated, and composed of widely available and clinically relevant variables derived from a multivariate logistic regression analysis. In contrast, the more complex recently published machine prediction bayesian models[34] from the INTERMACS database consisted of 33 to 34 preoperative variables.

Our model variable selection was based on biological plausibility and knowledge of experts in the field to avoid redundancy in the model and unexplained or unexpected predictors. This risk score includes intuitive predictors that are known to be relevant in the pathophysiology of early post-LVAD RHF and its associated mortality. Furthermore, the final model of the EUROMACS-RHF risk score was validated in a separate validation cohort.

This novel scoring system may provide clinicians with opportunity for tailored risk decision making before, during, or early after LVAD surgery. A patient with a high risk score may require perioperative optimization of RV support, biventricular assist device, or total heart support. Optimization of RV support could be achieved via reduction of preload, afterload, and RV contractility support. Aggressive diuresis, early use of pulmonary vasodilators such as NO, phosphodiesterase type 5 inhibitors, or early RV mechanical support may be indicated. Furthermore, measures such as tricuspid valve repair could be considered. Those patients would benefit from early recognition in terms of not only less need for prolonged ICU stay but also, more important, better survival. However, those corrective measures remain speculative and should be tested in some prospective randomized trials to prove their usefulness.

Limitations

Caution should be taken in general against using solely a risk model for clinical decision making without prospective validation in randomized clinical trials. There are several limitations that should be acknowledged in this study. First, a validation ROC of 0.67 of this risk score is not ideal. It could be due to the fact that onlyvery few patients were assigned to some high scores. The score could perform better in a larger population in which more patients are represented in all score levels. Another limitation is the semiquantitative assessment of RV function on echocardiography. A quantitative and preferably advanced RV assessment such strain analysis could improve the score performance. On the other hand, the widely used scores, also simple, such as $CHADS_2$-VASC[35] and even Pooled Cohort equations36 are not different from this score. Furthermore, it may not be appropriate to generalize our findings to other types of VAD not included in the present analysis. However, the 3 LVADs in this study represent the mainstream LVADs used worldwide. An important limitation of this study is the retrospective analysis of the EUROMACS database. However, data on MCS devices are derived largely from registry databases. A prospective randomized study such as in patients with cardiogenic shock on multiple inotropes, which had the highest weight among RHF predictors, is warranted to prove the predictive value of this risk score.

Furthermore, there are potential confounders that might not be accounted for here. In addition, potential mechanisms of RHF that take place exclusively after LVAD surgery such as an immediate increase in RV work to match the increase in LVAD flow are not considered. Missing data were present for many of our variables. However, we addressed this issue by using multiple imputations, and no variables were missing in >90% of cases. Medication dosages were not considered in the present model. Pharmacological interventions could alter many biological markers such as hepatic and renal functional biomarkers, thus affecting the meaning of those markers in a prediction model. Of note, only hemoglobin appeared in the final step of the EUROMACSRHF risk model.

CONCLUSIONS

We developed and validated the EUROMACS-RHF risk score, a simple 5-item scoring system for the prediction of early RHF and RHF-associated mortality after continuous-flow LVAD implantation. The score identified high-risk patients in whom timely optimization or mechanical RV support may be considered to reduce RHF-related mortality and morbidity.

Acknowledgments

All aspects of manuscript writing and revision were carried out by the coauthors. The authors have full access to the entire content. For a full list of contributors to EUROMACS, please see the Appendix I in the online-only Data Supplement.

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CHAPTER 4

Response to Letter Regarding Article "Derivation and Validation of a Novel Right-Sided Heart Failure Model After Implantation of Continuous Flow Left Ventricular Assist Devices: The EUROMACS (European Registry for Patients with Mechanical Circulatory Support) Right-Sided Heart Failure Risk Score"

Soliman, O. Akin, S. Muslem, R. Caliskan, K.

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In Response:

We thank Dr Aloia for his kind words and greatly appreciate his comments on our recent publication in Circulation.1 In addition, we praise his recent work reviewing the literature about right ventricular failure (RVF).2 We comment here on the issues raised.

It is widely accepted that the consequences of RVF after left ventricular assist device (LVAD) implantation are devastating. RVF has been stated as the Achilles heel of LVAD therapy.

Therefore, understanding the underlying mechanisms, triggers, and causes is vital to improve the early, and probably the late, outcome after LVAD implantation. During our work, we encountered a basic dilemma in finding an appropriate definition and classification of RVF, given that there is no universal accepted definition of RVF after LVAD. We used the (modified) INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) definition used in the EUROMACS (European Registry for Patients with Mechanical Circulatory Support) registry, which included a hard end-point (receiving right-sided mechanical circulatory support) and derivatives of RVF (inotropic support for ≥14 days, nitric oxide ventilation for ≥48 hours). Although this includes most of the spectrum of RVF, we believe that the next step is to appropriately define and classify RVF as a complex clinical syndrome of right-sided heart failure (RHF). The best definition of the RHF syndrome should probably include a composite of the clinical features (symptoms and signs), hemodynamics, and echocardiographic or imaging evidence of RVF.

We agree with Dr Aloia that the current literature is mostly heterogeneous, retrospective, and single-center experiences without "careful and precise" standardized diagnostic criteria. Therefore, we recently set up a multicenter longitudinal study, the EuroEchoVAD Study,3 aiming at clinical, hemodynamic, and echocardiographic quantification and prediction of the time course of right ventricular function to ultimately redefine RHF and to identify optimal management strategies after LVAD implantation. In addition, the lack of stratification for the cause of heart failure will also be tackled by this study, given the as much as comprising extensive imaging before LVAD implantation. The EuroEchoVAD study is expected to enroll 600 patients at >30 sites across Europe and Asia, awaiting the first enrollment in June 2018.

Our EUROMACS RHF risk score1 confirms the importance of stratifying for INTERMACS classes because patients with INTERMACS classes 1 through 3 have an independent odds ratio of 2.9 for early postoperative RHF. This group represents sicker

patients with severe hemodynamic derangement, biventricular origin of hemodynamic instability, and excess or prolonged use of intravenous inotropic agents associated with detrimental effects on the myocardial energetics and metabolism (albeit it will also reflect the dire need for inotropic support for very sick patients). In those patients with advanced INTERMACS classes and high EUROMACS RHF Risk Score, preoperative right ventricular optimization should be pursued, and early right ventricular mechanical circulatory support should be considered. Nonetheless, the preload, afterload, and contractility of the right ventricle should first
be optimized.

Finally, as Dr Aloia concluded, with the EUROMACS RHF Risk Score, better prediction of the need of RVAD should improve the optimal timing of an RVAD or biventricular assist device. We also believe in the credo "better prevent than cure," that is, "better elective than rescue therapy."

Refrences

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CHAPTER 5

Left Ventricular Assist Device Implantation With and Without Concomitant Tricuspid Valve Surgery: a Systematic Review and meta-analysis

Muslem, R.* Veen, K.M.* Soliman, O.I. Caliskan, K. Kolff, M.E.A. Dousma, D. Manintveld, O.C. Birim, O. Bogers, A.J.J.C. Takkenberg, J. J.M.

*contributed equally to this study

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Abstract

OBJECTIVES: Moderate-to-severe tricuspid regurgitation is common in end-stage heart disease and is associated with an impaired survival after left ventricular assist device (LVAD) surgery. Controversy remains whether concomitant tricuspid valve surgery (TVS) during LVAD implantation is beneficial. We aimed to provide a contemporary overview of outcomes in patients who underwent LVAD surgery with or without concomitant TVS.

METHODS: A systematic literature search was performed for articles published between January 2005 and March 2017. Studies comparing patients undergoing isolated LVAD implantation and LVAD + TVS were included. Early outcomes were pooled in risk ratios using random effects models, and late survival was visualized by a pooled Kaplan–Meier curve.

RESULTS: Eight publications were included in the meta-analysis, including 562 undergoing isolated LVAD implantation and 303 patients with LVAD + TVS. Patients undergoing LVAD + TVS had a higher tricuspid regurgitation grade, central venous pressure and bilirubin levels at baseline and were more often female. We found no significant differences in early mortality and late mortality, early right ventricular failure and late right ventricular failure, acute kidney failure, early right ventricular assist device implantation or length of hospital stay. Cardiopulmonary bypass time was longer in patients undergoing additional TVS [mean difference +35 min 95% confidence interval (16–55), P=0.001].

CONCLUSIONS: Adding TVS during LVAD implantation is not associated with worse outcome. Adding TVS, nevertheless, may be beneficial, as baseline characteristics of patients undergoing LVAD + TVS were suggestive of a more progressive underlying disease, but with comparable short-term outcome and long-term outcome with patients undergoing isolated LVAD.

INTRODUCTION

The favorable effects on survival of left ventricular assist devices (LVADs) as bridge-to-transplant and destination therapy for patients with end-stage heart failure are well established [1–3]. In approximately half of the patients undergoing LVAD implantation, moderate or severe tricuspid regurgitation (TR) is detected on echocardiography [2]. Usually, TR is secondary to changes in the right ventricular dimensions in response to a higher afterload due to left-sided heart disease [3]. Moderate-to-severe TR is associated with an impaired survival after LVAD surgery [2]. Significant TR has also been found to predict right ventricular failure (RVF) after LVAD implantation [2, 4], suggesting that concomitant treatment of the TR could be beneficial for these patients. However, spontaneous reduction in TR after LVAD implantation alone is also reported [5, 6]. Moreover, the sample size is small in most studies addressing this topic. Controversy remains whether TR should be surgically corrected at the time of LVAD implantation. Hence, some centres opt for an aggressive approach, whereas others are more conservative. Therefore, we conducted a systematic search of the literature to provide a comprehensive overview of outcomes in patients undergoing LVAD + tricuspid valve surgery (TVS) when compared with patient undergoing isolated LVAD implantation using a meta-analysis.

METHODS

Search strategy

To establish an overview of reported outcome, a systematic literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was conducted [7]. Search terms were developed in collaboration with the librarian in our centre. On 29 March 2017, Embase, MEDLINE, Web of Science, Cochrane and Google Scholar were searched for articles published after January 2005 (search terms are provided in Supplementary Material, Text S1). Inclusion and exclusion criteria were defined a priori. Randomized controlled trials and observational studies concerning adult patients undergoing LVAD implantation comparing patients with and without concomitant TVS were included. Studies with less than 20 patients or abstracts, poster and conference summaries were excluded. Reasons to exclude studies with less than 20 patients were that these studies were most likely early experiential series and do not reflect the general population and, in case of a small population, chances of zero events rise, resulting in a numerical problem in pooling the data. We did not include posters, abstracts, etc. because these formats did not undergo extensive peer reviewing. In the case of overlapping study populations, the study with the most patients-years of follow-

up were selected. Exceptions were made for studies that reported on more outcomes of interest. Two researchers (M.E.A.K. and D.D.) independently reviewed abstracts and full texts in an unblended standardized manner. In case of disagreement to include a study, an agreement was negotiated. References in selected articles were independently cross-checked by 2 researchers (M.E.A.K. and D.D.) for other relevant studies.

Data extraction

Study design, year of surgery period and follow-up (patient-years and mean) were documented. If follow-up was not provided, patient-years were calculated by multiplying the number of patients with the mean follow-up (or median, if the mean is not provided). The following baseline characteristics were extracted: mean age at operation, gender, aetiology (ischaemic and non-ischaemic), TR grade (none, mild, moderate and severe), creatinine, central venous pressure (CVP), mean systolic pulmonary artery pressure, type of tricuspid valve repair (suture, ring), prosthesis type in case of tricuspid valve replacement and concomitant valvular procedures. In addition, the following outcomes were documented: early mortality (in-hospital or <30-day mortality), mean cardiopulmonary bypass (CPB) time, length of intensive care stay, hospital stay, early RVF, acute kidney failure, late mortality and late RVF. The individual study definitions were used to define the outcomes. Microsoft Office Excel 2011 (Microsoft Corp., Redmond, WA, USA) was used for data extraction. Data were independently extracted by 2 authors (M.E.A.K. and D.D.). The Newcastle–Ottawa scale was used to assess methodological quality of the studies [8], and the ROBINS-I tool was used to assess bias in the individual outcomes [9].

Statistical analyses

Log-transformed inverse variance weighted pooled baseline characteristics were calculated. Risk ratios (RRs) and mean differences (MDs) were used to compare baseline characteristics with the use of a fixed effects model, as our goal was to compute comparisons for the identified population and not to generalize to other populations and analyses of baseline characteristics similar in most cases [10]. A P-value <0.05 was considered statistically significant. Random effects models using the Der Simonian and Laird method were used to pool outcomes [11]. RRs were used for dichotomous data and MDs for continuous data. The Cochrane Q statistic and I 2 were used to assess heterogeneity. Microsoft Excel 2010 was used to calculate linearized occurrence rate and risk. Comprehensive Meta-Analysis (CMA) v2.2.064 (Biostat, Engelwood, NY, USA) was used to calculate the pooled outcomes and to generate forest and funnel plots. Patient survival was visualized in a pooled Kaplan–Meier (KM) curve derived from the originally published KM curves using the method described by Guyot et al. [12]. The Engauge Digitizer v10.0 [13] was used to create a list of co-ordinates of the

KM curve, and an algorithm written in the R language was employed (Version 3.3.3) to reconstruct the original patient data. Thereafter, GraphPad Prism version 7.00 for Windows (GraphPad Software, La Jolla, CA USA) was used to plot the pooled KM curve. The reconstructed data were used to obtain hazard ratios (HRs) of late mortality in TVS + LVAD group versus isolated LVAD implantation by univariate cox regression. Thereafter, the HRs were pooled using CMA.

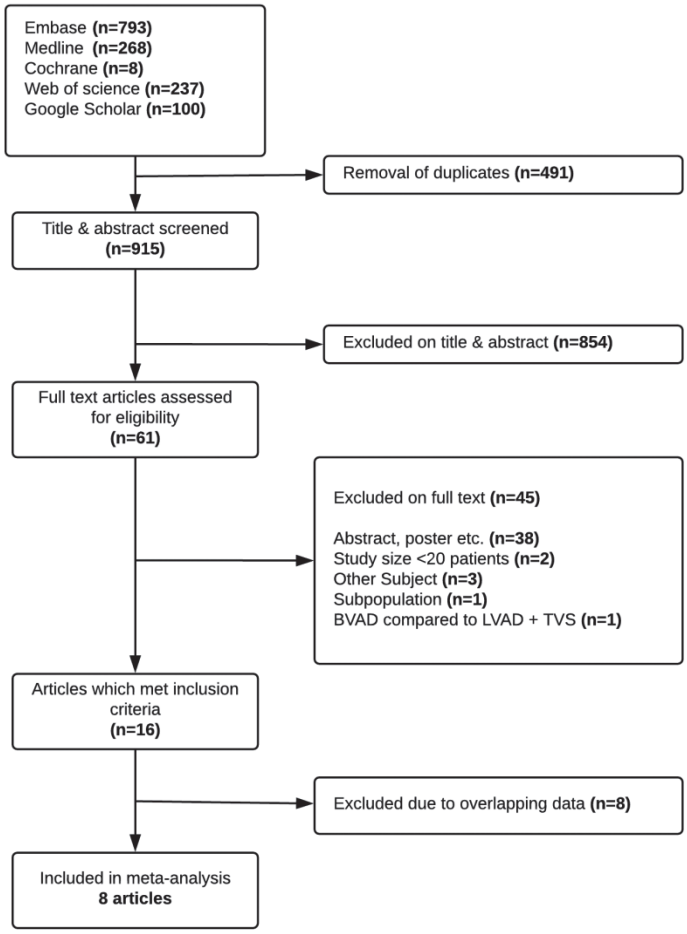
RESULTS

The search of the literature resulted in 915 studies, of which 16 articles met the inclusion criteria. Eight articles had to be excluded due to overlapping data, resulting in 8 inclusions for the meta-analysis (Fig. 1). References are presented in Supplementary Material, Text S2 (References S1–S9). In 1 study, we made an exception of the general rule to include the study with the most patient-years. Piacentino et al. in 2012 (Supplementary Material, Reference S7) reported on more outcomes of interest when compared with Piacentino et al. in 2011 (Supplementary Material, Reference S8), hence we included Piacentino et al. (Supplementary Material, Reference S7). However, in the 2011 study Piacentino et al. (Supplementary Material, Reference S8) reported on the KM curves, and therefore, this study was included in the KM analyses. The meta-analysis included 562 patients in the LVAD group and 303 in the LVAD + TVS group, of which 392 patients in the LVAD group had reported late follow-up time encompassing 697 patient-years when compared with 247 in the LVAD + TVS group who had reported late follow-up time encompassing 351 patient-years. Baseline and procedural characteristics of all individual studies are shown in Table 1. All studies were observational. Most studies lost points on comparability using the Newcastle–Ottawa scale, and most outcomes are at serious risk of bias due to confounding according the ROBINS-I tool (Supplementary Material, Tables S1–S4).

Baseline characteristics

Pooled baseline and procedural characteristics are shown in Table 2. Patients who underwent LVAD + TVS were more often female, had a higher TR grade, and higher CVP and bilirubin levels. In patients who underwent TVS, the tricuspid valve was repaired in 93.2% of patients; a ring repair was performed in 87% and a suture repair in 13%. Tricuspid valve replacement—all biological prostheses—was conducted in 6.8% of patients.

Figure 1. Flowchart of included studies in the meta-analysis. One of the 8 articles excluded due to overlapping contained a Kaplan–Meier curve which could be used in analysis, without including the article in other analysis. LVAD: left ventricular assist device; RVAD: right ventricular assist device; TVS: tricuspid valve surgery.

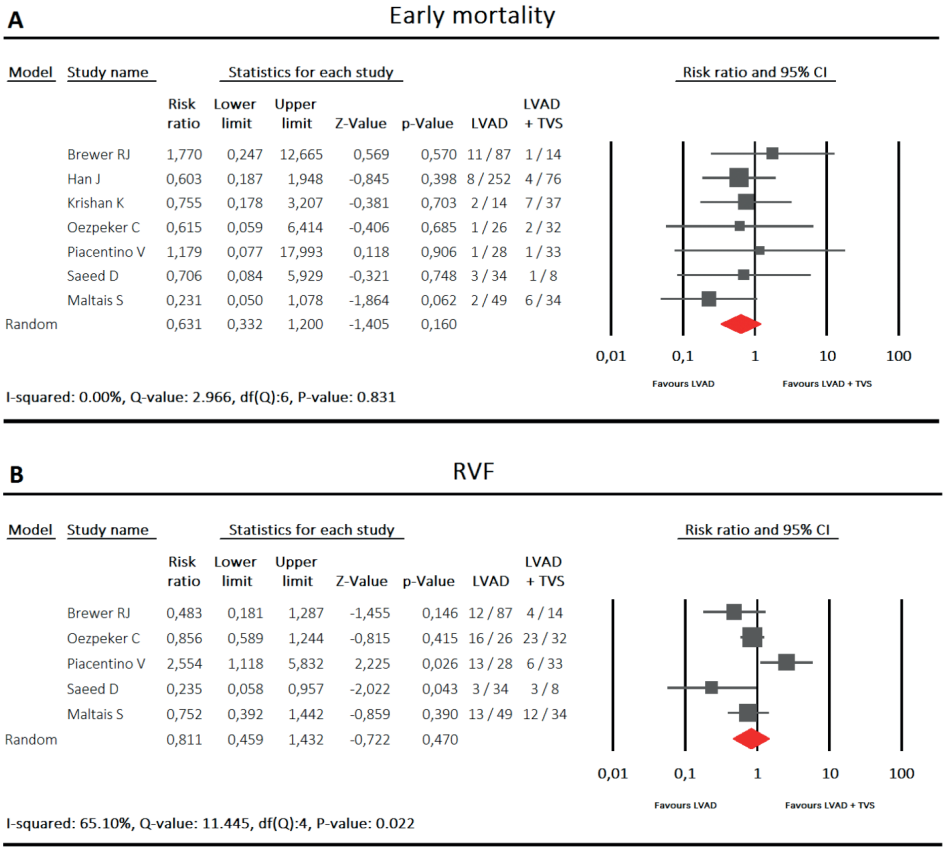


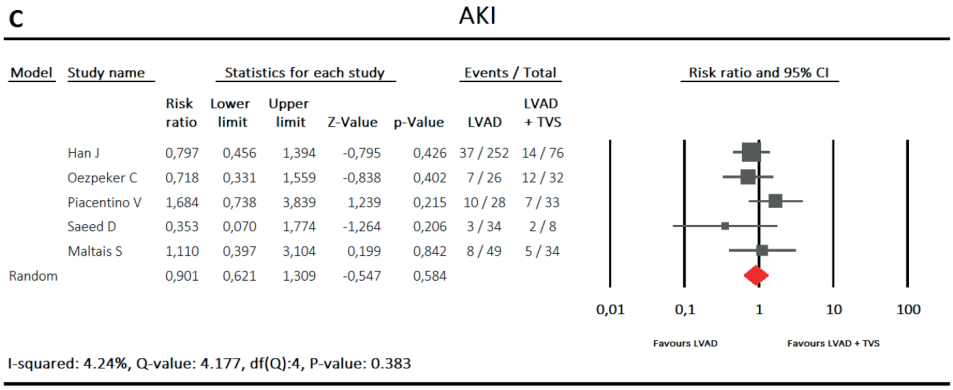
Early outcomes

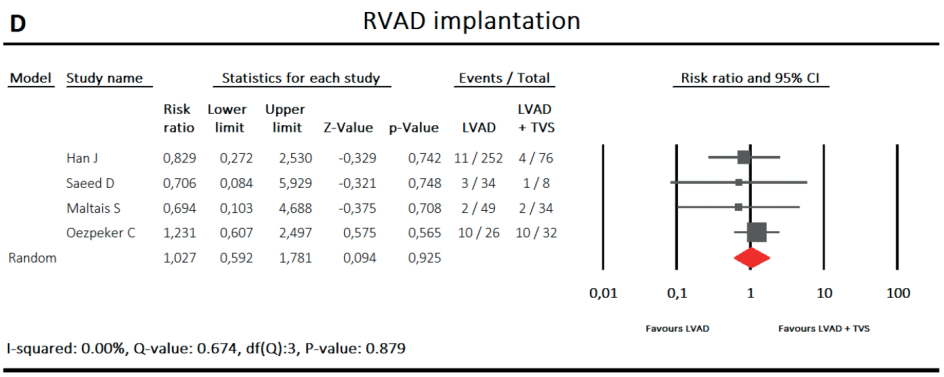
A forest plot containing the individual and pooled RRs for early mortality, RVF, acute kidney failure and RVAD implantation is presented in Fig. 2A–D. None of the pooled RRs were statistically significant between patients receiving LVAD + TVS and isolated LVAD. Three studies reported CPB time and length of hospital stay (Supplementary Material, References S3, S5 and S6). CPB time was longer in patients undergoing TVS

[129 min, 95% confidence interval (CI) (114–126)] when compared with isolated LVAD surgery [91 min, 95% CI (81–101)] with a pooled MD of 35 min [95% CI (16–55), P =0.001] with I 2 = 83.0%, Q-value 11.734 and P-value 0.003 (Supplementary Material, Fig. S1). Length of hospital stay did not differ significantly between patients undergoing LVAD + TVS [35 days, 95% CI (20–49)] and isolated LVAD [41 days, 95% CI (20–61)] with a pooled MD of 4 days, 95% CI (-1to 10), P = 0.126, with I 2 = 83.0%, Q-value 11.734 and P-value 0.003 (Supplementary Material, Fig. S2). Additionally, 2 other studies (Supplementary Material, References S4 and S7), which did not report data in extractable format, did not find significant differences in hospital stay (P < 0.05). Funnel plots are presented in Supplementary Material, Figs S4–S9. Leave-one-out analysis did not change the significance of all outcomes.

Figure 2. (A–D) Forest plots of early mortality (A), Right ventricular failure (RVF) (B), Acute kidney injury (AKI) (C) and Right ventricualr assist device (RVAD) implantation (D). CI: confidence interval; LVAD: left ventricular assist device; RR: risk ratio; TVS: tricuspid valve surgery.







Late outcomes

Seven studies (Supplementary Material, References S1–S3, S5, S6, S8 and S9) reported KM curves that could be pooled. The pooled KM curves showed comparable late survival in patients undergoing LVAD implantation with and without concomitant TVS (Fig. 3). The 1-, 2- and 3-year survival rates are 77.9 ± 3.0%, 71.8 ± 3.9% and 57.3 ± 6.0% in the LVAD + TVS group and 82.2 ± 1.9%, 73.3 ± 2.6% and 58.1 ± 5.2% in the LVAD group, respectively. Pooled HR of concomitant TVS for late mortality is 1.13 [95% CI (0.68–1.90), P-value= 0.634] with I 2 = 47.1%, Q-value 11.344 and P-value 0.078 (Supplementary Material, Fig. S3). Additionally, 3 studies reported late mortality and follow-up (Supplementary Material, References S4, S6 and S7). The linearized occurrence rate of mortality in these studies was comparable in the group undergoing LVAD + TVS [43%/year, 95% CI (32–59)] compared with isolated LVAD implantation [36%/year, 95% CI (25–52)]. Data on late RVF are scarce; only 2 studies reported late RVF (Supplementary Material, References S3 and S6). Han et al. (Supplementary Material,

Reference S3) found no significant differences in the cumulative readmission for RVF between patients with and without concomitant TVS during LVAD implantation (P = 0.95). Moreover, Oezpeker et al. (Supplementary Material, Reference S6) also found no differences in RVF at 1 year after LVAD implantation between patients receiving LVAD compared with LVAD +TVS [odds ratio 1.23 (0.18–8.44), P = 0.830].

Figure 3. A pooled Kaplan–Meier curve of survival of patients undergoing LVAD implantation with or without TVS. Patients are censored at heart transplant. As Piacentino et al. (Supplementary Material, Reference S8) contained more patients than Piacentino et al. (Supplementary Material, Reference S7), more patients are included in the Kaplan–Meier analysis than in the meta-analysis. LVAD: left ventricular assist device; TVS: tricuspid valve surgery

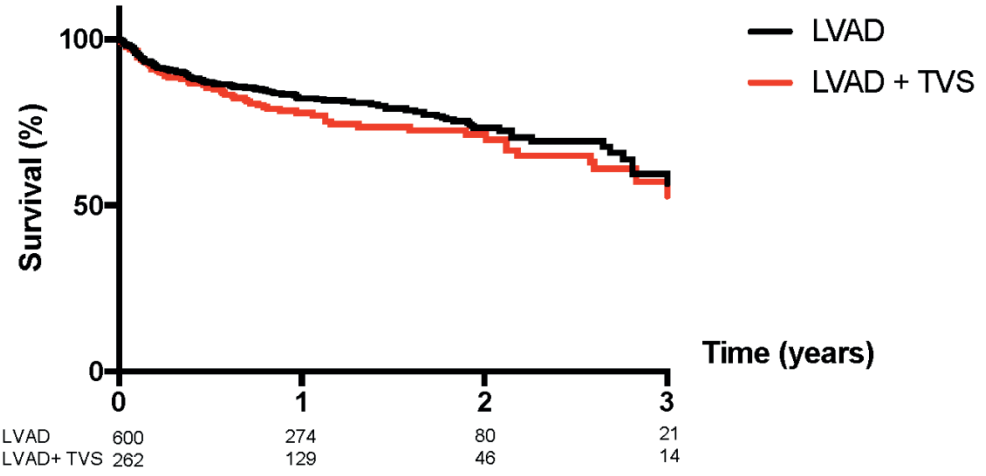


Table 2. Baseline characteristics of included studies. NR: not reported, TR: tricuspid regurgitation, TV: tricuspid valve, VC: vena contracta. *Only included in meta-analysis. **Only included in Kaplan Meier analysis.

Publication	Design	Study characteristics							Newcastle-Ottowa scale		
		Group	Indication TR surgery	N (% male)	Ischemic etiology	TR severity	TV repair (Ring/Suture)	TV replacement	*Selection*	*Comparability*	*Outcome*
Brewer 2014 (S1)	Retrospectivemono-center	LVAD	-	87 (74%)	37%	-	-	-			
		LVAD + TVS	NR	14 (71%)	14%	-	100% (100/0)	0%	***	**	*
Fujita 2014 (S2)	Retrospectivemono-center	LVAD	-	72 (NR)	NR	Mean grade: 1.3±0.8	-	-			
		LVAD + TVS	>moderate TR and >40 mm annulus dilatation	69 (NR)	NR	Mean grade: 2.6±1.0	100% (70/30)	0%	***	-	***
Han 2016 (S3)	Retrospectivemono-center	LVAD	-	252 (84%)	43%	≥moderate 19%	-	-			
		LVAD + TVS	≥moderate TR	76 (76%)	36%	≥moderate 99%	98% (95/3)	2%	***	**	***
Krishan 2012 (S4)	Retrospectivemono-center	LVAD	-	14 (100%)	36%	≥moderate 7%					
		LVAD + TVS	>moderate TR and >40 mm annulus dilatation	37 (84%)	27%	≥moderate 60%	100% (100/0)	0%	***	-	***
Maltais 2012 (S5)	Retrospectivemulti-center	LVAD	-	49 (90%)	52%	TR VC 2.9 mm					
		LVAD + TVS	NR	34 (71%)	50%	TR VC 5.6 mm	82% (12/70)	18%	***	*	***
Oezpeker 2015 (S6)	Retrospectivemono-center	LVAD	-	26 (92%)	58%	>moderate 100%	-	-			
		LVAD + TVS	>moderate TR	32 (88%)	25%	>moderate 100%	100% (100/0)	0%	****	**	***
Piacentino 2012* (S7)	Retrospectivemono-center	LVAD	-	28 (54%)	36%	≥moderate 100%	-	-			
		LVAD + TVS	NR	33 (67%)	56%	≥moderate 100%	88% (88/0)	12%	****	*	***
Piacentino 2011 (S8)**	Retrospectivemono-center	LVAD	-	81 (79%)	39%	Severe 33%	-	-			
		LVAD + TVS	NR	34 (65%)	26%	Severe 62%	75% (75/0)	15%	****	*	***
Saeed 2011 (S9)	Retrospectivemono-center	LVAD	-	34 (74%)	NR	-	-	-			
		LVAD + TVS	>moderate-severe (3) TR	8 (100%)	NR	-	100% (37/63)	0%	***	-	**

Table 2 Pooled baseline and procedural characteristics

Characteristic	LVAD N = 562	95% CI	LVAD + TVS N = 303	95% CI	RR/MD	95% CI	P value
Age (years)	56.0	(54.8 to 57.2)	56.9	(55.1 to 58.7)	-0.47	(-2.8 to 1.9)	0.693
Female (%)	24.0	(20.4 to 28.8)	40.8	(34.1 to 48.7)	0.71	(0.52 to 0.94)	0.020
Ischemic heart disease (%)	44.0	(39.6 to 48.8)	41.0	(34.8 to 48.2)	1.15	(0.93 to 1.4)	0.195
Diabetes (%)	37.5	(33.0 to 42.6)	34.7	(27.2 to 44.3)	1.01	(0.75 to 1.35)	0.952
IABP (%)	41.6	(36.6 to 47.2)	47.6	(41.1 to 55.1)	0.92	(0.76 to 1.20)	0.407
Other valve procedure (%)	46.3	(89.9 to 96.3)	45.0	(37.3 to 54.3)	1.01	(0.80 to 1.28)	0.912
Moderate - Severe TR (%)	93.1	(89.9 to 96.3)	97.5	(95.2 to 99.9)	0.93	(0.89 to 0.97)	<0.001
Severe TR	17.7	(11.8 to 26.4)	57.4	(49.9 to 66.6)	0.47	(0.28 to 0.80)	0.006
CVP (mmHg)	10.8	(10.3 to 11.3)	12.9	(12.0 to 13.8)	-2.04	(-3.08 to -0.99)	<0.001
PCWP (mmHg)	23.3	(22.5 to 24.1)	23.4	(22.4 to 24.4)	-0.37	(-1.69 to -0.95)	0.672
Creatinine (mg/dL)	1.4	(1.3 to 1.4)	1.4	(1.3 to 1.5)	-0.07	(-0.17 to 0.04)	0.236
Bilirubin (mg/dL)	1.4	(1.3 to 1.5)	1.7	(1.6 to 1.9)	-0.21	(-0.416 to -0.012)	0.038
Continuous flow device (%)	99.7	(99.2 to 100)	98.8	(97.3 to 100)	1.00	(0.998 to 1.02)	0.602

CI: confidence interval; CVP: central venous pressure; IABP: intra-aortic balloon pump; LVAD: left ventricular assist device; MD: mean difference; PCWP: pulmonary capillary wedge pressure; RR: risk ratio; TR: tricuspid regurgitation; TVS: tricuspid valve surgery.

Discussion

This meta-analysis showed that there are no significant differences in early mortality, RVF, acute kidney failure, hospital stay and RVAD implantation between patients receiving isolated LVAD implantation versus LVAD + TVS. Not surprisingly, CPB time was longer in patients receiving concomitant TVS. In addition, late mortality and late RVF were comparable for patients with and without TVS during LVAD implantation. To the best of our knowledge, this is the first systematic review that pools late survival using KM curves. Our results can be interpreted two-fold. First, one could argue that despite the fact that patients receiving concomitant TVS are sicker at baseline, concomitant TVS results in comparable outcomes as isolated LVAD implantation, and thus, TVS during LVAD may be beneficial. Several authors have mentioned this reasoning (Supplementary Material, References S2, S4, S5 and S7). Second, one could argue that LVAD alone is also able to improve the loading conditions of the heart, and TVS does not have clinical relevance. It is difficult to discriminate between these 2 interpretations as the ideal control group (patients with severe TR and impaired RVF at baseline undergoing isolated LVAD implantation) is rarely compared with patients undergoing LVAD + TVS in the literature, as is also indicated by the differences in pooled baseline characteristics. Nevertheless, the pooled data show that additional TVS is not associated with worse outcomes. Therefore, we question the clinical impact of the pop-off valve hypothesis, which states that the tricuspid valve regurgitation serves as a 'pop-off', reducing right ventricular afterload (Supplementary Material, References S1 and S4). The results of this meta-analysis agree in this respect with a prior systematic review that focused on early outcomes [14]. Severe TR is associated with impaired right ventricle function [15], and RVF is uniformly recognized as a risk factor for adverse events and mortality following LVAD implantation [16]. These 2 observations raise important questions. Does TR impact outcomes by itself or is it merely a marker for the severity of the right ventricular dysfunction? If so, does TVS improve right ventricular function? Some data suggest that TVS improves right ventricular function in the setting of functional TR [17, 18], adding to the rationale that TVS may be beneficial. However, whether this is true in the setting of LVAD implantation remains unclear. Complicating matters, significant TR can reduced to insignificant TR after optimizing loading conditions through diuretics use [3]. Therefore, baseline TR grade as sole operation criteria might not be sufficient. Dreyfus et al. [19] proposed that the decision of TVS should be based on annulus dilatation rather than TR grade in patients with functional TR. Some centres have adopted this approach in their decision-making process whether to operate on the TV during LVAD implantation (Supplementary Material, References S2 and S4). Current guidelines on management of TR recommend consideration of tricuspid valve repair if moderate or greater TR is present [20]. The data of the STS and

the INTERMACS registries have been used to shed some light on routinely repairing the tricuspid valve if significant TR is present [21, 22]. Analysing the STS registry, Robertson et al. reported that patients undergoing TVS had a higher postoperative risk of renal failure, dialysis, reoperation, greater total transfusion requirement and a higher rate of hospital length of stay >21 days. They concluded that routinely operating on the tricuspid valve based on TR grade should be avoided [21]. Our recent article confirms also the increased risk of RVF if the CPB time is increased [23]. Increased CPB is a marker for a difficult situation, subsequently requiring extended surgery, which may lead to RVF. We agree, therefore, with their suggestion to seek additional selection criteria for TVR. Nonetheless, their results should be interpreted with some caution, since they did not adjust for preoperative RVF, except for TR grade. Song et al. [22] showed comparable survival of patients undergoing TVS during LVAD implantation versus isolated LVAD implantation using the INTERMACS database. On the one hand, multicentre studies include more patients, increasing statistical power, and on the other hand, TR measurement and quantification

remain challenging, and adding different centres with different operators results in less reliable data. This point was also raised by Shah [22, 24] commenting on the publication of the INTERMACS data. Furthermore, a limitation is that these multicenter studies were not designed to specifically address these research questions. Therefore, data on tricuspid valve function, time of assessment and reason for TVR are not collected uniformly or not available at all, which is expected to have resulted in significant bias. The study on the STS database attempted to adjust for baseline differences using a propensity score model. However, data on right heart function, except for TR grade in their model, were not included. Additionally, the data from HeartMate II and ADVANCE trials have been retrospectively reviewed to assess the impact of TVS during LVAD implantation. Although patients undergoing TVS in the HeartMate II trial had worse baseline characteristics (higher CVP, higher CVP/PWCP ratio and lower right ventricular stroke work index) both early survival and late survival were comparable. The incidence of early RVAD implantation and early RVF was higher in the LVAD + TVS group [25]. However, the data from the ADVANCE trial showed that patients with moderate or severe TR receiving TVS have a lower incidence of late RVF when compared with patients with moderate or severe TR undergoing isolated LVAD implantation [26], suggesting that patients undergoing TVS may be at higher risk of early RVF, but this reverses during follow-up. We speculate that TR is part of an interplay of RVF, pulmonary pressures, systemic volume status and kidney function. Subsequently, TVS may only be beneficial in patients who have not reached the point-of-no-return but are sick enough to require TVS. For example, patients with TR and risk factors for postoperative RVF, but not yet with full-blown RVF, may benefit more

if TVS is able to improve right ventricular function or prevent further decrease in right ventricular function post-implantation. Therefore, identifying these patients should be a focus of further research, because clear insight in which subpopulation within the TR population may benefit from TVS remains yet to be elucidated. A randomized clinical trial including all patients with TR is not feasible, and multiple clinical trials in different subpopulations within the TR population would be a costly endeavour. However, newer innovative designs are rising that can possibly provide answers on this matter [27]. Currently, a clinical trial (NCT02537769) is being performed to assess the effect of TVS on patients with mild–moderate TR at baseline. This is already a subset of the general TR population; nevertheless it may be a subset which does not benefit from TVS. Therefore, it may still be elucidating to gain insights in the natural history of TR after LVAD implantation and to seek additional selection criteria for concomitant TVS.

Limitations

This study is a systematic review and meta-analysis of observational studies, which all are retrospective in nature. Therefore, the inherent limitations of meta-analysis and pooling retrospective data apply to this study [28]. Moreover, serious risk of bias due to confounding was found in most studies using the ROBINS-I tool. However, this bias mostly favours the LVAD group, further suggesting that there may be benefit of concomitant TVS that underlies our findings of comparable outcomes. Despite the inclusion of multiple studies, the sample size remains modest, possibly with too little power to show true differences. Funnel plots did not show clear evidence of publications bias. However, the small number of studies precludes unambiguous conclusions. Considerable heterogeneity was present in the RRs of early RVF, CBP and in the late mortality, including the pooled HRs. Unfortunately, exploring heterogeneity with meta-regression was not possible due to limited number of studies. The RVF heterogeneity may be explained by the fact that some studies included patients less prone to postoperative RVF in the LVAD group, resulting in different RRs. For example, Piacentino et al. (Supplementary Material, Reference S7) only included patients ≥ moderate TR, and in the cohort of Maltais et al. (SupplementaryMaterial, Reference S5), TR differed in groups, whereas TR is found to be a predictor of postoperative RVF after LVAD implant [29]. Additionally, CBP had significant heterogeneity, which can partly be explained by the fact that in the cohort of Maltais et al. (Supplementary Material, Reference S5), patients did not undergo other concomitant procedures (e.g. aortic valve procedure), whereas in the cohort of Han et al. (Supplementary Material, Reference S3), nearly half the population underwent concomitant procedures. Because of differences in

postoperative care and censoring due to heart transplantation, the heterogeneity found in late mortality can be explained.

CONCLUSION

Concomitant TVS during LVAD implantation is not associated with worse outcome when compared with LVAD implantation, and some data indicate that it may be beneficial. However, current literature is unable to offer a definitive answer, as the majority the compares unmatched groups. Additional effort should be made to identify which patients will benefit most from adding TVS to LVAD implantation.

Supplementary material can be found at
https://academic.oup.com/ejcts/advance-article/doi/10.1093/ejcts/ezy150/4980356

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CHAPTER 6

18F-FDG PET/CT in the diagnosis and management of continuous flow left ventricular assist device infections: A Case Series and Review of the Literature.

Akin, S. Muslem, R. Constantinescu, A.A. Manintveld, O.C. Birim, O. Brugts, J.J. Maat, A.P.W.M. Froberg, A.C. Bogers, A.J.J.C. Caliskan, K.

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Abstract

Implantable continuous flow left ventricular assist devices (LVADs) are increasingly used in end-stage heart failure treatment as a bridge-to-transplant and destination therapy (DT). However, LVADs still have major drawbacks, such as infections that can cause morbidity and mortality. Unfortunately, appropriate diagnosis of LVAD-related and LVAD-specific infections can be very cumbersome. The differentiation between deep and superficial infections is crucial in clinical decision-making. Despite a decade of experience in using fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) to diagnose various infections, its use in LVAD patients remains scarce. In this case series, we review the current evidence in literature and describe our single center experience using ^{18}F-FDG PET/CT for the diagnosis and management of LVAD infections.

INTRODUCTION

Continuous flow left ventricular assist devices (LVADs) are increasingly used as bridge-to-transplantation or destination therapy (DT).[1] However, driveline and pump infections remain a major point of concern, resulting in significant morbidity and mortality. The consequences of a LVAD infection depend on the location, depth, and the severity of the infection. There is currently no gold standard test available for the detection of the exact site of infection or to monitor the response to treatment of LVAD infections.[2] The International Society for Heart and Lung Transplantation (ISHLT) has proposed standard criteria for the clinical, microbiologic, and radiologic diagnosis of infection in LVAD patients.[2] These definitions allow for comparative analysis of time course, incidence, outcome, and risk factors for infection in ventricular assist device (VAD) recipients. However, data regarding the optimal imaging technique to detect infection and monitor the response to treatment in these patients is lacking. In this regard, ultrasound imaging and computed tomography (CT) angiography can be helpful in detecting fluid collections around drivelines, cannulas, and pump. Historically, nuclear imaging modalities described in case series about LVAD infections, are 99mTc-leucocyte and 67 Gallium scintigraphy.[3,4] However, nowadays ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is increasingly used in the diagnostic work-up of infectious endocarditis, especially in the detection of metastatic and primary extra-cardiac infections.[5] Despite a decade of experience in using ^{18}F-FDG PET/CT to diagnose various infections, its use in LVAD remains scarce.[6–8]

In this case series, we describe our single center experience using ^{18}F-FDG PET/CT in the diagnosis and management of LVAD infections. Additionally, we have conducted a literature review on LVAD-related and -specific infections and the use of diagnostic nuclear imaging with ^{18}F-FDG PET/CT scans.

METHODS

Patients

All consecutive HeartMate II (HMII) implantations performed between January 2011 (PET-CT camera installed in the hospital) and May 2016 in our tertiary referral center were reviewed. These data were extracted from the ongoing EuroMacs Registry (European Registry for Patients with Mechanical Circulatory Support) database.[9] Patients have agreed with the registry and signed the informed consent. The patients who had ^{18}F-FDG PET/CT scintigraphy to investigate suspected LVAD-related or LVAD-specific infections were included in this case series. Their clinical courses were reviewed, including medical history, comorbidities, microbiologic and laboratory

investigation, and imaging results (**Table 1**). We categorized these patients into three groups based on their clinical, microbiologic, and nuclear imaging characteristics: 1) persistent LVAD-specific infection with positive blood cultures, 2) persistent LVADspecific infection with negative blood cultures, and 3) fever of unknown origin with negative blood cultures and swab.

^{18}F-FDG PET/CT Imaging

All ^{18}F-FDG PET/CT images were acquired using a Siemens Biograph mCT (Siemens Medical Solutions USA Inc., Malvern, PA). Data were iteratively reconstructed (3 iterations, 21 subsets, and 5 mm Gaussian filter) using time-of-flight information and resolution recovery. Low-dose CT was used for attenuation correction. The protocol of patient preparation and scanning was according to the guidelines of Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the European Association of Nuclear Medicine (EANM). As we were interested in imaging of infection near the myocardium, it was important to avoid physiologic uptake of glucose by normal myocardium cells. Therefore a low carbohydrate diet for 24 h before the PET/CT study was recommended to switch the myocardium from using glucose as an energy source to using fatty acids, this is one of the options to reduce physiologic myocardial uptake as suggested in the mentioned guidelines.[10,11] In short, patients had a low carbohydrate diet 1 day before the regular fast of 6 h. A total of 2.3 MBq/kg body weight ^{18}F-FDG was administered after which patients were resting in a quiet and warm waiting room (to avoid uptake in muscles, brown fat, etc.). Imaging started 60 min after administration. Low-dose CT was directly followed by PET imaging: the latter for 3 min/bed position for patients <70 kg and for 4 min/bed position for patients >70 kg. This meant total imaging time of about 30 min for scintigraphy from skull to groin. Interpretation of scans was performed on both for attenuation corrected and noncorrected images to avoid false positive judgment caused by artifacts introduced by attenuation correction.

Literature Search

Additionally, we performed a PubMed/Medline search by using MeSH terms focusing on articles on LVAD-related and LVAD-specific infections and on use of diagnostic nuclear imaging with ^{18}F-FDG PET/CT scans. Basic information collected included journal, author, year published, number of patients, and types of LVAD. Specific data collected included the clinical problem, method(s) of (nuclear) imaging, and outcome.

RESULTS

Fifty-one HMII implantations were performed in 48 patients between January 2011 and May 2016. In 9 patients (7 males; mean age 54 ± 15 years) with suspected LVAD-related infections, a total of 10 ^{18}F-FDG PET/CTs were performed. The primary indications for LVAD implantation were bridge-to-transplant (8/9) and DT (1/9).

The median duration of LVAD support from implantation or exchange to ^{18}F-FDG PET/CT was 134 days (range 24–645 days). The long-term mortality rate was 11%. A (semi-)urgent listing for heart transplantation (HTx) caused by infectious complications was needed in 4 patients (44%), after a median of 59 days (range 49–200) after the first PET/CT. The detailed clinical characteristics of all patients are summarized in **Table 1**.

Overall, we describe 9 patients with suspected LVAD infection, either pump or driveline; in 33% blood cultures were positive and in 44% wound cultures were positive. ^{18}F-FDG PET/CT was performed to establish and determine the extent of LVAD-related or -specific infections. In 3 patients we performed the ^{18}F-FDG PET/CT within 90 days postoperative (= short term) and in 6 patients the ^{18}F-FDG PET/CT was performed at longer term follow-up. Sixty-seven percent of the patients had unexpected extensive deep infections. In 2/9 patients, ^{18}FFDG PET/CT was able to rule out any LVAD-related or -specific infections, both very early (24 and 29 days, respectively) in the postoperative phase. In only one patient there was an isolated pump inflow cannula infection (**see Table 1, Supplemental** Digital Content, http://links.lww.com/ASAIO/A138).

A. Persistent LVAD-specific infection with positive blood cultures: This type of infection was observed in 3 patients (**see Table 1; cases AI–AIII**), in which ^{18}F-FDG PET/CT scans were performed because of recurrent positive blood cultures despite antibiotics (AB) therapy for 3–6 weeks. In case I (**AI in Table 1**), the connection between the inflow cannula and the pump body was detected as the source of LVAD infection (**Figure 1A**). Unfortunately, replacing the LVAD would have been a very high risk operation because of a previous LVAD replacement caused by driveline fracture. The patient was placed on the high urgency list for HTx, and was transplanted 49 days later under AB treatment. After explantation of the LVAD, debris was found in the connection between inflow cannula and the pump housing (**Figure 1B**). Microscopy showed the same monoculture of *Staphylococcus epidermidis* as in patient's previous cultures. The patient is currently doing well and has not experienced any severe infections 3 years after HTx.

In case AII, this 67 year old male LVAD patient was admitted175 days after LVAD exchange by sternal infection with coagulase negative *Staphylococcus epidermidis* (CNS)

Figure 1A. Case AI: 18F-FDG PET/CT images of a high FDG ring around the inflow cannula of the LVAD. Banded ring with high degree of accumulation in the connection part of the inflow cannula with the housing.
1B. Case AI: Picture of the debris we found in the connection between inflow cannula and pump housing (hands of APWMM).

Figure 1A

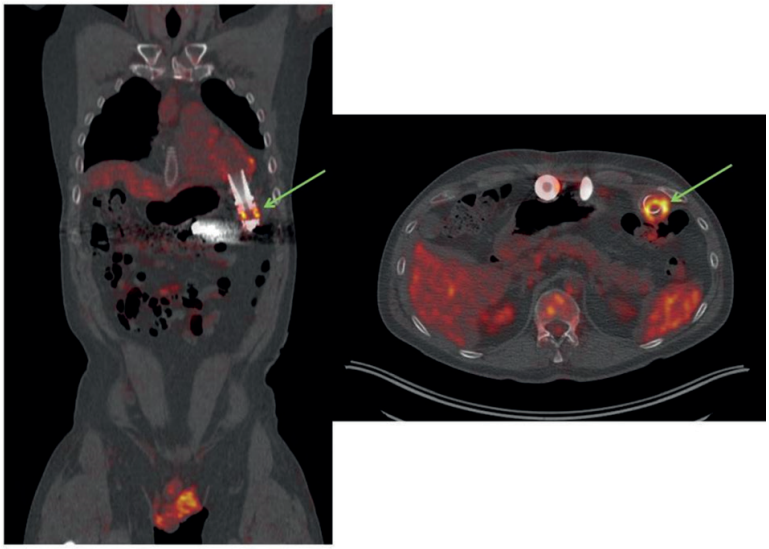
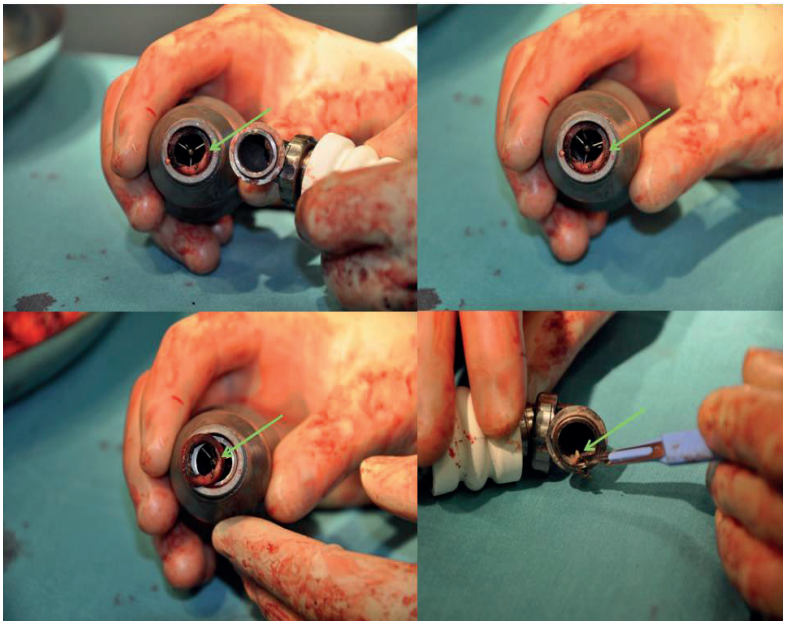


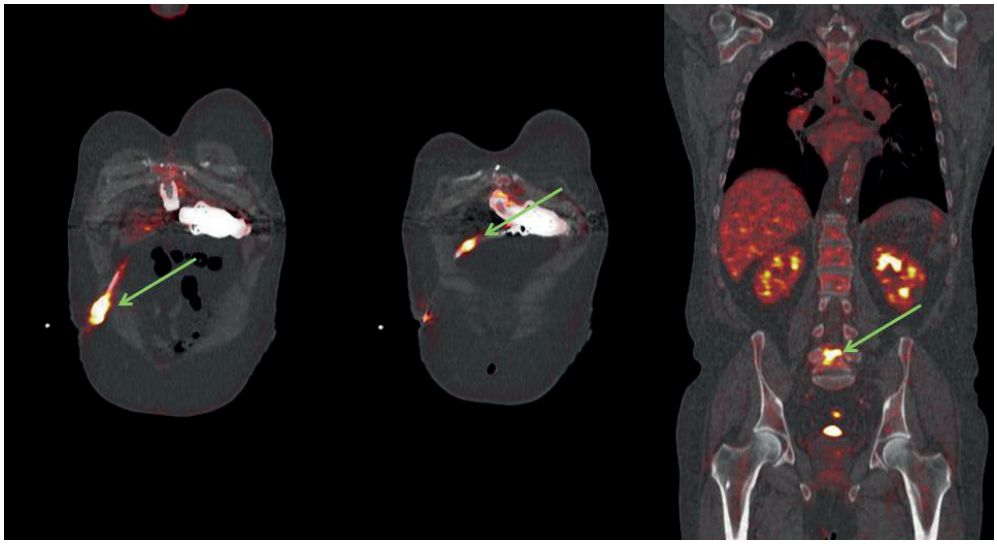
Figure 1B



bacteremia. Ongoing deep infection despite AB therapy proved by ^{18}F-FDG PET/CT led to semi-urgent HTx. The interval after LVAD removal and HTx was complicated by infection, and bacteremia with Enterobacter aerogenes detected in fluid aspirated from the substernal region and in the explanted driveline. A reoperation to address a possible mediastinitis was considered and planned. At day 17 post-HTx, a newly performed ^{18}F-FDG PET/CT showed a hot spot just caudal to the sternum, which was a nonencapsulated fluid collection from which the same Enterobacter species was cultured after an ultrasound-guided puncture. The former driveline route was no longer considered as infected and the planned operation for a mediastinitis was cancelled. The patient has had no infectious problems at 31 months of follow-up periode (FUP) post-HTx.

In one patient (**case AIII; Figure 2**), osteomyelitis was detected at the level of the 5th lumbar vertebra (L5), in addition to a LVAD and driveline infection. Unfortunately, because of severe infection, he became a DT patient and died after acute LVAD failure 1,219 days after implantation. Large bacterial growths were found at the insertion opening of the driveline, and around the LVAD on autopsy. The treatment of the rest of this group of patients varied according to the ^{18}F-FDG PET/CT findings from placement on urgent transplantation list, to continued AB therapy with or without vacuum-assisted closure (VAC) therapy.

Figure 2. Case AIII; 59-years-old man with inflammation of driveline, subcutaneous part as well as intra-abdominal portion close to pump housing. Beside this there is a strongly suspected osteomyelitis of Lumbar vertebra L5.



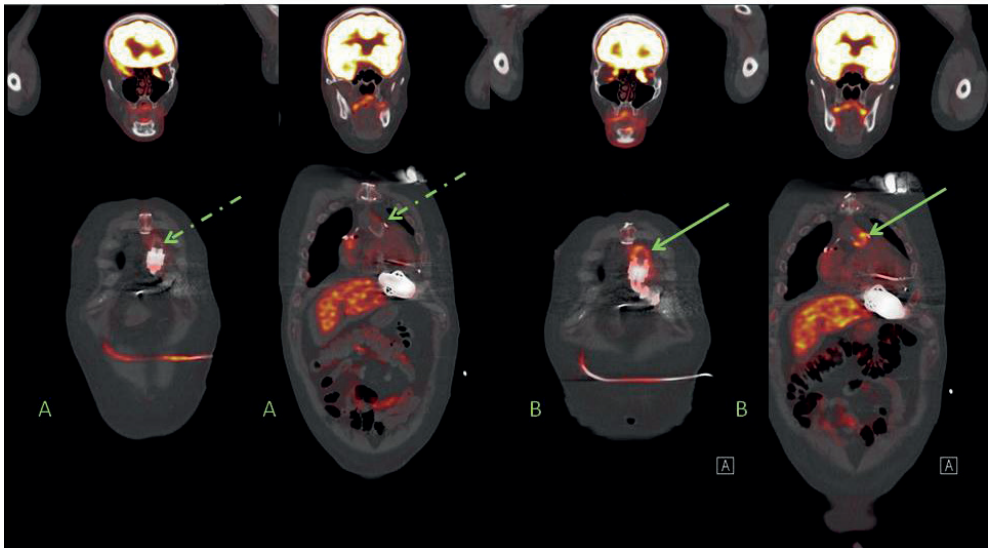
B. Persistent LVAD-specific infection with negative blood cultures: As shown in **Figure 3**, three patients were found in this group (**cases BI–BIII; Table 1**). In this group of three patients, clinical symptoms of infection that progressed during AB therapy, despite negative blood cultures, the clinical signs and symptoms of infection were progressive during AB. **Figure 3** is an example from this group of patients. These patients (**Table 1**) were all admitted or unable to be discharged after LVAD implantation because of fever with negative blood cultures. The time between implantation of LVAD and ^{18}F-FDG PET/CT varied from 37 days to 371 days. ^{18}F-FDG PET/CT showed infection of different parts of the LVAD or deep driveline infection despite negative blood cultures, patients had persistent fever.

Ongoing AB therapy was accepted in case BI because of extended LVAD-specific infection 37 days after HMII concomitant with aortic valve replacement (AVR). This patient had no deterioration of chronic infection at follow-up of 831 days on continuing LVAD support. In case BII, there was persisting driveline infection with Staphylococcus aureus 40 days after implantation until HTx and despite several AB regimens and surgical interventions. The abscess around the driveline exit was drained and treatment with intravenous (i.v.) flucloxacillin was started. However, the patient developed recurring cellulitis and the cultures taken from the driveline entrance remained positive despite of AB treatment. The ^{18}F-FDG PET/CT showed high intensity in the abdominal segment because of FDG accumulation along the driveline route. Two hundred days after LVAD implantation she underwent HTx and is still doing well.

In case BIII (**Figure 3A**), a 61 year old male with LVAD was admitted with a suspected driveline infection caused by cellulites of the abdominal skin at the driveline exit. The cultures showed *S. aureus* in the driveline exit, but blood cultures were negative. An abdominal ultrasound was performed which showed an infiltrated aspect of the skin. After 16 days of AB therapy, the fluid collection around the driveline decreased. The ^{18}F-FDG PET/CT showed subcutaneous fat infiltration along the driveline with abnormal FDG accumulation. There was no other suspicion of infection beside this deep driveline infection on ^{18}F-FDG PET/CT. The patient was listed for urgent HTx. Despite AB therapy, a control ^{18}F-FDG PET/CT showed extension of increased uptake in the infected region; from the driveline exit to the outflow cannula (**Figure 3B**). He was transplanted 5 days after the ^{18}F-FDG PET/CT scan. Postoperative cultures of the LVAD showed *S. aureus and Candida* species.

Figure 3A. Case BIII, 61-years-old male with example of a deep driveline infection; Driveline in situ with subcutaneous fat infiltration visible around the course of the line in the abdominal wall (dotted green arrows).

3B. In case B III, the second 18F-FDG PET/CT showed 54 days later persisting and increased metabolic activity around the subcutaneous driveline in abdominal wall. Furthermore appearance of increased metabolic activity around the outflow cannula of the LVAD near to ascending aortae (green arrows) .



C. LVAD patients with fever of unknown origin and negative cultures: In these three patients, 18F-FDG PET/CT was used after negative blood and swab cultures to either detect or excluded LVAD-specific or -related infection and detect other causes for fever. The first patient (**CI in Table 1**) is a 75 year old female who received a LVAD as DT. The patient was previously admitted with superficial sternum infection and was treated with empirical AB therapy, however the patient was re-admitted with fever and progression of the sternal wound infection. The 18F-FDG PET/CT showed an infected system and mediastinitis because of migration of the infection. The patient was treated with VAC therapy and AB because of a diffuse infected pump, driveline and mediastinum. There was no other infection unrelated to LVAD, particularly not around the implantable cardioverter defibrillator (ICD). At an optimal moment after VAC therapy, a rectus abdominis muscle flap reconstruction was performed 82 days after initiation of AB and VAC therapy to reconstruct the sternal wound. Figure 4 shows this case as an example of the worst case scenario for persisting progressive sternum infections with negative cultures during AB therapy.

The second patient (**CII in Table 1**) is a 54 year old man (**Figure 5**) with LVAD and concomitant AVR who was admitted to cardiac ICU because of driveline fracture with recurrent LVAD alarms more than two years post LVAD implantation. Because of driveline dysfunction, the LVAD device was exchanged. Three days after surgery because of fever and increased infection parameters, diagnostic CT thorax was performed which showed signs of empyema of the left pleural space. It was treated by thoracic drainage and vancomycin, cefuroxim, clindamycin, and rifampicin for 2 weeks (blood cultures showed growth of *Micrococcus luteus and S. aureus*). After discontinuation of i.v. AB, oral clindamycin was continued for 1 month. The ^{18}F-FDG PET/CT was performed 24 days after LVAD exchange to monitor the infection and the effect of treatment. There were no signs of an infected LVAD or active infections elsewhere. He is currently alive on LVAD support for more than 3 years.

The last patient (**CIII; 40 year old male**) with LVAD and AVR was admitted for recurrent cardiac tamponade. Because of persisting fever on day 19 post LVAD implantation a thoracic CT scan was done, showing air bubbles in the pericardium which was concluded to be a normal postoperative effect. Ten days later, after initiation of broad spectrum AB for 2 weeks, the ^{18}F-FDG PET/CT was performed which ruled out LVAD infections or prosthetic valve endocarditis. After 410 days on LVAD support, he has no signs of infection at the outpatient clinic.

Figure 4. Case CI: 74-years-old female with mediastinitis in diffuse LVAD infection after re-admission due to progressive clinical signs of sternal wound infection during antibiotic treatment.

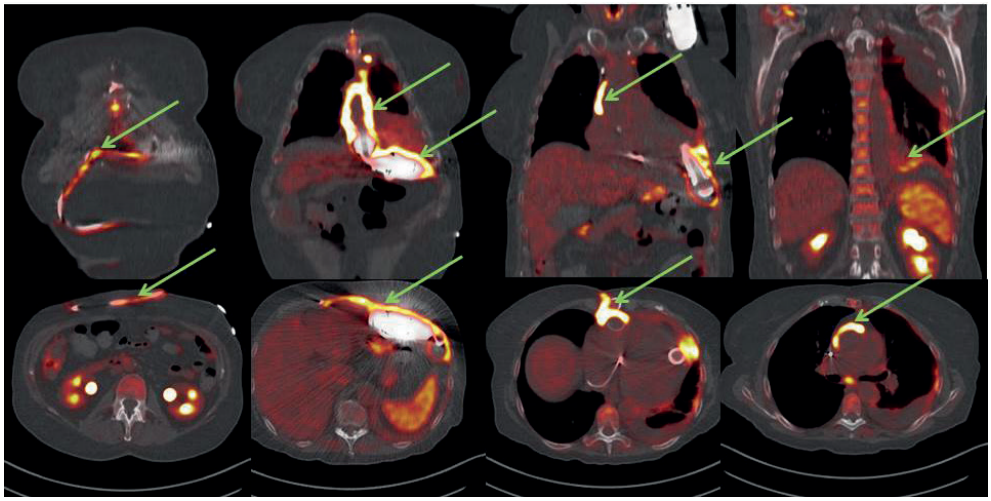
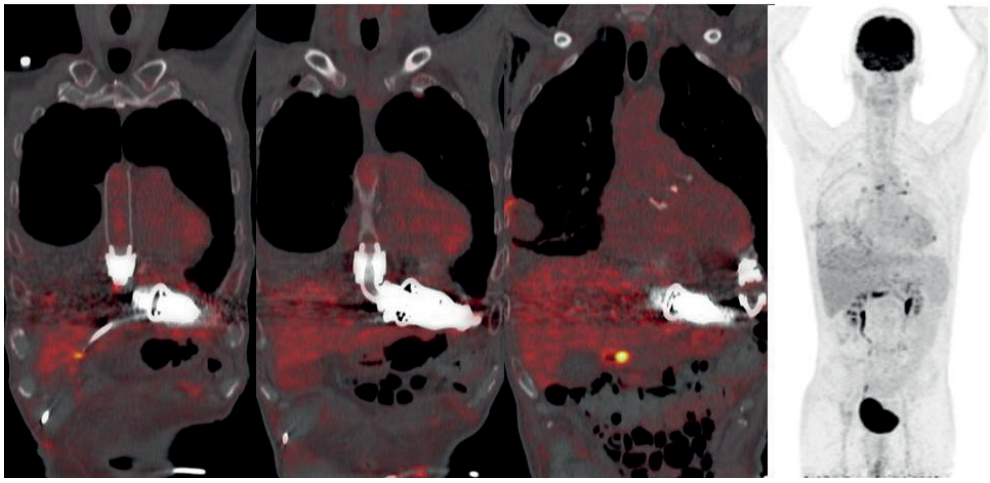


Figure 5. Case CII; 54-years-old male 24 days after LVAD exchange (678 days on support) PET/CT guided exclusion of active infection. Mild increased activity around the pleural fluid in the right lung, as well as slightly increased activity in multiple mediastinal and hilar lymph nodes bilaterally as well as in pleural nodular; all possible still reactive. There is no focus of infection. Other finding is subcutaneous emphysema with pneumothorax right sided.



Discussion

In this paper, we present nine different LVAD patients who suffered from clinically suspected or proven infections in which ^{18}F-FDG PET/CT imaging supported clinical decision making in LVAD-specific and -related infection. To our best knowledge, our case series contains yet the largest population of HMII patients ever managed by ^{18}F-FDG PET/CT. However, limited data exist regarding the management and outcomes of LVAD infections. In the current literature, we found only 4 studies with case reports and series with a total of 47 cases: 2 case reports and 2 case series with ^{18}F-FDG PET/CT were published between 2013 and 2016. The findings of these four studies are summarized in **Table 2**.

One of the major drawbacks for long-term LVAD support are LVAD-specific and LVAD-related infections resulting in high risk of morbidity and mortality.[12] Prompt diagnosis of LVAD-related infections can be particularly challenging in cases involving pump or cannula infections, pocket infections or deep sternal wound or mediastinal infections. Innovations in cardiovascular imaging strategies have emerged to resolve these issues such as: multi-slice CT, 3D echocardiography, ^{18}F-FDG PET scan, molecular imaging, and cardiac magnetic resonance.

^{18}F-FDG PET/CT appeared to be a useful nuclear imaging diagnostic tool to assess LVAD infections. In a clinical study of 31 LVAD patients, ^{18}F-FDG PET/CT had a sensitivity of 100% and a specificity of 80% of ^{18}F-FDG PET/CT in detecting infections of LVAD components, both in patients with and without obvious infection.[13] In our current case series we found a sensitivity and specificity of 100% in nine HMII patients including early and very early performed ^{18}F-FDG PET/CT in contrast to previous studies and recommendations. Additionally, the timing when to perform the ^{18}F-FDG PET/CT varies greatly in the current literature (**Table 2**). Although our sample size is small, ^{18}F-FDG PET/CT was able to evaluate and rule out LVAD infections as early as 3 weeks post-implantation, in contrast to the current paradigm of waiting 3–6 months after LVAD implantation. This was in line with the first paper on nuclear imaging in 8 HMII patients with suspected infection (mean durations after implantation 54 days) without any false positive result.[3] In our case series ^{18}F-FDG PET/CT was used to detect the site and extent of infection and to guide duration of AB treatment in 7/9 patients (**Table 1**). The study accurately ruled out infection in 2/9 patients. Therefore, given the clinical experience in the current literature and our paper, we believe that ^{18}F-FDG PET/CT is a crucial imaging tool in the diagnosis and management in infection specific and related to LVAD patients. However, some issues remain unresolved and require further investigation.

The optimal conditions for ^{18}F-FDG PET/CT acquisition that allows us to improve the image contrast and to better discriminate between positive and negative scans, have to be further determined. ^{18}F-FDG PET/CT could have a widespread use based on practical reasons, however it is limited by meticulous test preparation with low-carbohydrate diet. In the latter circumstance, physiologic myocardial uptake can be seen, reducing the specificity of scan findings. It is therefore unfortunate that among all of the studies reported so far, only two included a high-fat, low-carbohydrate diet in addition to the fasting period in the patients' preparation. Furthermore, image analysis should be standardized regarding both the pattern and the quantification of the uptake. Additionally, the impact of factors such as AB treatment and the type of infective agent needs to be evaluated more precisely. The initiation of AB therapy and, if present, its duration before imaging is likely to alter the inflammatory response of the host and thus FDG uptake.[5] Also, it is acknowledged that some bacteria strains may escape immune response either by producing a biofilm on prosthetic material, or by using an intracellular cycle, allowing them to be hardly detectable by immune cells.[7]

The timing of ^{18}F-FDG PET/CT remains controversial because of recent surgery.[13] Nevertheless, in our small cohort there is a promising use of this imaging technique to rule out function even in an early postoperative period (3–6 weeks). Larger studies and comparisons are needed to optimize timing of ^{18}F-FDG PET/CT when there is an ongoing suspicion of LVAD-specific infections without source control in both in the outpatient and inpatient setting. In particular, it is important to define who are the patients that would benefit the most from this test according to their probability of infection based on clinical evaluation, echo(cardio)graphy results and risk factors for development of infection during LVAD support.

CONCLUSION

In this case series of nine patients with continuous flow LVAD type HMII, ^{18}F-FDG PET/CT imaging provided accurate information on the localization and extent for LVAD-specific or -related infections as early as 3 weeks post-implantation. Review of the current literature with 2 case reports and 2 case series with a total of 47 cases, confirms the promising role of this novel imaging modality.

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Table 1. Overview of all patients with a left ventricular assist device patients, needing 18F-FDG PET/CT 's in the correct localization of infections. Clinical, microbiologic and nuclear imaging characteristics.

Group	Age/sex/ etiology	LVAD support duration	Clinical presentation	Culture results	PET/CT results	Summary	Intervention	**Patient outcome**
AI	46/Male/ICM	112 days after LVAD exchange	Fever of unknown origin. CRP: 27; Leuco's: 8; LDH: 497	**Driveline:** negative **Blood:** *Staph. epidermidis (CNS)*	Inflow cannula infection	**Clinical:** Fever of unknown origin **Culture:** *CNS bacteremia* **PET/CT:** Inflow cannula infection	Prolonged AB; High Urgent HTx due to persisting positive blood cultures (49 days after PET-CT)	High urgent HTx; alive
AII	67/Male/ ICM	178 days after LVAD exchange	Superficial sternal infection CRP 26; Leuco's 3; LDH 225	Driveline: *Proteus mirabilis* Blood: *Staph. epidermidis (CNS)*	Pump, mediastinum inflow cannula and driveline infection	**Clinical:** Superficial sternal infection **Culture:** *CNS bacteremia* **PET/CT:** pump, inflow cannula, mediastinum and driveline infection	Negative cultures after prolonged AB; Semi-urgent HTx (58 days after PET-CT)	Semi-urgent HTx; alive
AIII	59/Male/ICM	645 days	Fever and hemolysis complicated by CVA CRP 86; Leuco's 12; LDH 1817	Driveline: Negative Blood: *Staph. epidermidis (CNS)*	Pump, driveline and vertebral infection	**Clinical:** Fever and hemolysis complicated by CVA **Culture:** *CNS bacteremia* **PET/CT:** near pump housing and driveline infection plus suspected osteomyelitis	Negative cultures after prolonged AB; Destination therapy; Death (574 days after PET-CT)	Sudden death after 1219 days of LVAD support. At autopsy persistent deep VAD-specific infection
BI	61/Male/DCM	37 days	Sternal wound infection CRP 12; Leuco's 7; LDH 251	Sternal wound: *Candida parapsilosis, Staph. epidermidis (CNS) and Propionibacterium acnes* Driveline: Negative Blood: Negative	Pump, sternum and driveline infection	**Clinical:** Sternal wound infection **Culture:** *Candida parapsilosis, CNS and Propionibacterium acnes* **PET/CT:** pump connection to the heart, sternum and driveline infection	Negative cultures after debridement, VAC and prolonged AB therapy (794 days after PET-CT)	Ongoing support: 831 days; prolonged oral AB.

BII	26/Female/ DCM	182 days	Recurrent driveline exit infection CRP 33; Leuco's 10; LDH 267	Driveline: *Staph. aureus* Blood: Negative	Driveline infection	**Clinical:** recurrent driveline exit infection **Culture:** *Staphylococcus aureus* **PET/CT:** confirmed driveline infection	Prolonged AB and abscess exploration drive line; semi-urgent HTx (200 days after PET-CT)	Semi-urgent HTx; alive
BIII	61/Male/DCM	371 days	Driveline exit infection CRP 93; Leuco's 8; LDH 235	Driveline: *Staph. aureus* Blood: Negative	Outflow cannula LVAD and driveline	**Clinical:** Fever, pain and redness driveline **Culture:** *Staphylococcus aureus* **1st PET/CT:** only driveline infection **2nd PET/CT at 2 months**: driveline infection and outflow cannula near to ascending aortae	Negative cultures after prolonged AB therapy; HTx (59 days after 1st PET-CT and 5 days after 2nd PET-CT)	Semi urgent HTx; alive
CI	74/Female/ DCM	134 days	Sternal wound infection CRP 156; Leuco's 9; LDH 117	Driveline: Negative Blood: Negative Sternal wound: Negative	Pump, driveline, mediastinitis and pleuritis left	**Clinical:** Sternal wound infection **Culture:** Negative **PET-CT:** pump, driveline, mediastinitis and pleuritis left	Prolonged AB, VAC therapy and surgical reconstruction with rectus abdominis muscle	Ongoing support: 167 days; continuing i.e. prolonged AB and VAC therapy
CII	54/Male/ICM	24 days after LVAD exchange	Pleural empyema after LVAD-exchange due to driveline fracture; CRP 3; Leuco's 3; LDH 211	Driveline: Negative Blood: Negative	Negative	**Clinical:** Pleural empyema after LVAD-exchange due to driveline fracture **Culture:** negative **PET-CT:** negative	Pleural empyema drainage and AB treatment	Ongoing support: 1207 days; on HTx list.
CIII	40/Male/DCM	29 days	Fever and haematothorax early postoperative CRP 16; Leuco's 8; LDH 200	Driveline: Negative Blood: Negative	Negative	**Clinical:** Fever and haematothorax early postoperative **Culture:** negative **PET-CT:** negative	Empirical AB treatment	Ongoing support: 410 days; on HTx list

Table 2. Overview of all published studies on left ventricular assist device related infections and ^{18}F-FDG PET/CT .

Type study	Year of publication Journal	Study	Type of device (n)	Number of patients	LVAD support duration	^{18}F-FDG PET/CT results	Intervention (n, %)	Patient outcome (n, %)
Case report	2013 J Nucl Cardiol.	Ghoufrane Tlili et al. [11]	HeartMate II (1)	1	180 days	1 ^{18}F-FDG PET/CT • TP	HTx	Successful HTx
Case series	2014 JACC Cardiovasc Imaging.	Jongho Kim et al.[12]	HeartMate II (4) HeartWare (1)	5	425 days [range 180 – 1278]	5 ^{18}F-FDG PET/CT • 4 TP • 1 TN	HTx (2) Surgery (3) Antibiotics, antifungal (2)	Successful HTx (2) Ongoing LVAD support (1) Death (2)
Case report	2015 Eur Heart J Cardiovasc Imaging.	Takeo Fujino et al.[13]	DuraHeart (1)	1	240 and 30 days after AB	2 ^{18}F-FDG PET/CT • 1 TP • 1 TN	Antibiotics	Ongoing LVAD support (1)
Case series	2016 Ann Thorac Surg.	Angelo Maria Dell'Aquila et al.[9]	HeartMate II (4) HeartWare (28) Incor (6) Ventracor (2)	31	384 ± 348 days	40 ^{18}F-FDG PET/CT • 30 TP • 8 TN • 2 FP	(Semi-urgent) HTx (16) Surgical revision (2) Antibiotics (9) Others (3)	Successful HTx (16) Ongoing LVAD support (7) Death (8)
Case series	2016	*Current report*	HeartMate II (9)	9	Median 134 days [range 24-645]	10 ^{18}F-FDG PET/CT: • 8 TP • 2 TN	(Semi-urgent) HTx (4) Surgical revision / VAC therapy (2) Prolonged antibiotics (7), antifungal (2)	Successful HTx (4) Ongoing LVAD support (4) Death (1)
Summary	**2013-2016**		**HeartMate II (18) HeartWare (29) Rest (9)**	**47**		**58 ^{18}F-FDG PET/CT • 44 TP • 12 TN • 2 FP**	(Semi-urgent) HTx (23; 41%) Surgical revision (7; 13%) Antibiotics (19; 34%) Others (7; 13%)	Successful HTx (23; 49%)) Ongoing LVAD support (13; 28%) Death (11; 23%)

CHAPTER 7

Safety and Feasibility of Contrast Echocardiography for the Evaluation of Patients with HeartMate 3 Left Ventricular Asist Devices

Schinkel, A.F.L. Akin, S, Strachinaru, M. Muslem, R. Soliman, O.I.I. Brugts, J.J. Constantinescu, A.A. Manintveld, O.C. Caliskan, K..

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Abstract

AIMS: Patients with a left ventricular assist device (LVAD) are challenging to evaluate using conventional imaging techniques, such as standard echocardiography (SE). The aim of this pilot study was to evaluate the potential of contrast echocardiography (CE) for the evaluation of the left ventricle (LV).

METHODS AND RESULTS: This prospective study included 14 ambulatory patients (mean age 58 ± 9 years, 79% male) with a LVAD (all HeartMate 3, Abbott Laboratories, Chicago, IL, USA). Nine (64%) patients had an ischaemic cardiomyopathy, and 5 (36%) had a non-ischaemic cardiomyopathy. All patients underwent SE and CE using intravenous administration of Sonovue contrast agent (Bracco, Milan, Italy). The echocardiograms were assessed by three observers, using a standard 17-segment model of the LV. Left ventricular end-diastolic volume (LVEDV) was assessed using the biplane Simpson method. The contrast agent was well tolerated by all patients, without any side effects. Overall, SE allowed visualization of 57% of LV segments (135/238) and CE allowed visualization of 79% of LV segments (187/238), $P < 0.001$. Per patient, SE resulted in visualization of 9.6 ± 5.2 segments and CE was able to visualize 13.4 ± 5.8 segments ($P < 0.001$). Administration of contrast agent significantly improved the assessment of LVEDV (feasibility SE: 36% vs. CE: 79%, $P < 0.05$).

CONCLUSION: Routine use of a contrast agent appears safe when used in patients having a new third generation LVAD and may enhance the diagnostic accuracy of transthoracic echocardiography in these patients. LV size determination can be obtained more often due to improved LV visualization using contrast agent.

INTRODUCTION

Left ventricular assist devices (LVADs) are an increasingly used treatment option for patients with advanced heart failure refractory to optimal medical therapy, either as a bridge to cardiac transplantation or destination therapy.1–3 The introduction of the LVAD has resulted in a good long-term survival with substantial improvement in the patient's quality of life.3 Non-invasive imaging plays an important role in the follow-up of patients with a LVAD, for the evaluation of LV function, monitoring of treatment response, and screening for potential complications.4,5 However, a substantial number of these patients exhibit an impaired image quality or may even deemed unsuitable for conventional imaging techniques including standard echocardiography (SE). Multiple studies have demonstrated that contrast echocardiography (CE) may substantially improve the endocardial border delineation and the evaluation of the LV function.6,7 CE was recently proposed as an imaging modality for the evaluation of the LV in patients with a LVAD, particularly to overcome the limitations of SE.8,9 The aim of the current pilot study was to evaluate the safety, feasibility and potential of CE in patients with a novel continuous-flow LVAD, type HeartMate 3. This a third generation LVAD, with a magnetically levitated impellor, which is a potential source of destruction of echocardiography contrast agents.

The hypothesis of this study was that CE use was safe and feasible in patients with HeartMate 3 LVAD to improve visualization of the LV cavity and facilitates the determination of LV size.

METHODS

Patient population and study protocol

This prospective study included all patients with a LVAD that underwent CE. The study protocol was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, TheNetherlands. All patients provided informed consent. Consecutive ambulatory patients with a LVAD (all patients had a HeartMate 3, Abbott Laboratories, Chicago, IL, USA) because of advanced heart failure due to ischaemic or non-ischaemic cardiomyopathy were asked to participate in this prospective pilot study. All patients underwent a SE examination in conjunction with CE. Exclusion criteria were contraindications for the use of ultrasound contrastagent, such as unstable angina, acute cardiac failure, acute endocarditis, known right-to-left shunts, and known allergy for microbubble contrast agents.

Echocardiographic acquisition

The SE and CE examinations were performed using a Philips EPIQ 7C ultrasound system (Philips Medical Systems, Bothell, USA), with an X5-1 transducer. For SE and CE, a standardized image acquisition protocol based on the American Society of echocardiography guideline was used.[10] In short, parasternal long-axis and short axis views, and apical 4-, 2- and 3-chamber views were obtained using B-mode ultrasound and colour Doppler imaging. For the CE examination, the ultrasound system was switched to its contrast mode. The contrast mode was using amplitudemodulation techniques and a mechanical index of 0.1–0.5 to optimize the CE images. CE was performed using intravenous administration of SonoVue™ ultrasound contrast agent (sulphur hexafluoride microbubble suspension, Bracco S.p.A., Milan, Italy). The ultrasound contrast agent was injected in boluses of 0.5mL, the bolus administration was repeated when necessary up to a total dose of 5.0mL. During and after contrast administration, the patients were observed for potential side effects or complications and LVAD function parameters were monitored. For both SE and CE, cineclips were digitally stored and reviewed offline.

Echocardiographic analysis

The SE and CE studies were reviewed offline by three independent observers unaware of the clinical data. A 17-segment model of the LV was used to analyse the LV in three standard views: parasternal long-axis, apical 4- and 2-chamber view. The image quality of each LV segment on the SE and CE clips was independently scored as (i) interpretable or (ii) uninterpretable. If there was a discrepancy in the scores of the independent readers, a consensus was reached. LV end-diastolic dimension (LVEDD) and LV end-diastolic volume (LVEDV) were assessed on the SE and CE datasets using TomTec Arena software (TomTec Imaging Systems GmbH, Unterschleissheim, Germany). The LVEDD was measured from leading edge to leading edge on the parasternal long-axis view. The LVEDV was assessed with the biplane Simpson method using the 4- and 2-chamber apical view.

Statistical analyses

Statistical analyses were performed using SPSS for Windows (version 17.0, SPSS, Chicago, IL, USA) and Excel (Excel 2003, Microsoft, Redmont, USA). Continuous variables are reported as mean± standard deviation. Categorical variables are expressed as number (%). The v2 test was used to evaluate differences between proportions. A P-value <0.05 was considered to indicate a statistically significant difference.

RESULTS

Patient characteristics

The patient characteristics (mean age 58±9 years, range 43–75 years, 11 (79%) men and 3 (21%) women) are summarized in **Table 1.** The majority of the patients had received a LVAD because of an ischaemic cardiomyopathy (9, 64%), whereas the remaining 5 (36%) patients had a non-ischaemic cardiomyopathy. LVAD implantation was considered as a bridge to transplantation in 8 (57%) patients and a destination therapy in 6 (43%).

Safety and feasibility

All CE studies were performed without adverse reactions and were well tolerated. None of the patients had signs of an allergic reaction and no known or unknown side effects occurred during or after intravenous administration of the contrast agent. No changes in LVAD function parameters were observed during or after CE. The dose of the contrast agent that was necessary for an adequate CE examination in these patients with an LVAD was not different from the dose that is regularly used in our centre for CE in patients without an LVAD. Hence, there were no signs that the HeartMate 3 LVAD caused a substantial destruction of the contrast agent.

Table 1. Clinical characteristics of the study population

Characteristic	Data
Age (y)	58 ± 9
Men	11 (79)
Height (cm)	179 ± 9
Weight (kg)	80 ± 14
BMI (kg/m^2)	25 ± 4
Intermacs class 1-3	8 (57)
Intermacs class 4-7	6 (43)
NYHA class 3	7 (50)
NYHA class 4	7 (50)
Ischemic cardiomyopathy	9 (64)
Nonischemic cardiomyopathy	5 (36)
Paroxysmal atrial fibrillation	6 (43)
Ventricular tachycardia	11 (79)
Percutaneous coronary intervention	7 (50)
Coronary bypass surgery	2 (14)

BMI = Body mass index. Data are presented as numbers of patients (percentages) or as mean ± standard deviation.

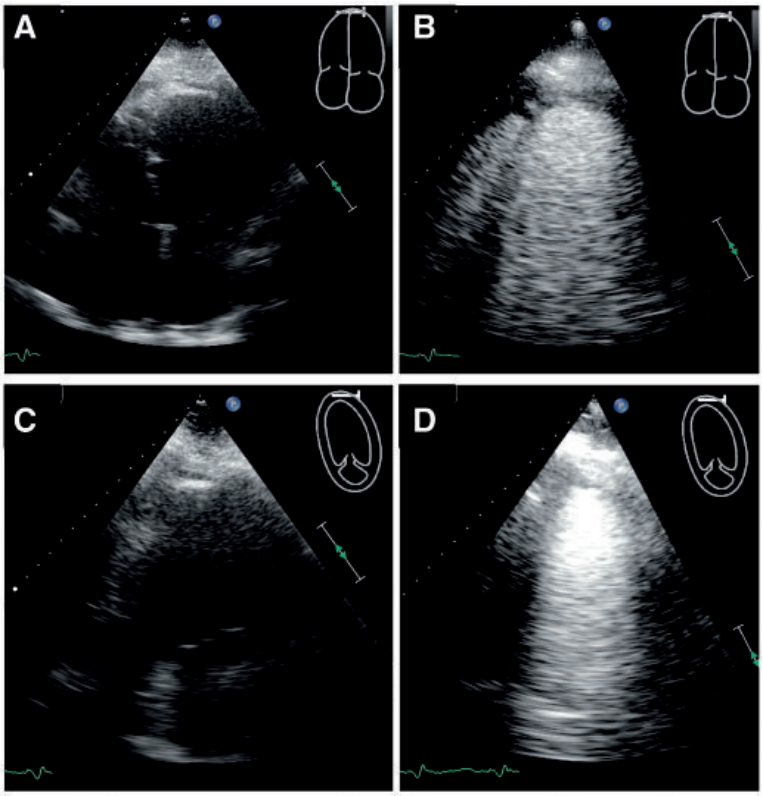
Image quality

SE resulted in an interpretable visualization of all 17 segments in 2 (14%) patients. In the remaining 12 (86%) patients, visualization of the LV segments was impaired (range 0–16 interpretable segments). Using SE, visualization of 57% (135/238) of LV segments was possible. Per patient, SE leads to interpretable image quality in on average 9.6± 5.2 LV segments. CE led to an improvement in the number of interpretable LV segments in 10 (71%) patients. **Figure 1** demonstrates an improved visualization of the LV endocardial borders using CE. In 4 (29%) patients, CE did not change the image interpretation. Overall, CE resulted in a significant improvement of image quality, and visualization of 79% (187/238) LV segments was possible (P< 0.001). Per patient, CE yielded visualization of on average 13.4± 5.8 LV segments, an improvement of 3.8± 2.7 segments as compared to SE.

Assessment of LVEDD was possible in all patients, both on SE (LVEDD 66± 14mm) and CE (LVEDD 64± 11 mm). Using SE, assessment of LVEDV using the biplane Simpson method was possible in 5/14 (36%) patients on SE, with an average LVEDV of 177± 55mL. In four remaining patients assessment of LVEDV on SE was possible only in the 4-chamber apical view, and in five patients assessment of LVEDV was not possible at all.

Administration of contrast agent significantly improved the assessment of LVEDV (feasibility SE: 36% vs. CE: 79%, P< 0.05). Using CE, assessment of LVEDV was possible in 11/14 (79%) of patients with a LVAD (LVEDV 229± 68mL). In two remaining patients assessment of LVEDV on CE was possible only in the 4-chamber apical view, and in one patient assessment of LVEDV was not possible.

Figure 1. Standard echocardiography (SE) and corresponding contrast echocardiography (CE) images in a patient with advanced heart failure and a HeartMate 3 LVAD. SE resulted in a poor visualization of the LV, in both 4-chamber (A) and 2 chamber (C) apical views. After intravenous administration of the ultrasound contrast agent, CE yielded an improved visualization of the LV endocardial borders, in both 4-chamber (B) and 2 chamber (D) apical views. Videos of this example are available online.



Discussion

The main findings of the present study are: (I) that CE in patients with an LVAD is safe and feasible and (II) CE significantly improves the visualization of the endocardial borders of the LV. Imaging of the LV and evaluation of LVEDV is clinically relevant to monitor changes in LV function and size in response to therapy and to detect potential complications, such as intra-cardiac thrombi and blood flow stasis.

Continuous-flow LVADs are increasingly being used in patients with advanced heart failure, as a bridge to LV recovery, cardiac transplantation, or as destination therapy.[1–3]

The evaluation of LV shape, function and intra-cardiac blood flow in patients with a LVAD may be challenging. SE is currently used as the main imaging method in the evaluation of these patients. The current study demonstrates that SE in these patients is associated with a significantly impaired image quality. Several factors may explain the impaired image quality. First, the LVAD and the inflow and outflow cannulas limit the acoustic window. Second, the device may cause artefacts. Third, patients with a LVAD cannot always be optimally positioned for echocardiography. Finally, additional factors like bandages and concomitant lung disease hinder accurate visualization of segmental and global LV function. Computed tomography has been used in the evaluation of these patients, but this technique is also limited by artefacts caused by the LVAD. Additionally the use of iodinated contrast agent is a limitation of that technique, particularly in those with an impaired renal function. Cardiac magnetic resonance imaging cannot be used because of the metal components of the LVAD.

The American Society of Echocardiography and the European Association of Echocardiography have recognized the clinical value of CE and issued position papers providing guidelines.[10–12] It has become clear that CE is a safe imaging modality[13,14] that may provide improved image quality or information that cannot be obtained by SE in stable and critically ill patients.[15,16] Clinical applications of CE include: improvement of LV endocardial border delineation, reduction of variability in assessment of LV volumes and function, increase reader confidence, and assessment of LV structural abnormalities: apical variant of hypertrophic cardiomyopathy, ventricular noncompaction, apical thrombus, aneurysm, pseudo aneurysm, myocardial rupture and intracardiac masses (tumours and thrombi).[6,7,10–12]

Recently, CE has been proposed, in a case-report[8] and a retrospective case series,[9] as a potentially useful imagingmodality in the evaluation of patients with a LVAD. Moser et al.[8] reported the case of a 25-yearold woman with a non-ischaemic cardiomyopathy and a LVAD (HeartMate II). Echocardiography revealed an apical pseudo aneurysm on SE, additional CE demonstrated a bidirectional flow between the LV and the pseudo-aneurysm evident by contrast enhancement. This case demonstrates the critical role of SE and CE in the follow-up of patients with a LVAD to confirm circulatory function and exclude device-related complications. Fine et al.[9] retrospectively reviewed the records of 251 patients with a LVAD implantation who received a clinically indicated echocardiogram. Of them, 10 (4%) patients with a LVAD (HeartMate II in 9, Heartmate XVE in 1 patient) underwent a CE study, of whom 2 patients had a repeat CE study. No adverse events or known side-effects occurred during or after CE. These patients underwent a CE because of a suboptimal endocardial border delineation during

SE. The use of contrast agent (Definity in 9 and Optison in 3 patients) aided image interpretation in 10 (83%) CE examinations.

The current prospective study confirms that CE in patients with a LVAD (all patients had a HeartMate 3) is safe, and can be performed with a regular dose of contrast agent (Sonovue). There were no signs that the LVAD caused a substantial destruction of the contrast agent. This study has clinically relevant implications. This study shows that the SE allowed visualization of 57% of LV segments. After safe and easy intravenous administration of the ultrasound contrast agent, CE resulted in visualization of 79% of LV segments. Moreover, LV size determination could be obtained more often due to improved LV visualization using CE. Clearly, segmental and global LV function and LVEDV are important parameters in patients with a LVAD to monitor alterations in response to therapy and to diagnose potential complications.

This study has several limitations. First, because this was a pilot study, the number of patients that was considered was small. Second, potential destruction of the contrast agent by the LVAD was visually assessed and could not be quantitatively assessed. Third, this study was performed with Sonovue contrast agent, and it is not clear whether the results can be extrapolated to CE using other agents. Fourth, all of the patients had a HeartMate 3 LVAD, and it is not sure whether the current results can be extrapolated to patients with other LVAD systems. Fifth, the mentioned contraindications were considered at the time of the study conception and design, recently the contraindications have been removed by the US Food and Drug Administration

CONCLUSION

Routine use of a contrast agent appears safe when used in patients having a new third generation LVAD and may enhance the diagnostic accuracy of transthoracic echocardiography in these patients. LV size determination can be obtained more often due to improved LV visualization using contrast agent.

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CHAPTER 8

Acute kidney injury and 1-year mortality after left ventricular assist device implantation.

Muslem, R. Caliskan, K. Akin, S. Sharma, K. Gilotra, N.A. Constantinescu, A.A. Houston, B. Whitman, G. Tedford, R.J. Hesselink, D.A. Bogers, A.J.J.C. Russell, S.D. Manintveld, O.C.

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Abstract

BACKGROUND: Data on the consequence of acute kidney injury (AKI) after continuous-flow left ventricle assist device (LVAD) implantation are scarce and inconsistent. In the current study, the incidence, predictors and the impact of AKI on mortality and renal function in the first year after LVAD implantation was evaluated.

METHODS: A retrospective multi-centre cohort study was conducted, including all patients (age ≥18) undergoing LVAD implantation (91% HeartMate II, 9% HVAD). The definition proposed by the Kidney Disease Improving Global Outcome criteria (KDIGO) was used to define AKI.

RESULTS: Overall, 241 patients (mean age 52.4±12.9 years, 76% male) were included. AKI criteria were met in 169 (70%) patients, of whom 109 (45%) had AKI stage I, 22 (9%) stage II and 38 (16%) stage III. The need for pre-operative inotropic support and pre-existent chronic kidney disease stage ≤ 2 (eGFR <30 ml/min/1.73 m2) were independently associated with the development of AKI and the severity of AKI stages. One-year mortality rates in patients without AKI, AKI stages I, II and III were 18.7%, 26.4%, 23%, and 51%, respectively (log-rank p=0.001). In multivariable analysis, AKI stages ≥ II were independently associated with mortality (HR 2.2 (95% CI 1.1-4.5), p=0.027) and worse renal function (β -7.4 (95% CI -12.6 to -2.1), p<0.01) at 1 year.

CONCLUSION: AKI is highly frequent after LVAD implantation. More severe AKI stages are associated with higher mortality rates and impaired renal function at one year after LVAD implantation.

INTRODUCTION

Continuous flow left ventricular assist devices (CF-LVADs) have become an important tool in the treatment of end-stage heart failure (HF) and may be used as a bridge-to transplantation (BTT) or as destination therapy (DT). This has led to a significant improvement in the quality of life and survival of patients with end-stage HF when all other therapeutic options have been exhausted.(1) The new generation of LVADs is smaller, more durable and has resulted in improved complication profiles and survival as we have gained experience in their peri- and post-operative management.(1)

Prior to pump placement, many LVAD candidates already have compromised renal function secondary to HF.(2) In addition, it has been demonstrated that impaired pre-operative renal function is associated with worse survival after CF-LVAD implantation.(3) Acute kidney injury (AKI) has been identified as a risk factor for mortality after cardiac surgery.(4-8) Therefore, after implantation of a CF-LVAD, patients are also at risk for developing AKI in the early post-operative phase. However, inconsistent results are reported regarding the incidence of AKI after CF-LVAD implantation, ranging from 10% to 45%.(2, 3, 9-14) In addition, results on the impact of AKI on mortality and long-term renal function after CF-LVAD implantation are conflicting. This is likely due to inconsistent definitions of AKI, uncertainty about the exact onset of AKI and an inadequate description of long-term clinical outcomes and survival. Therefore, we sought to evaluate the early post-implantation incidence of AKI, defined by the AKI criteria proposed by the Kidney Disease: Improving Global Outcome (KDIGO) group,(15) corresponding risk factors and the impact of AKI on mortality and renal function during the first year after CF-LVAD implantation.

METHODS

Study design and population

We conducted a retrospective cohort study evaluating all patients in whom a CF-LVAD was implanted between October 2004 and August 2015 in the two participating tertiary referral centres (Thorax center, Erasmus MC, Rotterdam, the Netherlands and Johns Hopkins Heart and Vascular Institute, Baltimore, USA). The CF-LVADs were either a HeartMate II (St. Jude Medical, MN) or a HeartWare (HeartWare International Inc.) device. Exclusion criteria were age younger than 18 years or death within 48 hours after CF-LVAD implantation. Data were obtained from a computerized database and electronic patient records, which was systematically collected during follow up. This study was approved by the Institutional Review Board of the Erasmus MC, University Medical Center Rotterdam as well as the Johns Hopkins Hospital.

Study Endpoint, Definitions and Data Collection

The primary study endpoint was the incidence of AKI as defined by the KDIGO criteria (**Table 1**) during the first 7 days after CF-LVAD implantation. Secondary endpoints included the impact of AKI on mortality, renal function at one year after CF-LVAD implantation and the requirement of renal replacement therapy (RRT) following CF-LVAD implantation.

Patients were grouped in the RRT-group if they required RRT within the first 7 days after CF-LVAD implantation. RRT was defined as the need for treatment with either continuous veno-venous hemofiltration (CVVH) or intermittent haemodialysis (IHD). Deaths were classified as "cardiac" when a definitive cause of death related to a cardiovascular event could be identified. Deaths were classified as "non-cardiac" when the cause of death did not relate to the cardiovascular system. When the cause of death was unknown, deaths were classified as "undetermined". Serum creatinine concentrations were collected at baseline, daily for the first seven post-operative days, and at 1, 3, 6, 9 and 12 months following CF-LVAD implantation, respectively. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula.(16) Patients were grouped according to their eGFR at baseline based on the Kidney Disease Outcomes Quality Initiative guidelines.(17) Since previous studies have demonstrated that chronic kidney disease (CKD) is one of the most important risk factors for AKI (18-20), eGFR at baseline was categorized to evaluate the association between an impaired renal function at baseline and the aforementioned study endpoints.

Statistical Analyses

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, ANOVA or Kruskal-Wallis test. Categorical parameters were expressed as number and percentage and compared by Chi^2 test, Fisher's exact test or Mantel-Haenszel test for trend. Multivariable ordinal logistic regression analysis was performed for the identification of risk factors associated with (the severity of) AKI. Kaplan-Meier curves stratified by AKI stage were constructed for the evaluation of mortality in the first year after CF-LVAD implantation. Differences were compared by log-rank test. A multivariable Cox proportional hazards analysis was performed for the identification of parameters associated with mortality and a multivariable linear model analysis was performed for the association with eGFR 1 year after implantation. Variables were included in the multivariable models if $p<0.10$ 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 20.0 for Mac (SPSS Inc., IBM company, Chicago, IL) and GraphPad Prism version 5.0a for Mac (GraphPad Software, La Jolla, CA).

Table 1. Definition of AKI by the Kidney Disease Improving Global Outcome criteria

AKI stage	Serum Creatinine (μmol/L)
I	≥26.4 μmol/L (0.3 mg/dL) within 48 hours, or 1.5 to 2.0 times baseline within 7 days
II	2.0 to 2.9 times baseline
III	≥3.0 times baseline, or increase in SCr to ≥353.6 μmol/L (≥4.0 mg/dL), or initiation of renal replacement therapy

Modified from the Kidney Disease Improving Global Outcome: Acute Kidney Injury Workgroup. (18) Conversion factor creatinine: divide by 88.42; SCr, serum creatinine concentration**.**

RESULTS

AKI Incidence and Associated Risk Factors

During the study period, 251 patients underwent CF-LVAD implantation, of which 241 patients with a mean follow-up of 265 ± 138 days were included for further analysis. Ten patients were not included because they were younger than 18 years (n = 7) or died within 48 hours following CF-LVAD implantation (n = 3). The baseline characteristics of the 241 included patients are shown in **Table 2**.

In total, 169 (70%) patients developed AKI, of which 109 (45%) developed stage I, 22 (9%) developed stage II, and 38 (16%) stage III. Overall, 23 (9.5%) patients required RRT within 7 days following implantation. Twenty-one of these patients were treated with CVVH and two with IHD, for a median duration of 20 days (interquartile range, 7-34 days). Baseline demographic and comorbidities did not differ significantly between AKI stages (**Table 2**). Furthermore, 75%, 79%, 91%, and 92% of the patients without AKI, AKI stage I, II, and III received inotropic support prior to LVAD implantation.

When stratified by AKI stage, a significant linear association existed between the requirement for intra-aortic balloon pump (IABP) (p = 0.04) or inotropic support (p = 0.02) pre-implantation and subsequent increased severity of AKI. In addition, a significant association existed (p = 0.03) between a higher CKD stage (lower grouped eGFR) at baseline and an increased risk of developing AKI (**supplementary Figure 1**). Univariate analysis confirmed the association with baseline eGFR and AKI. Furthermore, in the univariate analysis lower INTERMACS class and the need for inotropic support were associated with an increased risk of developing AKI, and subsequent its severity. In the multivariable analysis, factors independently associated with the development of AKI, and its severity were baseline eGFR <30 mL/min per 1.73m^2 (2.98; 95%-CI 1.37 – 6.51l p = 0.006) and need for inotropic support before CF-LVAD implantation (2.43; 95%-CI 1.06 – 5.58; p = 0.037).

Table 2. Demographic and clinical characteristics of the study population stratified by AKI stage

	No AKI, n = 72	AKI Stage I, n = 109	AKI Stage II, n = 22	AKI Stage III, n = 38	p-value
	n (%)	n (%)	n (%)	n (%)	
Age, y*	52.1±13.4	51.9±13.0	51.8±13.5	55.0±11.7	0.62
Male	52 (72)	84 (77)	15 (68)	31 (82)	0.58
BMI, kg/m²*	26.5±6.1	26.7±6.3	26.2±7.5)	27.5±5.3	0.86
African American	21 (29)	43 (39)	6 (27)	15 (40)	0.40
Comorbid conditions					
• Diabetes Mellitus	23 (32)	41 (38)	10 (46)	17 (45)	0.50
• Hypertension	35 (49)	51 (47)	9 (41)	22 (58)	0.58
• ICD or PM	61 (85)	93 (85)	17 (77)	31 (82)	0.79
• CABG	6 (8)	13 (12)	2 (9)	6 (16)	0.67
• TIA or CVA	12 (17)	21 (19)	1 (5)	10 (26)	0.20
Primary cardiac disease					0.87
• Ischemic	22 (31)	39 (36)	8 (36)	14 (37)	-
• Non-Ischemic	50 (69)	70 (64)	14 (64)	24 (63)	-
eGFR stage at baseline, mL/min per 1.73 m²					0.001
• ≥60	46 (50)	50 (46)	17 (77)	11 (29)	-
• 30-59	31 (43)	47 (43)	5 (23)	16 (42)	-
• <30	5 (7)	12 (11)	-	11 (29)	-
Pre-operative hemodynamic support					
• IABP	28 (39)	37 (34)	12 (55)	21 (55)	0.06
• ECMO	6 (8)	7 (6)	-	2 (5)	0.56
• Inotropic med.	54 (75)	86 (79)	20 (91)	35 (92)	0.09
INTERMACS score					0.13
• Class I	12 (17)	19 (17)	7 (32)	13 (34)	
• Class II	25 (35)	42 (39)	6 (27)	16 (42)	
• Class III	19 (26)	22 (20)	7 (32)	4 (11)	
• Class ≥IV	16 (22)	26 (24)	2 (9)	5 (13)	
Device Type					0.39
• HeartMate II	65 (90)	99 (91)	22 (100)	33(87)	-
• HeartWare	7 (10)	10 (9)	-	5 (13)	-
LVAD indication					
• BTT	48 (67)	75 (69)	13 (59)	19 (50.0)	0.19
• DT	23 (32)	33 (30)	7 (32)	17 (45)	0.43

*Continuous variables are presented as mean ± standard deviation, Categorical variables are presented as number (percentage). BMI, Body mass index; BTT, Bridge-to-transplant; CABG, Coronary Artery Bypass Graft; CVA, Cerebrovascular accident; DT, Destination Therapy; ECMO, Extracorporeal membrane oxygenation; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; IABP, Intra-aortic balloon pump; Inotropic med, on Inotropic medication; ICD, Implantable Cardioverter Defibrillator; PM, Pacemaker; TIA, Transient Ischaemic Attack.

Clinical outcome in the first year after CF-LVAD implantation

Thirty-three (14%) patients underwent heart transplantation (**Table 3**) and 65 patients (27%) died during the first year after CF-LVAD implantation. The most frequent cause of death was non-cardiac (58.5%) followed by cardiac (38.5%). In two (3.1%) patients the cause of death was undetermined. Overall 30-day mortality was 12%. Stratified by AKI stage, the absolute 30-day mortality was 8.3%, 10.1%, 13.6% and 26.3% for those without AKI, AKI stage I, II and III, respectively (p = 0.04).

Figures 1. Kaplan-Meier curves for survival during the first year after CF-LVAD implantation.
The Kaplan-Meier curves show the cumulative survival of patients during the first year after CF-LVAD implantation, stratified by AKI stage (A) and by patients requiring RRT (B).

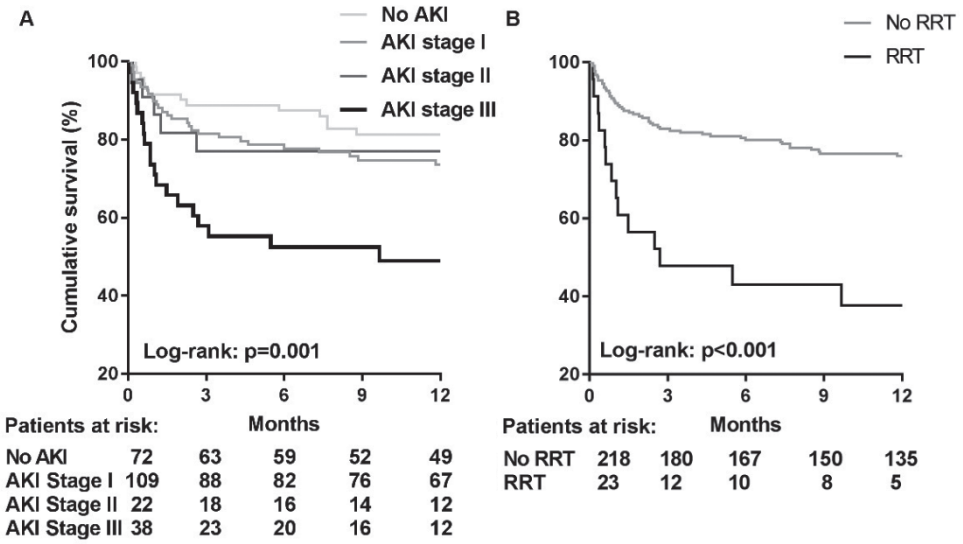


Table 3. Clinical outcomes during the first year after CF-LVAD implantation

	No AKI n = 72 n(%)	AKI Stage I n = 109 n(%)	AKI Stage II n = 22 n(%)	AKI Stage III n = 38 n(%)	p-value
30-day mortality	6 (8.3)	11 (10.1)	3 (13.6)	10 (26.3)	0.04[a]
1-year mortality*	13 (18.1)	28 (25.7)	5 (22.7)	19 (50.0)	0.004[a]
Heart transplantation	10 (13.9)	15 (13.8)	3 (13.6)	5 (13.2)	1.00
RVAD	2 (2.8)	7 (6.4)	1 (4.5)	3 (7.9)	0.64
CRRT	-	5 (4.6)	-	4 (10.5)	0.03[a]

*Cumulative mortality at one year. CRRT, Chronic Renal Replacement Therapy, RVAD, Right Ventricle Assist Device. a Statistically significant (P < 0.05).

Separate analysis of patients who received RRT within 7 days compared to those without the need for RRT showed an absolute 30-day mortality of 30.3% compared to 10.6% (p = 0.006), respectively. Kaplan-Meier survival curves stratified by AKI stage or RRT requirement are presented in **figures 1A & B**. The expected one-year mortality was 27.7%, and stratified by AKI stage, one-year mortality was 18.7%, 26.4%, 23% and 51% for patients without AKI, AKI stage I, II and III (Log-rank p = 0.001), respectively. Patients with RRT requirement had an expected one-year mortality of 62.3% compared to 24% in those without RRT requirement (Log-rank p < 0.001). Univariate analysis of the relationship with mortality identified an association with AKI stage ≥II, older age, eGFR <60mL/min per 1.73m^2 at baseline, destination therapy, INTERMACS classification I & II, and RVAD requirement. Furthermore, these factors remained independently associated with 1-year mortality in the multivariable analysis (**Table 4**).

Table 4. Multivariable Cox proportional-hazards analysis of characteristics for the association with mortality during the first year after CF-LVAD implantation

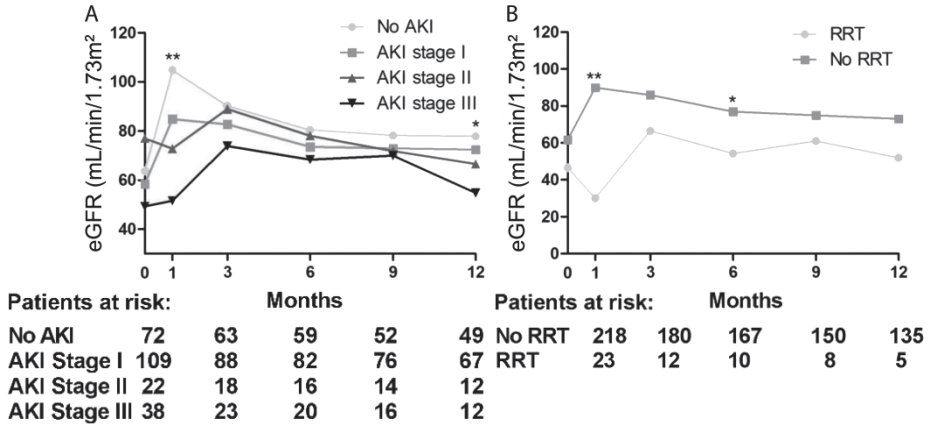
	Multivariate		
	HR	95% CI	p-value
AKI stage			
- No AKI	1	-	-
- Stage I	1.33	0.69 – 2.59	0.397
- Stage ≥II	2.42	1.20 – 4.86	0.013 [a]
Age, years	1.03	1.00 – 1.05	0.037 [a]
Destination Therapy	1.74	1.03 – 2.93	0.038 [a]
eGFR stage at baseline, mL/min per 1.73 m^2			
≥60	1	-	-
30-59	2.24	1.24 – 4.04	0.008 [a]
<30	2.67	1.25 – 5.70	0.011 [a]
INTERMACs			
- Class I & II	1.95	1.09 – 3.49	0.024 [a]
- Class ≥III	1	-	-
RVAD*	4.77	2.10 – 10.83	<0.001 [a]

HR, hazard ratio. 95% CI, Confidence interval.
[a] Statistically significant (P < 0.05). *event occurring in the first year.

Renal function in the first year after CF-LVAD implantation

The course of renal function (eGFR) stratified by AKI stage or RRT requirement during the first year after CF-LVAD implantation is presented in **figures 2A and 2B**. The mean baseline eGFR was 63, 58, 77, and 49 mL/min per 1.73m^2 in patients without AKI, AKI stage I, II, and III (p <0.001), respectively. Of the 142 patients supported by a CF-LVAD at 1 year, 2 patients had missing laboratory values. The mean eGFR at 1 year was 78, 72, 67 and 55 mL/min per 1.73 m^2, in patients without AKI, stages I, II, and III, respectively (p = 0.038). Within AKI stages, mean eGFR improved significantly at one year compared to baseline in patients without AKI and those with AKI stage I (p = 0.001 & p < 0.001). However, in patients with AKI stage II, the mean eGFR deteriorated during the first year (p = 0.016). In addition, the mean eGFR at one year in AKI stage III patients did not differ significantly compared to baseline and remained impaired (eGFR <60 mL/min per 1.73m^2). A significant difference was observed in mean eGFR at baseline, one month and six months post-implantation between patients that received RRT and those who did not. However, this effect was not presented at one year after CF-LVAD implantation between these two groups.

Figure 2. Renal function assessment during the first year after CF-LVAD implantation



Renal function presented as mean estimated glomerular filtration rate, stratified by AKI stage (A) and by patients requiring RRT (B), *P<0.05, **P<0.001.

Furthermore, only a significant improvement in renal function was observed in patients free from RRT (p < 0.001) at one-year. During the first year, 9 patients (4%) became chronically dependent on RRT. Univariate analysis for the relationship with eGFR at one year identified an association for age, ethnicity, baseline eGFR, ischemic cardiac disease as primary cardiac disease and AKI stages ≥II. As presented in **table 5**, factors independently associated with a lower eGFR 1 year after CF-LVAD implantation were higher age, AKI stages ≥II and eGFR <60 mL/min per 1.73 m^2.

Table 5. Multivariable linear model analysis of characteristics for the association with renal function (eGFR) one year after CF-LVAD implantation

	Multivariate		
	β	95% CI	p-value
AKI stage			
- No AKI	0	-	-
- Stage I	3.46	-0.373 to 10.65	0.342
- Stage ≥II	-7.35	-12.56 to -2.14	0.006 [a]
African American	4.52	-2.82 to 11.85	0.225
Age, years	-0.54	-0.85 to -0.23	0.001 [a]
eGFR stage at baseline, mL/min per 1.73 m^2			
- ≥60	0	-	-
- 30-59	-16.78	-24.33 to -9.24	<0.001 [a]
- <30	-35.93	-49.49 to -22.36	<0.001 [a]
Ischemic cardiomyopathy	-1.91	-9.93 to 6.11	0.638

95% CI, Confidence interval. [a] Statistically significant (P < 0.05).

Table 6. Comparison of the RIFLE and the KDIGO criteria

RIFLE criteria	n (%)	**KDIGO criteria**	n (%)
None	130 (54%)	No AKI	72 (30%)
Risk	59 (25%)	AKI stage I	109 (45%)
Injury	32 (13%)	AKI stage II	22 (9%)
Failure	20 (8%)	AKI stage III	38 (16%)
Univariate cox-regression analysis for mortality			
	Stage	OR (95% CI)	p value
RIFLE	None	1	
	Risk	1.05 (0.57-1.95)	0.87
	≥Injury	1.58 (0.88-2.81)	0.12
KDIGO	No AKI	1	
	AKI stage I	1.50 (0.78-2.89)	0.23
	AKI stage ≥II	2.72 (1.38-5.34)	0.004

RIFLE, Risk, Injury, Failure, Loss, End-stage Renal Disease; KDIGO, Kidney Disease Improving Global Outcome; AKI, acute kidney injury

Comparison of the RIFLE- with the KDIGO-criteria

When comparing the Risk, Injury, Failure, Loss, End-stage Renal Disease (RIFLE) criteria for AKI with the KDIGO criteria , we observed a difference in the classification of AKI stages (Table 6). Furthermore, the KDIGO criteria performed better when predicting mortality at one year after LVAD implantation than the RIFLE criteria (AUC 0.62 VS. 0.55). In addition, only the KDIGO criteria was a significant predictor of mortality at one year (**Table 6**).

Discussion

This work demonstrates that AKI is a frequent complication of CF-LVAD implantation and that it has significant consequences for patients supported with a CF-LVAD. To the best of our knowledge, this is the largest series to evaluate the incidence and impact of AKI after CF-LVAD implantation. With an incidence of 70%, AKI was a highly frequent complication, and strongly associated with death both at 30 days, as well as at 1-year post-implantation. Furthermore, the severity of AKI was a strong prognostic factor for mortality and poor renal function one year after CF-LVAD implantation.

The incidence of Acute Kidney Injury

Previous studies investigating the incidence of AKI in CF-LVAD patients were limited because of their single centre study design and by the varying criteria used for the definition of AKI. These studies generally defined AKI based on the need for RRT,(3, 9, 11, 12, 21) the RIFLE criteria or non-standardized definitions.(10, 13, 14, 22, 23) Consequently, there has been a large variation in the reported AKI incidence between these studies, ranging from 10% up to 45%. Defining AKI as the need for RRT limits the ability to stratify patients adequately. More importantly, an impaired renal function pre-operative, is an independent and major risk factor for mortality.(24) Stratifying patients based on their pre-implant renal function and subsequently classifying them based on post-operative changes in renal function may therefore be more appropriate. The KDIGO criteria does take this into account when classifying patients into AKI stages. When compared to the RIFLE criteria, the KDIGO criteria demonstrates a higher sensitivity for small increase in serum creatinine concentration, resulting in a larger number of patients classified as AKI stage I.(15, 25) This is in line with our observations. We report an overall high incidence of AKI and distributed this in AKI stages I (45%), II (9%) and III (16%) according to the KDIGO criteria. Furthermore, we observed an incidence of 9.5% for the need of RRT within the first 7 post-operative days. Other studies have reported a need for RRT ranging from 10% to 35% in CF-LVAD patients during the first year.(3, 9, 11) In our cohort, 13.3% and 16.6% of the

patients needed RRT at one month and one year after CF-LVAD implantation. The lower incidence of RRT is likely because we evaluated renal function within 7 days of CF- implantation, while other studies included subjects who required RRT later in their post-operative course.

Predictors of AKI

Pre-implantation eGFR, use of IABP, older age, higher LVAD risk scores, longer cardiopulmonary bypass times, intraoperative bleeding, and need for reoperation have been suggested to predict renal failure post-implantation.(3, 14, 26) The definition of renal failure post-implantation used by these studies included renal failure requiring CVVHD (3, 26) and the definition proposed in the RIFLE criteria.(14) Additionally, only higher LVAD risk scores were an independent predictor of post-operative renal failure. (26) This is supported by our final model, only pre-implantation inotropic support or eGFR <30 mL/min per 1.73 m^2 were independently associated with an increased risk for AKI and subsequent severity. In combination with the association between requirement of an IABP or inotropic support and increased severity of AKI stages, this suggest that sicker patients with severely impaired renal function before CF-LVAD implantation are at the highest risk for developing AKI and more severe AKI stages. In addition, they are also prone to have a worse renal function one year after LVAD implantation.

The impact of AKI on mortality

Prior studies that investigated the impact of AKI on mortality after CF-LVAD implantation reported that AKI is an independent predictor of mortality.(23, 27) However, in these studies AKI was defined according to the creatinine based RIFLE "Risk" Criteria and included a high percentage of patients needing RRT in the AKI groups. Other studies defining AKI as RRT-requirement reported mortality rates as high as 40-70% in AKI patients, emphasizing that patients requiring RRT are at the highest risk for mortality after CF-LVAD implantation.(3, 9, 11) Based on our data, stratifying patients by AKI stages according to the KDIGO criteria may be superior to stratifying by the need for RRT, as the former method allows a more precise assessment of graded mortality risk. Our study shows that AKI constituted a crude predictor proportional to the stage of severity for both 30-day and 1-year mortality. Furthermore, a similar pattern of survival was observed when stratified by the need for RRT. In addition, a more pronounced effect of AKI on mortality was observed in recipients that had a baseline eGFR less than 60 mL/min per 1.73 m^2 (Supplementary Figure 2), confirming the independent protective effect of higher baseline eGFR. Furthermore, after multivariable adjustment, we observed that the association between AKI and mortality was due to AKI stage II and III. This includes the patients that required RRT. The increased mortality of the RRT

patients might be due to a greater number of comorbidities, the development of multi-system organ failure, or an independent systemic process associated with AKI.

Renal function at 1 year after CF-LVAD implantation

Due to decreased renal perfusion in the setting of low cardiac output as well as reno-vascular congestion, it is not unexpected that heart failure patients undergoing CF-LVAD implantation frequently have baseline impaired renal function.(28) However, previous studies have demonstrated that the majority of patients experience renal improvement during CF-LVAD support. Stratified by AKI stages, one can see that it is the patients experiencing no AKI or AKI stage I that had significantly improved renal function at one year after implantation compared to baseline, while those with AKI stage II and III did not have any significant improvement in renal function. This could be due to the intrinsic renal damage suffered by these patients before CF-LVAD implantation or in the peri-operative period, which seems to be irreversible in these patients. However, our study is limited due to the low number of survivors in the AKI stage II and III groups, and therefore, this finding requires validation in a larger cohort using longitudinal data.

Clinical implications

A growing number of ventricular assist devices are being implanted as destination therapy.(1, 29) This rise is partially explained by patients that are referred for LVAD as DT because of their ineligibility for heart transplantation, due to a variety of reasons, including for example; advanced age and renal failure.(30, 31) Older age (>70 year) and worse baseline eGFR are reported to be predictors of mortality and worse renal function during LVAD support.(3, 32) Preventing AKI or intervening before patients develop severe AKI could positively affect the renal function of patients and reduce mortality. However, in line with our data, it seems that patients in lower INTERMACs classes with severe renal impairment develop AKI.(12, 26) Therefore, LVAD implantation should be considered before extreme hemodynamic instability develops. Furthermore, studies that have addressed AKI after general cardiac surgery, have noted several interventions to prevent AKI,(33) including the management and monitoring of intravenous fluid administration, vasoactive agent administration, effects of fluid challenges on left ventricle stroke volume and balanced-salt fluid administration.

Limitations

There are certain limitations to our study that should be taken into consideration while interpreting the results. First, the retrospective observational study design does not offer the possibility to establish causality. Furthermore, the AKI stage II group consisted of a relatively small number of patients, which could have affected the outcome of the analysis. Also, the mean eGFR was compared between groups at different time points. A

non-linear longitudinal mixed model has been mentioned to be a comparable method to analyse continuous variables over time. However, due to the large sample size, excellent follow-up data, multi-centre study design and the use of a consensus definition of AKI, it was possible to perform extended multivariable analysis. Also, the inclusion of different types of CF-LVADs, and American as well as European patients strengthens the conclusions in our study and its generalizability.

CONCLUSION

Our study demonstrates that AKI is a highly frequent complication after CF-LVAD implantation and that AKI adversely affects early and long-term renal function and survival of CF-LVAD patients during the first year. The association with mortality is strongly related to the severity of AKI. Prevention or mitigation of the severity of AKI after CF-LVAD implantation should therefore be an important goal of peri-operative care.

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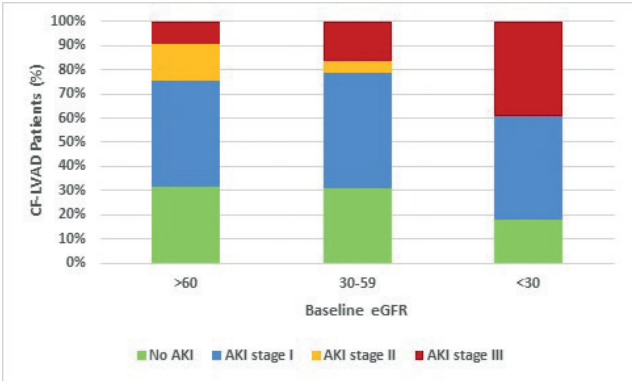
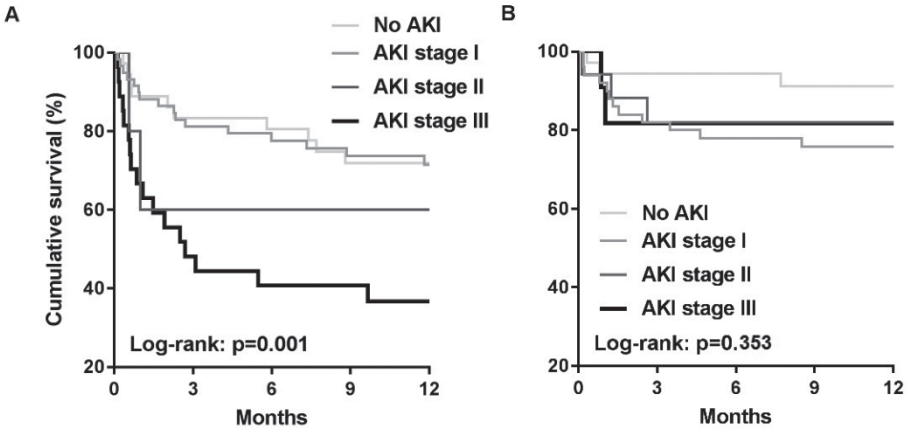
Appendix

Appendix Figure 1. Proportion of AKI categorized by estimated glomerular filtration rate at baseline



Appendix Figure 2. Survival curves based on renal function during the first year after CF-LVAD implantation

The Kaplan-Meier curves show the cumulative survival based on (A) the analysis of patients with mean eGFR below 60 mL/min per 1.73 m2, and (B) the Analysis of patients with mean eGFR above 60 mL/min per 1.73 m2, stratified by AKI stage.



CHAPTER 9

Pre-operative proteinuria in left ventricular assist devices and clinical outcome.

Muslem, R. Caliskan, K. Akin, S. Sharma, K. Gilotra, N.A. Brugts, J.J. Houston, B. Whitman, G. Tedford, R.J. Hesselink, D.A. Bogers, A.J.J.C. Manintveld, O.C. Russell, S.D.

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Abstract

BACKGROUND: This study evaluated the association of pre-operative proteinuria before CF-LVAD implantation in relation to mortality and the need for RRT during the first year of follow-up.

METHODS: A retrospective, multicenter cohort study was conducted, evaluating all CF-LVAD patients (n=241) implanted in the two participating tertiary referral centers. Patients were included if they had a urine dipstick performed within 7 days before CF-LVAD implantation. Proteinuria was defined as ≥ trace.

RESULTS: In total, 173 (72%) patients were included (mean age 52.3 ± 13.3, 78% male, mean estimated GFR 60.1 ± 25.9 mL/min per 1.73 m^2). Forty-two patients (24%) had pre-operative proteinuria. The observed 3-months and 1-year survival in patients with proteinuria *vs*. without proteinuria was 57% vs 86% and 52% *vs*. 78% (Log-rank $p < 0.001$), respectively. In addition, during the first year post-implantation, 32% of the patients with proteinuria and 15% of the patients without proteinuria required RRT (Log-rank $p = 0.02$). Multivariate Cox-regression analysis confirmed that pre-operative proteinuria was an independent predictor for mortality (adjusted hazard ratio 2.09, 95%-CI 1.10 to 3.80, $p = 0.02$) and for the need of RRT during the first year (adjusted hazard ratio 2.23, 95%-CI 1.13 to 4.84, $p = 0.02$).

CONCLUSION: One quarter of all tested LVAD patients had proteinuria, which predicts worse outcome in terms of all-cause mortality and need of RRT in patients with a CF-LVAD. This warrants for the use of proteinuria in risk stratification, when selecting patients for CF-LVAD therapy.

INTRODUCTION

Continuous-flow left ventricle assist devices (CF-LVADs) are increasingly used as standard care of therapy for end-stage heart failure (HF). As a consequence of the improvement in technology and medical expertise, a trend towards an improvement in patient survival has been noted.(1) This improved survival is partially due to better patient selection, accomplished through acknowledgement of important risk factors that play a key role in predicting clinical outcomes. Furthermore, these risk factors are used to inform patients and family members concerning their risk factors that might impair their quality of life or even result in death post-implantation. In addition, clinicians also benefit from identifying risk factors, which are often used in risk models in order to improve decision making processes regarding patient selection.

Reduced estimated glomerular filtration rate (eGFR), higher blood urea nitrogen level (BUN) and proteinuria are independent predictors of cardiovascular and all-cause mortality in the general population.(2, 3) However, several risk scores, that predict overall outcomes and survival in CF-LVAD patients, only include creatinine or BUN. (4, 5) Therefore, proteinuria measurements are currently not used in clinical practice to risk stratify patients preoperatively.

A recent publication from Topkara *et al, (6)* reported that pre-operative proteinuria, determined through a qualitative dipstick assessment, predicts the need for renal replacement therapy after CF-LVAD implantation. However, the impact of proteinuria on the survival of CF-LVAD patients remains unknown.

The aim of the present study was to assess if proteinuria could be of additional value in classifying patients in to risk groups for worse outcome. Therefore, we evaluated the association of proteinuria before CF-LVAD implantation in relation to mortality and the need for RRT during the first year of follow-up.

METHODS

Study Design

We conducted a retrospective cohort study evaluating all adult (age ≥18) CF-LVAD recipients (n=241) implanted between 2004 and 2016 in the two participating tertiary referral centers (Thorax center, Erasmus MC, University Medical Center Rotterdam, the Netherlands and Johns Hopkins Heart and Vascular Institute, Baltimore, USA). The devices were either the HeartMate II (Abbot, Chicago, IL) or the HeartWare (HeartWare

International Inc., Framingham, MA). In order to be included in this analysis, a urine dipstick measurement within a 7-day period before CF-LVAD implantation had to be available. Proteinuria was measured and determined qualitatively using a standard urinary dipstick and quantified as negative, trace (protein < 30 mg/dL), 1+ (30 to 100 mg/dL), ≥2+ (≥100 mg/dL). Due to hematuria, the dipstick result can be false-positive. (7) We used the definition proposed by the American Urological Association (AUA) and defined hematuria as >3 red blood cells/high-power field (RBC/hpf) on microscopic examination of the centrifuged urine samples or as a positive dipstick for hematuria. (8) Patients with missing data regarding proteinuria (n = 30, 12%) and patients with hematuria (n = 38, 16%) were excluded from further analyses. Based on age, gender, eGFR and INTERMACS class, these patients were fairly comparable with the included cohort. In addition, there were no significant difference in the study outcomes between these patients.

The primary study endpoint was to determine the association of proteinuria before CF-LVAD implantation in relation to mortality and the need for RRT during the first year follow-up. Secondary endpoints included the composite end-point during the first year post-implantation.

Data collection

All data were obtained from the electronic patient records. One hundred and forty (81%) patients form the Johns Hopkins Hospital (125 HM II, 15 HVAD) and 33 (19%) from the Erasmus MC were included (all HM II). Baseline laboratory values were collected pre-operative for all patients. In order to validate the calculated eGFR the Modification of Diet in Renal Disease (MDRD) formula was used. This was at the time being also the standard in both centers.(9) RRT after CF-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 HD before or at the time of LVAD implantation. Patients were classified into two groups based on their dipstick results for proteinuria (trace or greater vs. none). For the present analysis we used a composite end-point which included mortality or the need for RRT, whichever occurred first. This study was approved by the institutional review board of the Erasmus MC and the Johns Hopkins Hospital.

Statistical Analysis

Continuous parameters were expressed as median and interquartile range or as mean and standard deviation and compared with Student's t-test or Mann-Whitney U test. Categorical parameters were expressed as number and percentage and compared by Pearson's $\chi 2$ test or Fisher's exact test. Kaplan-Meier curves stratified by group

were constructed for the evaluation of mortality in the first year post-implantation. Patients were censored at time of heart transplantation. Differences pooled over strata were compared by log-rank test. Multivariable Cox proportional hazards analysis was performed for identification of parameters associated with mortality and RRT after CF-LVAD implantation. Variables were included in the multivariable Cox regression model with p-value <0.10 in the univariate analysis. Finally, through a stepwise variable selection, excluding variables with p > 0.05, the final model was constructed. Two-tailed p-values < 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were calculated to determine discriminatory power of eGFR and of proteinuria for predicting mortality, RRT, and to assess the ability of the final model to predict the composite end-point. Optimal cutoff points were identified by using the maximum value of the Youden index. Analyses were performed using statistical software SPSS, version 20.0 for Mac (SPSS Inc., an IBM company, Chicago, IL) and GraphPad Prism version 5.0a for Mac (GraphPad Software, La Jolla, CA).

RESULTS

Baseline characteristics

In total, 173 patients met the inclusion criteria (78% male, mean age 52.3 ± 13, 37% destination therapy, 91% HeartMate II) with a mean follow-up duration of 264 ± 139 days. Forty-two patients (24%) had proteinuria before CF-LVAD implantation, of whom 16 (38%) had a positive dipstick graded as 'trace', 20 (48%) graded as 1+, and 6 (14%) graded as ≥2. The baseline characteristics of the groups are presented in **Table 1**. Patients with proteinuria were more often DT patients (67% *vs*. 28%, p <0.001), insulin dependent diabetes mellitus (IDDM) patients (p=0.016), required more often an intra-aortic balloon pump (IABP) (52% *vs*. 31%, p = 0.013), and had lower INTERMACS classes at baseline (p = 0.033), in comparison to patients without proteinuria, respectively. In addition, 73% of the patients were on angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers (ACE/ARB). This did not differ between the two groups (p=0.152) The baseline total bilirubin was higher in patients with proteinuria *vs*. without proteinuria (1.9 ± 2.3 *vs*. 1.1±1.1 μmol/L, p = 0.032). There was a trend towards a higher incidence of hypertension in patients with proteinuria. The mean eGFR, BUN, AST or ALT at baseline did not differ between the two groups.

Clinical outcomes during the first year after CF-LVAD implantation.

Twenty-two (13%) patients underwent cardiac transplantation (**Table 2**) and 48 (28%) patients died during the first year after CF-LVAD implantation. The most frequent cause of death was of non-cardiac origin (58%) followed by death of cardiac origin

Table 1. Baseline characteristics of the study population

	All patients n=173	Proteinuria n=42	No Proteinuria n=131	p-value
Demographic				
Sex, Males	135 (78)	32 (76)	103 (79)	0.74
Age (SD)	52.3 (13)	54 (12)	52 (14)	0.34
BMI (SD)	27.3 (6.3)	27 (5.8)	27 (6.4)	0.82
Ischemic Cardiomyopathy	57 (33)	19 (45)	38 (29)	0.05
Diabetes Mellitus				0.02
- IDDM	35 (20)	15 (36)	20 (15)	
- NIDDM	28 (16)	5 (12)	23 (18)	
Hypertension	85 (49)	26 (62)	59 (45)	0.06
PCI	52 (30)	17 (41)	35 (27)	0.09
CABG	18 (10)	4 (10)	14 (11)	0.83
ICD/PM	151 (87)	36 (86)	115 (88)	0.73
TIA or CVA	33 (19)	8 (19)	25 (19)	1
Destination Therapy	64 (37)	28 (67)	36 (28)	**<0.001**
IABP	63 (36)	22 (52)	41 (31)	**0.01**
ECMO	9 (5)	4 (10)	5 (4)	0.22
Inotropic support	135 (78)	37 (88)	98 (75)	0.07
INTERMACS				**0.03**
• Class I	32 (19)	11 (26)	21 (16)	
• Class II	66 (38)	21 (50)	45 (34)	
• Class III	35 (20)	5 (12)	30 (23)	
• Class ≥IV	40 (23)	5 (12)	35 (27)	
Device Type				0.12
• HeartMate II LVAD	158 (91)	41 (98)	117 (89)	
• HeartWare HVAD	15 (9)	1 (2)	14 (11)	
Laboratory values				
eGFR (mL/min/1.73m^2)	60 (26)	60 (32)	61 (24)	0.95
Blood Urea Nitrogen (mg/dL)	36 (19)	36 (20)	36 (19)	0.84
White Blood Cells (10^9/L)	8.7 (3.1)	9.1 (3.1)	8.5 (2.9)	0.30
Aspartate aminotransferase (U/L)	58 (88)	79 (102)	51 (83)	0.08
Alanine aminotransferase ((U/L)	68 (116)	74 (122)	66 (115)	0.71
Total Bilirubin (μmol/L)	1.5 (1.5)	1.9 (2.3)	1.4 (1.1)	**0.03**
ACE/ARB	126 (73)	27 (64)	131 (76)	**0.15**

*Continuous variables are presented as mean (standard deviation), Categorical variables are presented as number (percentage). BMI, Body mass index; BTT, Bridge-to-transplant; BUN, Blood Urea Nitrogen; CABG, Coronary Artery Bypass Graft; CVA, Cerebrovascular accident; DT, Destination Therapy; ECMO, Extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; IABP, Intra-aortic balloon pump; (N)IDDM, (non-)Insulin dependent diabetes mellitus; Inotropic med, on Inotropic medication; ICD, Implantable Cardioverter Defibrillator; PCI, Percutaneous coronary intervention; PM, Pacemaker; TIA, Transient Ischaemic Attack.

(38%). The cause of death was undetermined in n = 2 (4%) patients. Patients with proteinuria required more often right ventricular assist devices (RVAD) in comparison to patients without proteinuria (17% *vs.* 2%, p = 0.002). There was no significant difference in confirmed pump thrombosis rate between the two groups. The overall 30-day mortality was higher in patients with proteinuria (26% *vs.* 8%, p = 0.003) compared with patients without proteinuria. The one-year actuarial survival rate was 52% in patients with proteinuria compared to 78% in patients without proteinuria (Log rank p <0.001, **Figure 1**). In addition, when stratified by none vs. trace vs. ≥1+, the survival was 78±4, 56±12 and 50±10 at 1 year (log rank p<0.001), respectively. Pairwise comparison revealed that patients with ≥1+ and trace had significant lower survival compared to none, the survival did not differ significantly between ≥1+ and trace. Next, we analyzed risk factors for one-year mortality during the first year by means of univariate analysis. Several risk factors were identified (**Appendix Table 1**). The presence of proteinuria at baseline, older age, INTERMACS class I, lower baseline eGFR and higher total bilirubin continued to be independently associated with 1-year mortality in multivariate analysis (**Table 3**).

Figure 1. Kaplan-Meier survival curve comparing patients with and without proteinuria.

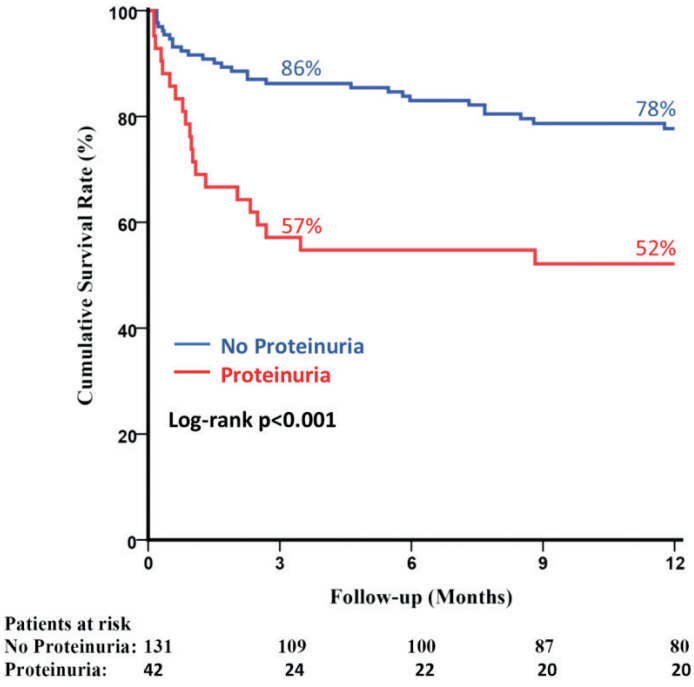


Table 2. Clinical outcomes at one year

	All Patients	Proteinuria	No Proteinuria	p-value
Cardiac transplantation	22 (13%)	2 (5%)	20 (15%)	0.11
Renal replacement therapy	31 (18%)	12 (29%)	19 (15%)	0.04
Chronic renal replacement therapy	6 (4%)	3 (7%)	3 (2%)	0.16
Right ventricle assist device	10 (6%)	7 (17%)	3 (2%)	0.002
Confirmed pump thrombosis	15 (9%)	5 (12%)	10 (8%)	0.39

Renal replacement therapy in the first year after CF-LVAD implantation

The mean baseline eGFR did not differ between the two groups at baseline (eGFR 60 ± 32 vs. 61 ± 24 mL/min/1.73 m^2, p = 0.95). Stratifying by chronic kidney disease stages(CKD) (eGFR ≥60, 30-59, <30 mL/min/1.73 m^2) did not result in a significant dissimilarity between patients with or without the existence of baseline proteinuria (p = 0.65). One patient was on CVVH at the time of LVAD implantation. Overall, 10% of the patients required RRT within 7 days post-implantation and 18% at one year (Table 2). Nineteen percent of the patients with proteinuria required RRT within 7 days post-implantation compared to 7% of the patients without proteinuria (p = 0.02). This difference was also noted at one-year post CF-LVAD implantation. The cumulative event rate for RRT at one year between patients with and those without proteinuria was 32% vs. 15%, p = 0.02 (**Figure 2)**.

Figure 2. Kaplan-Meier event curve for the cumulative incidence of renal replacement therapy post-LVAD implantation

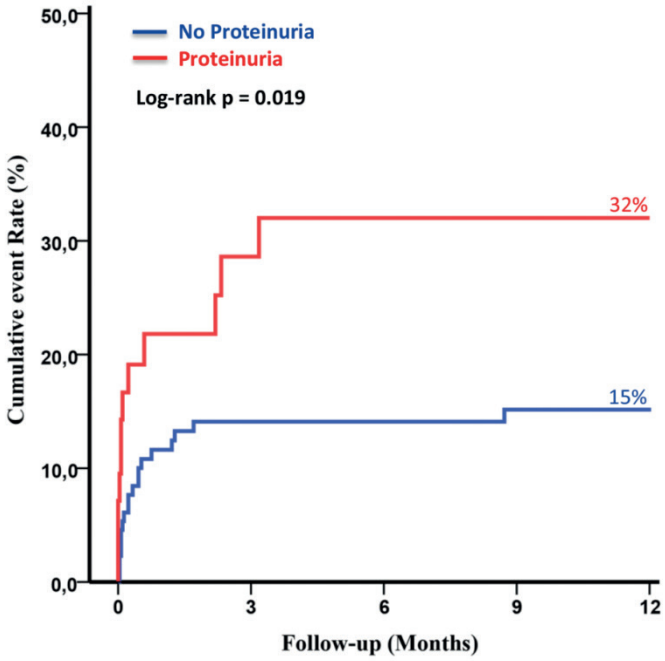


Table 3. Multivariate analysis of proteinuria with mortality, renal replacement therapy and the composite end-point.

	Hazard ratio (95% CI)	p-value
All-cause mortality		
Proteinuria	2.091 (1.1 – 3.8)	0.017
Age	1.033 (1.0 – 1.1)	0.016
eGFR (increase by 1 unit)	0.982 (0.97 – 0.99)	0.008
Total bilirubin (increase by 1 unit)	1.345 (1.2 – 1.6)	<0.001
INTERMACS		
• Class I	3.373 (1.3 – 8.8)	0.013
• Class II	1.517 (0.6 – 3.7)	0.355
• Class III	1.029 (0.4 – 3.0)	0.958
• Class ≥ III	1.0	-
Renal replacement therapy		
Proteinuria	2.340 (1.13 – 4.84)	0.022
Sex (male)	2.908 (0.88 – 9.57)	0.079
eGFR (increase by 1 unit)	0.980 (0.96 – 0.99)	0.015
Composite end-point (RRT and mortality)		
Proteinuria	2.274 (1.03 – 5.04)	0.002
Sex (male)	2.282 (1.03 – 5.04)	0.041
eGFR (increase by 1 unit)	0.978 (0.97 – 0.99)	<0.001
Total bilirubin (increase by 1 unit)	1.221 (1.07 – 1.39)	0.003

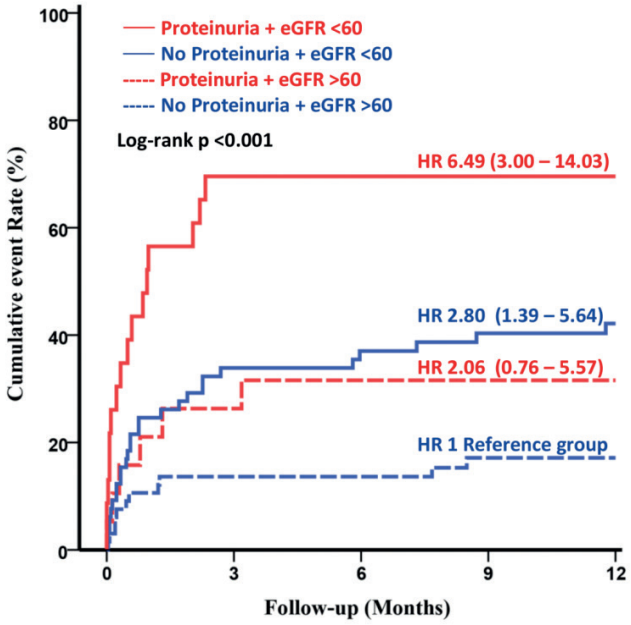
INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support;
eGFR, estimated glomerular filtration rate;

The predictive value of proteinuria

The presence of proteinuria and eGFR 55 ml/min/1.73 m^2 were selected as cutoff points based on their respective Youden index **(Appendix Table 2)**. To assess the predictive value of proteinuria for the composite end-point, a multivariable Cox regression was performed including the pre-implantation parameters that were independent predictors of mortality or RRT. The factors independently associated with the composite end-point were the presence of pre-operative proteinuria, lower eGFR and higher total bilirubin, and male sex (**Table 3**). The C-statistic showed its predictive value for the composite end-point, noting an area under the curve of 0.67. The usefulness of renal function defined as baseline eGFR has been determined in the literature (6). In order to assess the additional value of proteinuria in risk stratification of patients screened for CF-LVAD therapy, we calculated the hazard ratio for the composite end-point of mortality or RRT in patients who presented with proteinuria and an impaired renal function (eGFR <55 ml/min/1.73m^2) vs. patients who did not present with this combination. Stratification based on proteinuria and impaired renal function differentiated patients in a low, intermediate and high risk group for the composite end-point. The incidence

of the composite end-point was significantly higher in patients with proteinuria and impaired renal function, Log-rank p<0.001 (**Figure 3**). Among patients with impaired renal function, the concomitant presence of proteinuria resulted in a significantly higher rate of the composite end-point (75% vs. 46%, p = 0.004, respectively).

Figure 3. Freedom from mortality or RRT at one year.



Discussion

This study shows that proteinuria is an independent predictor of death and the need for RRT in the first year after CF-LVAD implantation. Stratification based on both renal function and proteinuria differentiated patients in a low, intermediate and high risk group for the composite end-point mortality or RRT. In addition, the concomitant presence of proteinuria in patients with an impaired renal function significantly worsened their outcome. Therefore, we conclude that measurement of proteinuria is of additional value for pre-operative risk stratification regarding mortality or the need for RRT after CF-LVAD implantation.

Proteinuria as a clinical marker in CF-LVAD patients

Chronic proteinuria and microalbuminuria have been identified as markers of renal pathology and as a predictor of cardiovascular morbidity and mortality across different populations.(10) In addition, proteinuria at the time of percutaneous coronary intervention or cardiac surgery has been identified as a risk factor for death and acute kidney injury.(11, 12) However, there is limited literature regarding the association between pre-operative proteinuria and the risk for mortality or for the need of RRT in patients assessed for CF-LVAD therapy. The present findings confirm those of a recent study by Topkara *et al.*, (6) who reported that proteinuria and reduced GFR are independent predictors of RRT requirement post-LVAD. In addition, the present study demonstrates that pre-operative proteinuria is also an independent predictor for mortality after CF-LVAD implantation, regardless of renal function. This difference in survival arises by the increased mortality rate in the proteinuria group during the first three months. This indicates that the predictive value of proteinuria measured within 7 days before CF-LVAD implantation is likely confined to the post-operative period. Most clinical risk-scoring systems that have been developed to predict renal complications following LVAD implantation utilize pre-operative serum creatinine or eGFR. Estimated GFR has been identified as the best predictor for renal failure after LVAD implantation. (6) However, in this study both eGFR and proteinuria were incorporated in a single model, with a satisfying predictive value for the composite endpoint mortality or RRT. Furthermore, utilizing both eGFR and proteinuria adequately grouped patients in a low, intermediate and high risk group for mortality or the need for RRT after CF-LVAD implantation. Therefore, proteinuria could be of additional value regarding pre-operative risk stratification for patients awaiting implantation. Men were treated more with dialysis than women. This is in line with the finding of a large international population study with over thirty-five thousand patients.(13) In our cohort men tended to be older, more hypertensive and have a higher rate of myocardial infarction (data not shown). It can be deduced that men had more often atherosclerotic kidney disease and higher risk of chronic kidney damage, subsequently, leading to a higher risk for RRT post CF-LVAD implantation.

Right-sided congestion and proteinuria

In the study by Katz et al., conducted in HF patients with preserved ejection fraction, albuminuria was independently associated with right ventricle (RV) remodeling and dysfunction.(14) This study attributed this association to diastolic left ventricular dysfunction causing pulmonary hypertension, in turn leading to RV remodeling, dysfunction and ultimately, to right-sided congestion with elevated central venous pressure, and renal venous congestion. Chronic renal venous congestion is a known cause of renal damage ("cardio-renal syndrome"), consequently, resulting in an increase

in albuminuria.(15) The higher rate of RVAD requirement in the proteinuria group seems to confirm that patients with proteinuria suffer from more severe chronic RV dysfunction pre-implantation. Analysis of the differences in the right atrial pressure (RAP) before implantation showed a trend toward higher RAP in patients with proteinuria compared to those without (data not shown). However, our finding regarding the association between proteinuria and right-sided heart failure is limited by the small number of patients that required a RVAD and by the number of patients without right heart catheterization data. Therefore, this finding has to be confirmed in a larger cohort.

Clinical implications

Certain predictors for proteinuria have been recognized, including blood pressure, cholesterol levels, fasting glucose and body mass index.(16) In this study, patients with proteinuria also trended to be more often diabetic and hypertensive. In order to reduce the risk for mortality in patients with proteinuria, these predictors could be potential targets for intervention.(17) Clinical trials with renin-angiotensin-aldosterone system (RAAS) inhibition has been noted to reduce the leakage of proteins in some patients,(18) and have showed that reduction of proteinuria can be "renoprotective". (19, 20) However, these trials are predominantly limited to subjects with diabetic kidney disease. Furthermore, these "renoprotective" medications are often standard treatment for HF patients. New therapeutic strategies for proteinuria have been mentioned in the literature, which suggest a role for the albumin / endoplasmic reticulum stress / lipocalin-2 pathway in modulating the progression of CKD.(21) However, these strategies have to be further developed and its clinical usefulness for patients awaiting CF-LVAD implantation has to be validated. Furthermore, in CF-LVAD patients the RAAS is less activated, and usually these patients use less RAAS inhibitors, or sometimes even none, compared to pre-LVAD.(22) This neuro-hormonal equilibrium prompts an additional effort, including a search for the underlying pathophysiological mechanism, for novel biomarkers and for new treatment strategies that protect the renal function of CF-LVAD patients on the long-term. This is especially relevant due to the rise in DT patients, who are deemed not suitable for cardiac transplantation. For these patients, it is of paramount importance to inform them on their risk factors that might impair their quality of life or even result in death post-implantation. In addition, improvement of the current risk models is needed, in order to accurately determine which of these patients will benefit from a CF-LVAD implantation.

Limitations

There are several limitations to our study that should be taken into consideration while interpreting the results. First, the retrospective observational study design does not offer the possibility to establish causality. Furthermore, the presence of transient proteinuria in some patients might have diluted the effect of severe proteinuria and therefore underestimated its impact on the need for RRT and mortality. Pre-operative proteinuria was not available in all patients, and patients that had microscopic hematuria were excluded from the analysis, in order to prevent misclassification due to a false positive urine dipstick. Furthermore, proteinuria measurements was not available post-LVAD implantation. In addition, a major limitation of our study is that urine protein/creatinine ratio and albumin/creatinine ratio were not available and therefore proteinuria could not be quantified. Strengths of our study include the relatively large sample size, complete and detailed follow-up data, the multi-center study design and the possibility to perform extended multivariable analysis.

CONCLUSION

Our findings suggest that pre-operative proteinuria, which is readily available through dipstick analysis, is an independent predictor for mortality and need of RRT during the first year after CF-LVAD implantation. Proteinuria could be of clinical use in decision making processes and risk assessment for mortality and morbidity of LVAD candidates. Further research has to determine the predictive value of proteinuria changes during CF-LVAD support.

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Supplementary Table 1. Univariable analysis for the primary and secondary outcome.

	Univariable analysis for all-cause mortality			Univariable analysis for Renal replacement therapy			Univariable analysis For the composite end-point		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Proteinuria	2.758	1.5 – 4.9	0.001	2.303	1.12 – 4.75	0.024	2.213	1.308 – 3.745	0.003
Age	1.035	1.0 – 1.1	0.005	1.01	0.98 – 1.04	0.599	1.028	1.007 – 1.050	0.009
Sex (male)	2.191	0.9 – 5.2	0.072	2.923	0.89 – 9.62	0.078	2.455	1.116 – 5.401	0.026
BMI	0.978	0.9 – 1.0	0.354	1.033	0.98 – 1.09	0.216	0.997	0.958 – 1.038	0.887
IDDM	1.601	0.9 – 3.0	0.139	1.79	0.84 – 3.81	0.129	1.651	0.950 – 2.869	0.075
Hypertension	1.357	0.8 – 2.4	0.294	1.657	0.80 – 3.41	0.171	1.275	0.766 – 2.120	0.350
Destination Therapy	2.801	1.6 – 5.0	0.000	2.027	1.00 – 4.10	0.050	2.126	1.280 – 3.530	0.004
INTERMACS									
Class I	3.227	1.3 – 8.0	0.011	1.668	0.56 – 4.97	0.358	2.097	0.962 – 4.572	0.062
Class II	1.924	0.8 – 4.6	0.136	1.489	0.57 – 3.88	0.415	1.446	0.708 – 2.954	0.311
Class III	1.246	0.4 – 3.6	0.681	0.795	0.22 – 2.82	0.722	1.103	0.468 – 2.597	0.823
Class ≥IV	1	-	-	1	-	-	1	-	-
IABP	1,791	1.0 – 3.2	0.044	1.364	0.67 – 2.79	0.394	1.492	0.895 – 2.487	0.125
Inotropic support	1.533	0.7 – 3.3	0.270	1.294	0.53 – 3.16	0.571	1.603	0.813 – 3.162	0.173
Lab Values at baseline									
Higher eGFR	0.979	0.97 – 0.99	0.001	0.979	0.96 – 1.00	0.010	0.978	0.967 - 0.990	<0.001
Total bilirubin	1.328	1.15 – 1.54	0.000	1.147	0.94 – 1.40	0.171	1.221	1.065 – 1.400	0.004
White Blood Cells	1.078	0.99 – 1.17	0.073	0.986	0.88 – 1.11	0.822	1.050	0.972 – 1.135	0.217
AST	0.998	0.99 – 1.00	0.415	1.001	1.00 – 1.00	0.784	1.000	0.996 – 1.003	0.832
ALT	0.998	1.00 – 1.00	0.338	1.000	1.00 – 1.00	0.774	0.999	0.996 – 1.002	0.413

Supplementary Table 2. Receiver-Operating Curve Characteristics of proteinuria and eGFR for Prediction of mortality, and RRT

Variable	Area under the curve	Optimal cutoff	Sensitivity (%)	Specificity (%)
Mortality at one year				
eGFR, ml/min/m^2	0.68	55.0	69	66
Dipstick proteinuria	0.67	Trace	52	82
Renal replacement therapy at one year				
eGFR, ml/min/m^2	0.66	55.0	71	63
Dipstick proteinuria	0.63	Trace	48	77

Optimal cutoff points based on Youden index

CHAPTER 10

Effect of Age and Renal Function on Survival After Left Ventricular Assist Device Implantation.

Muslem, R. Caliskan, K. Akin, S. Yasar, Y.E. Sharma, K. Gilotra, N.A. Kardys, I. Houston, B. Whitman, G. Tedford, R.J. Hesselink, D.A. Bogers, A.J.J.C. Manintveld, O.C. Russell, S.D.

Am J Cardiol. 2017 Dec 15;120(12):2221-2225.

Abstract

Left ventricular assist devices (LVAD) are increasingly used, especially as destination therapy in in older patients. The aim of this study was to evaluate the effect of age on renal function and mortality in the first year after implantation. A retrospective multicenter cohort study was conducted, evaluating all LVAD patients implanted in the 2 participating centers (age ≥18 years). Patients were stratified according to the age groups <45, 45-54, 55-64, and ≥65 years old. Overall, 241 patients were included (mean age 52.4±12.9 years, 76% males, 33% destination therapy). The mean estimated Glomerular Filtration Rate (eGFR) at 1 year was 85, 72, 69, and 49 mL/min per 1.73m^2 in the age groups <45(n=65, 27%), 45-54(n=52, 22%), 55-64(n=87, 36%), and ≥65 years (n=37, 15%) p<0.001)), respectively. Older age and lower eGFR at baseline (p<0.01) were independent predictors of worse renal function at 1 year. The 1-year survival post-implantation was 79%,84%, 68%, and 54% for those in the age group <45, 45-54, 55-64 and ≥65 years (Log-rank p=0.003). Older age, lower eGFR and, INTERMACS class I were independent predictors of 1-year mortality. Furthermore, older patients (age>60 years) with an impaired renal function (eGFR <55 mL/min per 1.73m^2) had a 5-fold increased hazard ratio for mortality during the first year after implantation (p<0.001). In conclusion, age >60 years is an independent predictor for an impaired renal function and mortality. Older age combined with reduced renal function pre-implantation had a cumulative adverse effect on survival in patients receiving a LVAD.

INTRODUCTION

Despite recent improvements in survival, the morbidity and mortality associated with continuous flow – left ventricular assist device (CF-LVAD) implantation remain high.[1] This is more pronounced in patients with advanced age.[2] The aim of this study was to evaluate the effect of age on mortality and renal function after CF-LVAD implantation, either as a BTT or DT, in a multicentre setting and to explore the combined effect of age and renal function on mortality during the first year after CF-LVAD implantation.

METHODS

This retrospective cohort study evaluated all patients in whom a CF-LVAD was implanted between October 2004 and August 2015 in the 2 participating tertiary referral centres. The devices were either the HeartMate II (Thoratec corp. CA.) or HVAD (HeartWare international, Inc.) CF-LVADs. Exclusion criteria were age <18 years at the time of LVAD implantation. Data were obtained from a computerized database and electronic patient files. Patients were classified into 4 groups according to their age in years (younger than 45 (<45), 45 through 54 (45-54), 55 through 64 (55-64) and 65 or greater (≥65)) at time of CF-LVAD implantation. Patients were followed up to 1 year after CF-LVAD implantation. This study was approved by the institutional review boards of the Erasmus MC, University Medical Center, Rotterdam, the Netherlands and the Johns Hopkins Hospital, Baltimore, Maryland, USA.

The primary study endpoints were all-cause mortality and renal function (defined as estimated glomerular filtration rate (eGFR)) in the first year after CF-LVAD implantation. Secondary endpoints included the need for renal replacement therapy (RRT), and improvement of renal function at 1-month post-implantation. For the evaluation of renal function after CF-LVAD implantation, serum creatinine concentrations were collected at baseline, and at 1, 3, 6, 9 and 12 months of follow-up, respectively. The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula.[3] Deaths were defined as "cardiac" when a definitive cause of death related to a cardiovascular event could be identified and as "non-cardiac" when the cause of death did not relate to the cardiovascular system. When the cause of death was unknown deaths were classified as "indeterminate". Patients were grouped in the RRT-group if they required RRT during the first year after CF-LVAD implantation and were treated with either continuous veno-venous hemofiltration (CVVH), or intermittent haemodialysis. During the time that patients required RRT, their eGFR was set at zero. Patients were evaluated for renal improvement after CF-LVAD implantation, which was

defined as an improvement in eGFR of ≥20% at 1 month after implantation compared with baseline.

Continuous parameters were expressed as median and interquartile range or mean and standard deviation and compared by Student's t-test, ANOVA or Kruskal-Wallis test. Categorical parameters were expressed as number and percentage and compared by Chi2 test, Fisher's exact test or Linear-by-Linear Association. Kaplan-Meier curves stratified by groups were constructed for the evaluation of mortality the first year after implantation. Patients were censored at the time of HTX or LVAD explantation. Differences pooled over strata were compared by log-rank test. A multivariable Cox proportional hazards analysis was performed for identification of parameters associated with mortality and a general linear model analysis was performed for the association with eGFR 1 year after implantation. Variables were included in the model with $p<0.10$ in the univariate analysis. Both analyses were performed in a backward stepwise manner, excluding variables with $p>0.05$. Time-dependent receiver-operating curves (ROC) were calculated to determine discriminatory power of age and renal function. Using the maximal value of the Youden index, an optimal cut-off point for age and renal function was identified. A two-tailed p-value of <0.05 was considered statistically significant. Analyses were performed using statistical software SPSS, version 20.0 for Mac (SPSS Inc., an IBM company, Chicago, IL) and GraphPad Prism version 5.0a for Mac (GraphPad Software, La Jolla, CA).

RESULTS

Overall, 241 patients underwent CF-LVAD implantation (mean age 52.4 ± 12.9 years, 76% male). Stratified by age, there were 65 (27%), 52 (22%), 87 (36%) and 37 (15%) patients in the age groups <45, 45-54, 55-64, ≥65. The baseline characteristics stratified by age group are reported in **Table 1**. Older patients were more likely to be Caucasian ($p = 0.001$), male ($p = 0.01$), treated as DT, and suffered more from ischemic cardiomyopathy as the primary cause of HF ($p < 0.001$). Furthermore, older patients more often had higher CKD stages at baseline ($p = 0.001$) and had more hypertension ($p = 0.002$). Younger patients required more often Intra-Aortic Balloon Pump (IABP) support pre-implantation ($p = 0.013$). In addition, patients aged <45 years required more often RVAD therapy ($p = 0.004$) post-implantation (**Table 1**).

Table 1. Demographic and clinical outcome of the study population

Age groups (years)	**<45 n=65 (27%)**	**45-54 n=52 (22%)**	**55-64 n=87 (36%)**	**≥65 n=37 (14%)**	**p-value**
Age (years)	37±5	51±3	60±3.0	69±4	
Male	40 (62%)	40 (77%)	69 (79%)	33 (89%)	0.010
Black	32 (49%)	23 (44%)	24 (28%)	6 (16%)	0.001
Body mass index, (kg/m^2)	28.0	26.7	25.9	26.4	0.208
Estimated glomerular filtration rate at baseline, (mL/min per 1.73 m^2)					0.001
• ³90	14 (22%)	5 (9.6%)	11 (13%)	1 (3%)	
• 60-89	33 (51%)	19 (37%)	23 (26%)	8 (22%)	
• 30-59	15 (23%)	23 (44%)	40 (46%)	21 (57%)	
• <30	3 (5%)	5 (10%)	13 (15%)	7 (19%)	
Primary cardiac disease					<0.001
• Ischemic	10 (15%)	18 (35%)	35 (40%)	20 (54%)	
• Non-Ischemic	55 (85%)	34 (65%)	52 (60%)	17 (46%)	
Comorbidities					
• Diabetes mellitus	20 (31%)	22 (42%)	34 (39%)	15 (41%)	0.573
• Hypertension	20 (31%)	23 (44%)	53 (61%)	21 (57%)	0.002
• Implantable cardioverter defibrillator or pacemaker	49 (75%)	44 (85%)	74 (85%)	35 (95%)	0.082
• Transient ischaemic attack or cerebrovascular accident	12 (19%)	9 (17%)	16 (18%)	7 (19%)	0.997
Hemodynamic support					
• On inotropes	55 (85%)	42 (81%)	74 (85%)	24 (65%)	0.052
• Intra-aortic balloon pump	29 (45%)	24 (46%)	39 (45%)	6 (16%)	0.013
• Extracorporeal membrane oxygenation	7 (11%)	4 (8%)	4 (5%)	-	0.148

Table 1. continued					
Interagency Registry for Mechanically Assisted Circulatory Support					0.279
• I	18 (28%)	9 (17%)	21 (24%)	3 (8%)	
• II	25 (39%)	17 (33%)	34 (39%)	13 (35%)	
• III	11 (17%)	14 (27%)	18 (21%)	9 (24%)	
• ≥IV	11 (17%)	12 (23%)	14 (16%)	12 (32%)	
Device Type					0.765
• HeartMate II	60 (92%)	48 (92%)	79 (91%)	32 (87%)	
• HeartWare ventricular assist device	5 (8%)	4 (8%)	8 (9%)	5 (14%)	
Left ventricular assist device indication					0.007
• Bridge-to-transplant	45 (69%)	37 (71%)	59 (68%)	14 (38%)	
• Destination Therapy	19 (29%)	15 (29%)	23 (26%)	23 (62%)	
Clinical outcome					
Mean follow-up days	281±121	300±120	256±144	210±158	0.014
Heart transplantation	12 (19%)	7 (14%)	11 (13%)	3 (8%)	0.510
Right ventricular assist device	9 (14%)	1 (2%)	1 (1%)	2 (5%)	0.004
Renal replacement therapy	10 (15%)	7 (14%)	18 (21%)	5 (14%)	0.627
Chronic renal replacement therapy	2 (3%)	2 (4%)	4 (5%)	1 (3%)	0.946
Confirmed pump thrombosis	8 (12%)	4 (8%)	3 (3%)	3 (8%)	0.234
Neurologic event	8 (12%)	5 (10%)	11 (13%)	5 (14%)	0.940

Thirty patients (12%) died within 30 days post-implantation. Stratified by age the 30-day mortality rate was 5%, 8%, 15%, and 27% for those in the age groups <45, 45-54, 55-64 and ≥65 years (p=0.006), respectively. During the first year after CF-LVAD implantation 65 patients (27%) died. The most frequent cause of death was non-cardiac (58.5%) followed by cardiac (38.5%). In 2 (3.1%) patients the cause of death was undetermined. The actuarial 1-year mortality was 21%, 16%, 32% and 46%, for those in the age groups <45, 45-54, 55-64 and ≥65 years (Log-rank p = 0.001, **Figure 1**), respectively. The HTX rate did not differ between the groups (p=0.51). Factors associated with 3-months mortality are reported in the **appendix Table 1**. Univariate analysis for the relationship with mortality at 1 year identified an association with age, INTERMACS class, eGFR, and the need for IABP at baseline. After multivariate analysis, older age, lower eGFR and, INTERMACS class I at baseline, remained associated with 1-year mortality (**Table 2A**).

Figure 1. Kaplan-Meier curve for survival during the first year after continuous-flow left ventricular assist device implantation stratified by age group. Patients were censored at the time of heart transplantation or left ventricular assist device explantation.

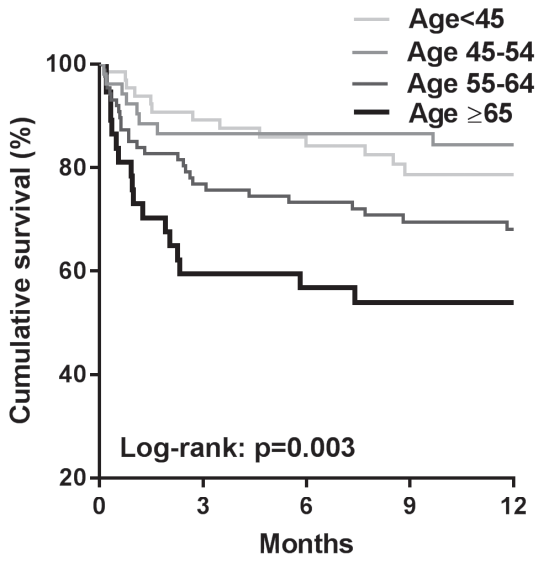
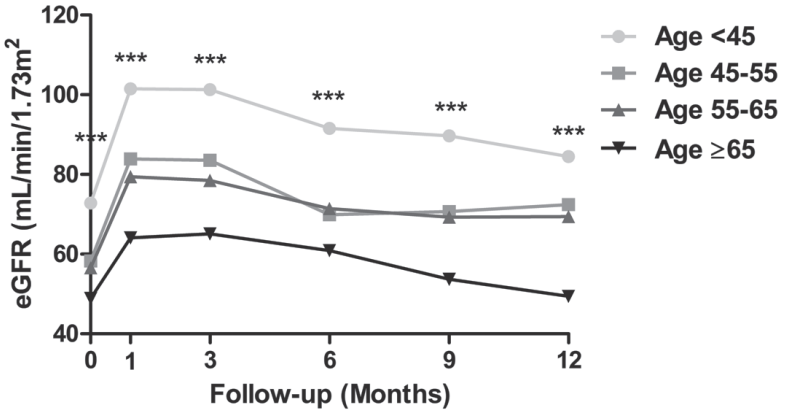


Table 2. Multivariable regression analysis of characteristics for the association with mortality and renal function 1 year after continuous-flow left ventricular assist device implantation

A. Cox regression analysis for mortality			
Variable	**Hazard Ratio**	**95% CI**	**p-value**
Age	1.03	1.01 – 1.05	0.02
Estimated glomerular filtration rate	0.98	0.97 – 0.99	<0.01
Interagency Registry for Mechanically Assisted Circulatory Support			
- Class I	4.78	2.11 – 10.83	<0.01
- Class II	1.93	0.87 – 4.29	0.11
- Class III	1.13	0.44 – 2.94	0.80
- Class [3]IV	1	-	-
B. Linear regression analysis for renal function			
Variable	**Beta**	**95% CI**	**p-value**
Age	-0.57	-0.87 to -0.27	<0.01
Estimated glomerular filtration rate	0.48	0.34 – 0.63	<0.01

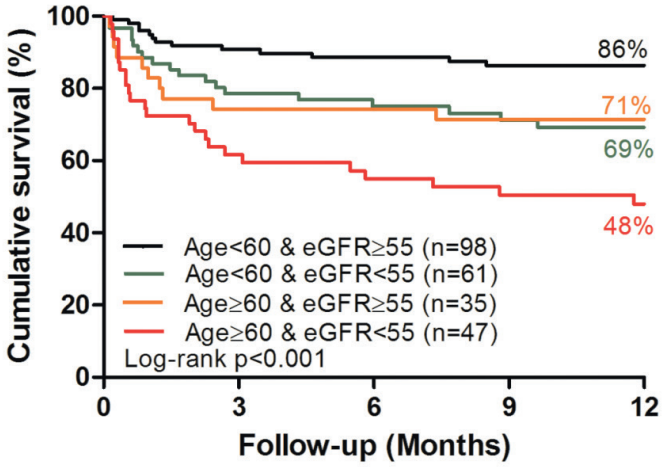
The course of renal function (eGFR) stratified by age group during the first year after transplantation is presented in **Figure 2**. Mean eGFR at baseline for the whole group was 60±25 mL/min per 1.73 m^2 and stratified by the age groups <45, 45-54, 55-64, and ≥65 years this was 72, 58, 57, and 49 mL/min per 1.73 m^2 (p<0.001), respectively. There was a significant difference in mean eGFR between the age groups over all time points during the first year post-implantation (P < 0.001). Of the 142 patients supported by a CF-LVAD at 1 year, 2 patients had missing laboratory values and according to their age groups <45, 45-54, 55-64 and >65 years, there were 38 (58%), 37 (71%), 51 (59%) and 14 (38%) patients alive and on CF-LVAD support, with a mean eGFR of 85, 72, 69, and 49 mL/min per 1.73 m^2 (p<0.001) at 1 year, respectively. Within the different age groups, the mean eGFR improved significantly at 1 year with 12, 14, and 13 mL/min per 1.73 m^2, compared to baseline in patients aged <45 (p<0.008), 45-54 (p<0.004), and 55-64 years (p<0.004), respectively. However, there was no significant difference in mean eGFR at 1 year compared to baseline in patients aged 65 years or older (p=0.73). Univariate analysis for the relationship with eGFR at 1 year identified an association with age, Ischemic cardiomyopathy as primary cardiac disease, and eGFR at baseline. As presented in **Table 2B**, factors independently associated with a lower eGFR at 1 year after CF-LVAD implantation were lower eGFR at baseline and older age.

Figure 2. Renal function during the first year after continuous-flow left ventricular assist device implantation presented as mean estimated glomerular filtration rate stratified by age group. ***p<0.001



To assess the effect of age and renal function on mortality, we stratified patients into four groups based on cut-off points determined through their respective Youden index. This resulted in age 60 years and eGFR 55 mL/min per 1.73 m^2 as optimal cut-off points. Time to event analysis showed that the 1-year survival was 86%, and 69% for younger patients (age<60 years) with eGFR ≥55 and <55 mL/min per 1.73 m^2. In addition this was 71% and 48% for older patients (age ≥60 years) with eGFR ≥55 and <55 mL/min per 1.73 m^2 (Log-rank p<0.001, **Figure 3**), respectively. Furthermore, older patients (age>60 years) with an impaired renal function (eGFR <55 mL/min per 1.73 m^2) had a 5-fold increased hazard ratio for mortality during the first year after implantation (p<0.001).

Figure 3. The 60/55 Rule



Groups	HR	95% CI	p-value
Age <60 & eGFR ≥55	1	-	-
Age <60 & eGFR <55	2.45	1.2 – 5.0	0.014
Age ≥60 & eGFR ≥55	2.45	1.2 – 5.6	0.033
Age ≥60 & eGFR <55	5.00	2.5 – 9.8	<0.001

HR, hazard ratio. 95% CI, Confidence interval.

Discussion

As patients with advanced are more frequently referred for CF-LVAD implantation due to ineligibility for HTX, age-related factors related to prognosis and outcome become more important. We determined that older age adversely affects renal function as well as survival 1-year post-implantation. In addition, older patients are less likely to experience an improvement in renal function following CF-LVAD implantation. Furthermore, due to the cumulative adverse effect on survival of older age and reduced renal function, these factors should be assessed in combination when selecting patients for LVAD implantation, especially in patients assessed for DT.

Renal insufficiency in patients with advanced HF is a complex syndrome and often a combination of intrinsic renal parenchymal disease and potentially reversible hemodynamic abnormalities.[4] In the present study, we report that older age is an independent predictor of eGFR at 1 year. Older patients had a lower mean eGFR before LVAD implantation, as well as at all time points after LVAD implantation compared to younger patients. In addition, only patients age ≥65 years had at any point of time an impaired renal function and did not experience an improvement in renal function at 1-year post-implantation. Recovery of renal function post-implantation has been extensively investigated. For most patients, CF-LVAD support optimizes circulation and improves renal function. A recent paper published by Brisco *et al*. reported that after CF-LVAD implantation, the mean eGFR remained above the baseline eGFR indifferent of INTERMACS class or device strategy.[5] However, when we stratified for age, patients aged ≥65 years did not experience renal improvement at 1 year and had lower mean eGFR compared to patients aged <65 years. This suggest that older patients are less likely to experience lasting renal recovery after CF-LVAD implantation. It has been suggested that the lack of improvement in renal function in LVAD patients may be related to the number of co-morbidities, reno-vascular disease or due to the development of cardiorenal syndrome.[4] Older patients are more likely to have more comorbidities and in combination with the prolonged duration of HF, this could explain the lack of improvement of renal function in patients age ≥65 years after CF-LVAD implantation. However, data on this specific topic is scarce and additional research is needed to confirm this.

In line with other studies, we demonstrated that age was an independent predictor of mortality at 1 year.[2,6,7] In addition, we report that older patients (age≥60 years) with an impaired renal function (eGFR <55 mL/min per 1.73 m^2) had higher mortality rates at 1 year. This suggests a cumulative effect of eGFR and age on mortality in CF-LVAD patients. The definition of CKD is an eGFR <60 mL/min per 1.73 m^2 for > 3 months.[8]

However, a lower cut-off point is clinically more relevant when selecting patients for CF-LVADs, due to the high rate of CKD in HF patients. Very few patients are treated with a HTX above the age of 65 years and a considerable number of patients aged <65 years are deemed ineligible for HTX due to co-morbidities.[9,10] Based on our data, patients aged ≥60 years and with an eGFR <55 mL/min per 1.73 m^2 are at high risk for mortality and therefore need more consideration prior to CF-LVAD implantation. These factors should have a combined weight when patients are selected to receive a CF-LVAD, often as DT. In addition, extensive examination and consideration of other comorbidities in relation to their impact on renal function and survival is recommended before CF-LVAD implantation in these patients.

There are certain limitations to our study that should be taken into account when interpreting the present results. Our study is hampered by its retrospective study design. Furthermore, the age group ≥65 years consisted of a relatively small number of patients, which may have affected the outcome of our study. However, the number of patients age >65 years undergoing a LVAD implantation is growing since recently. Subsequently, the number of patients receiving a CF-LVAD as DT is rising with this number and this group will continue to grow. Based on the present findings it is important to consider the changing epidemiology and to anticipate on the impact of age on outcomes after LVAD implantation. Strengths of our study include, the relatively large sample size with a third of the patients receiving a CF-LVAD as DT and the multi-centre study design. Older age is an independent predictor of impaired renal function and increased mortality after CF-LVAD implantation. Our study requires validation in a larger cohort study of patients with advanced age selected for DT.

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Appendix Table 1. Cox-regression analysis for 3-months mortality

Cox-regression analysis for 3-months mortality	Univariable analysis			Multivariable analysis		
	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
Age	1.04	1.01 – 1.07	0.003	1.03	1.00 – 1.06	0.035
Estimated glomerular filtration rate	0.99	0.97 – 0.99	0.017	0.99	0.98 – 1.00	0.046
Bridge-to-transplant (vs. other)	0.27	0.15 – 0.48	<0.001	0.35	0.19 – 0.64	0.001
Interagency Registry for Mechanically Assisted Circulatory Support						
- Class I	4.05	1.50 – 10.9	0.006	4.93	1.79 – 13.58	0.002
- Class II	2.32	0.87 – 6.20	0.092	2.33	0.87 – 6.23	0.093
- Class III	1.41	0.48 – 4.44	0.559	1.70	0.53 – 5.40	0.370
- Class ≥IV	Ref.	-	-			

CHAPTER 11

Incidence, Predictors and Clinical outcome of Early Bleeding Events in Patients Undergoing a Left Ventricular Assist Device Implant.

Muslem, R, Caliskan, K. van Thiel, R. Kashif, U. Akin, S. Birim, O. Constantinescu, A.A. Brugts, J.J. Bunge, J.J.H. Bekkers, J.A. Leebeek, F.W.G. Bogers, A.J.J.C.

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Abstract

OBJECTIVE: Bleeding is a common complication following left ventricular assist device (LVAD) implantation. The goal of this study was to investigate the incidence, predictors and clinical outcome of early bleeding events in patients after LVAD implantation. Methods: A total of 83 patients (age 50±13, 76% men) had an LVAD implanted (77% HeartMate II, 19% HeartMate 3 [Abbott, Chicago, IL, USA]) over a period of 11 years. Patients were included consecutively. An early bleeding event was defined as the need for thoracic surgical re-exploration or transfusion with >4 units of packed red blood cells before discharge.

RESULTS: Overall, 39 (47%) patients (age 50±14, 77% men) experienced an early bleeding event (median time 6 days [IQR, 1-9 days]). Furthermore, 10 of these patients (26%) had ≥ 2 bleeding events. Twelve of the 14 patients (92%) with venoarterial extracorporeal membrane oxygenation (ECMO) support before LVAD implantation experienced an early bleeding event versus 27 of the 69 (39%) patients without ECMO support (p<0.001). No difference was found in early bleeding rates between HeartMate II and HeartMate 3. Predictors for early bleeding events were lower pre- and post-implant platelet counts and ECMO support preimplantation. After multivariable adjustment, early bleeding events were associated with ECMO support preimplantation (OR 6.3, 95% CI 1.2-32.4, p=0.03) and thrombocytopenia (<150x10^9/L) post-implant (OR 5.9, 95% CI 1.9-18.7, p=0.002). Patients who experienced an early bleeding event had a significantly worse 90-day survival rate compared to patients who did not (79% vs. 96%, p=0.03).

CONCLUSION: An early bleeding event needing surgical exploration is highly prevalent after LVAD implantation, especially in patients bridged with ECMO and with pre- and post-implant thrombocytopenia.

INTRODUCTION

Left ventricular assist devices (LVAD) have evolved to an accepted treatment option for patients with end-stage heart failure, either as a bridge to transplant or as destination therapy for patients ineligible for a heart transplant.(1, 2) The use of LVADs has grown exponentially over the last decade, with currently more than 2000 LVADs implanted yearly in the United States.(1)

Although an improvement in survival and a reduction in adverse events after LVAD implantation have been reported over time, the adverse event rate remains high.(1) The Interagency Registry for Mechanically Assisted Circulatory Support reports that bleeding is the most common adverse event followed by infection and cardiac arrhythmia.(1) In addition, the recent European Registry for Patients with Mechanical Circulatory Support registry reports that a major bleeding event within the first 3 months is the most frequently observed adverse event after LVAD implantation (6.45 [95% CI 5.62-7.36] events per 100 patient months) followed by major infection.(3) The main focus, however, is on late gastrointestinal and neurological bleeding events. Consequently, the literature regarding early bleeding events requiring surgical exploration is limited. Early bleeding may delay recovery and extend the period of hospitalization and can be life-threatening when it leads to haemodynamic compromise. In addition, the abundant use of transfusions may lead to sensitization, right heart failure and a longer waiting time for a heart transplant.(4-6) Therefore, it is important to identify risk factors for bleeding events and predictors to guide protocols for their prevention and diagnosis.

This study was designed to investigate the incidence, predictors and clinical outcome of early bleeding events requiring thoracic surgical re-exploration or transfusion in the postoperative period after LVAD implantation.

METHODS

Study Design

We conducted a retrospective cohort study evaluating all HeartMate II (HMII) and HeartMate 3 (HM3) continuous-flow LVAD (Abbott, Chicago, IL, USA) implanted between December 2006 and February 2017 in the Thoraxcenter, Erasmus MC, University Medical Center Rotterdam, the Netherlands, a tertiary referral center. This study was approved by the institutional review board of the Erasmus MC (MEC-2017-1013).

The primary outcome was the occurrence of an early bleeding event, defined as the need for surgical thoracic re-exploration due to bleeding (loss or accumulation) or transfusion with >4 units of packed red blood cells (PRBC) before discharge. The indication for re-exploration was assessed by a heart team that consisted of a cardiothoracic surgeon or a cardiologist and/or intensivist and was based on one of the following criteria: the need for transfusion(s) despite well-regulated anticoagulation parameters; haemodynamic instability and the need for inotropes or vasopressors due to tamponade/pericardial effusion (diagnosed by ultrasonography); reduced LVAD flow despite optimal filling and fluid status; reduced SvO2, and increased lactate, haemothorax (diagnosed on radiograph or ultrasonography) or persistent excessive thoracic tube production. The secondary outcome was all-cause mortality. Patients were classified into 2 groups based on the occurrence of an early bleeding event.

Data collection and protocol

All data were obtained from electronic patient records. Laboratory values were collected directly preoperatively and postoperatively for all patients and used separately in the analysis. Our target activated partial thromboplastin time (aPTT) in our extracorporeal membrane oxygenation (ECMO) protocols was 60-70 s with a blood flow > 3000 ml, 70-80 s with a blood flow > 2000 and < 3000 ml, and 90-100 s with a blood flow < 2000 ml. Postoperative transfusion triggers for the transfusion of PRBC were haemoglobin levels less than 5 mmol/L. Low platelet counts were managed through substitution of platelets, which is indicated in our centre in anticoagulated patients when the patient has a platelet count lower than the target platelet count (>50,000/L in non-bleeders and >100,000/L in patients who have an active bleeding.

In addition, information regarding anticoagulation medication was included if one was used within 7 days prior to LVAD implantation. Depending on the condition and indications (ECMO [n=14], intra-aortic balloon pump [n=21], high thrombotic risk [n=1]), patients were given therapeutic unfractionated heparin (UH) prior to LVAD implantation with a target activated partial thromboplastin time (aPTT) of 60-80 s or higher, depending on the ECMO flow. The UH was discontinued 6 hours preoperatively. Postimplant, UH was started on day 1 according to our institutional protocol as follows: days 1-2: if thoracic drain production is < 50 ml/h, start UH 600 IU/h, target aPTT 35-45 s; days 3-4: target aPTT 40-50 s; days 5-6: target aPTT 50-65 s; day 6: add aspirin 80 mg daily; day 7: start Coumadin; the target international normalized ratio (INR) is 2.0-3.0. Stop UH when the target INR is reached.

Patients received venoarterial ECMO by bifemoral cannulation (using 21-29 Fr multistage venous and 17-21 Fr arterial cannula) via percutaneous (Seldinger) or surgical access. A permanent life support or Cardiohelp set (Maquet Cardiopulmonary, Rastatt, Germany) was used to reach a blood flow of 3.5-5.0 L/min. The goal of the treatment was stabilization of the haemodynamics (SvO2>60%, mean arterial pressure >60 mm Hg, low lactate level and diminishing need for vasopressors) with regular aortic valve opening.

Statistical Analysis

Continuous parameters were expressed as the median and interquartile range or as the mean and standard deviation and compared with the Student *t*-test results unless the data were not normally distributed (Kolmogorov-Smirnov test); in these instances, the Mann-Whitney U-test was used. Categorical parameters were expressed as number of patients and percentage and compared using Pearson's χ^2 test, or if a group had fewer than 5 members, by the Fisher exact test. Kaplan-Meier curves stratified by group were constructed to evaluate the incidence of early bleeding and the number of deaths in the first 90 days and 1 year postimplant. Patients were censored at the time of a heart transplant. Differences in 90-day and first-year survival rates pooled over strata were compared by the log-rank test with the Breslow rule for handling ties. In addition, the Kaplan-Meier curve was also used to evaluate the time to discharge, with patients censored at time of death or heart transplant. Multivariable logistic regression analysis was performed for identification of parameters associated with an early bleeding event after continuous-flow LVAD implant. Variables with a p-value <0.10 in the univariable analysis were included in the multivariable regression analysis model. Finally, through a stepwise variable selection, excluding variables with $p > 0.05$, the final model was constructed. Two-tailed p-values < 0.05 were considered statistically significant. Receiver operating characteristic curves were generated to assess the ability of independent associated variables and the final model to predict the primary outcome. Analyses were performed using statistical software SPSS, version 20.0 for Mac (SPSS Inc., Chicago, IL, USA).

RESULTS

Overall, 83 patients were implanted with a continuous-flow LVAD during the study period. Baseline characteristics of the patient population are reported in **Table 1.** The mean age was 50.7±12.8 years, 76% were men and 54% had ischaemic cardiomyopathy as the primary cardiac diagnosis. In the majority of the patients, the continuous-flow LVAD was implanted as a bridge to transplant (89%), and most received an HMII (77%). There were no significant differences in demographic characteristics, indications for an LVAD, device type or Interagency Registry for Mechanically Assisted Circulatory Support class between the 2 groups based on the occurrence of an early bleed. However, patients who experienced an early bleeding event had significantly lower rates of implantable cardioverter defibrillators (p=0.03) and low platelet counts (p=0.006) at baseline. In addition, patients who experienced an early bleeding event were more often supported by ECMO preimplantation (29% vs. 13, p=0.002).

Forty-five patients (54%) experienced an early bleeding event requiring reoperation in 39 (47%) cases and >4 units PRBC in 6 (7%) cases. The median time to a bleeding event was 5 [IQR 3-7] days (**Fig. 1A**). Among these patients, 69% of the events occurred within 7 days following LVAD implantation and 91%, within 14 days. Patients who experienced an early bleeding event were significantly more often transfused with PRBC (7.8±7.1 vs. 1.3±1.4, p<0.001), fresh frozen plasma (0.9±2.0 vs. 0.3±0.8, p=0.04), and platelets (0.6±1.6 vs. 0.03±0.17, p=0.02) compared to patients who did not experience an early bleeding event, respectively. No difference was found in the early bleeding rate between HMII and HM3 (p=0.87). When stratified by ECMO, patients who were on ECMO support had a significantly higher rate of early bleeding events compared to the non-ECMO group (100% vs. 46%, p=0.002, **Fig. 1B**). A subanalysis excluding ECMO patients, presented in **Supplementary Tables 1 and 2**, includes baseline characteristics and surgical exploration summaries. The median time to discharge was 29 [IQR 26-32] days vs. 46 days [38-54] for the non-bleeder vs. the bleeders group (p=0.009), respectively.

A description of the surgical exploration procedure is presented in **Table 2.** Of the 39 patients requiring re-exploration, no bleeding focus was found in 17 (44%) patients; in 8 (21%) patients the end-to-side anastomosis of the outflow cannula to the ascending aorta was oozing or leaking. In 9 (23%) cases, there was pleural blood accumulation. In approximately half of the cases (n=18.46%), no specific action was taken, and only a thoracic lavage with isotonic saline was done. In 12 (31%) cases, an additional stitch to the end-to-side anastomosis of the aorta or of a substernal bleeding focus was necessary. Overall, 10 (12%) patients required a second and 4 (5%) patients, a third surgical re-exploration for bleeding before discharge.

Table 1. Baseline characteristics of the study population

	All (n=83)	No early bleeding event (n=38)	Early bleeding event (n=45)
Age, years ± SD	50.7±12.8	50.6±11.8	50.8±13.6
Male gender	63 (76%)	30 (79%)	33 (73%)
Body mass index, kg/m^2± SD	23.4±3.9	24.0±4.3	22.9±3.4
Aetiology			
- Non-ischaemic CMP	45 (46%)	18 (47%)	27 (60%)
- Ischaemic CMP	38 (54%)	20 (53%)	18 (40%)
Co-morbidities			
- Diabetes mellitus	9 (11%)	3 (8%)	6 (13%)
- Hypertension	13 (16%)	8 (21%)	5 (11%)
- ICD/PM	55 (66%)	30 (79%)	25 (56%) *
- Myocardial infarction	37 (45%)	21 (55%)	16 (37%)
- CABG	6 (7%)	1 (3%)	5 (11%)
- CVA	5 (6%)	4 (11%)	1 (2%)
IABP	31 (37%)	15 (40%)	16 (36%)
ECMO	14 (17%)	1 (3%)	13 (29%) *
- Days on ECMO	6 [3-12]	8 [-]	4 [3-13]
Bridge to transplantation	74 (89%)	36 (95%)	38 (84%)
Device type			
- HeartMate II	64 (77%)	29 (76%)	35 (78%)
- HeartMate 3	19 (23%)	9 (24%)	10 (22%)
INTERMACS			
- Class 1	16 (19%)	5 (13%)	11 (24%)
- Class 2	30 (36%)	13 (34%)	17 (38%)
- Class 3	17 (21%)	9 (24%)	8 (18%)
- Class ≥4	20 (24%)	11 (29%)	9 (20%)
Medication			
Vitamin K antagonist	50 (60%)	27 (71%)	23 (51%)
Heparin	36 (43%)	14 (37%)	22 (49%)
Baseline Laboratory data			
Platelet count 10^9/L	216±76	240±71	196±76*
Creatinine µmol/L	145±70	155±64	136±74
Haemoglobin mmol/L	7.4±1.3	7.4±1.1	7.4±1.4
CRP mg/L	43±59	39±54	45±63
INR	1.8±0.8	1.9±0.9	1.8±0.7
aPTT, s	59±28	57±20	62±33

* For *p* value <0.05; continuous variables are presented as mean (standard deviation) or median [interquartile range]; categorical variables are presented as number (percentage).
SD: standard deviation; CMP: cardiomyopathy; ICD: implantable cardioverter defibrillator; PM: pacemaker; CABG: coronary artery bypass graft; CVA: cerebrovascular accident; IABP: intra-aortic balloon pump; ECMO: extracorporeal membrane oxygenation; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support; CRP: C-reactive protein; INR: international normalized ratio; aPTT: activated partial thromboplastin time

Figure 1. Cumulative incidence rate of early bleeding events. **A.** Overall cumulative incidence rate of early bleeding events. **B.** Cumulative incidence rate of early bleeding in patients on ECMO vs. No ECMO support.

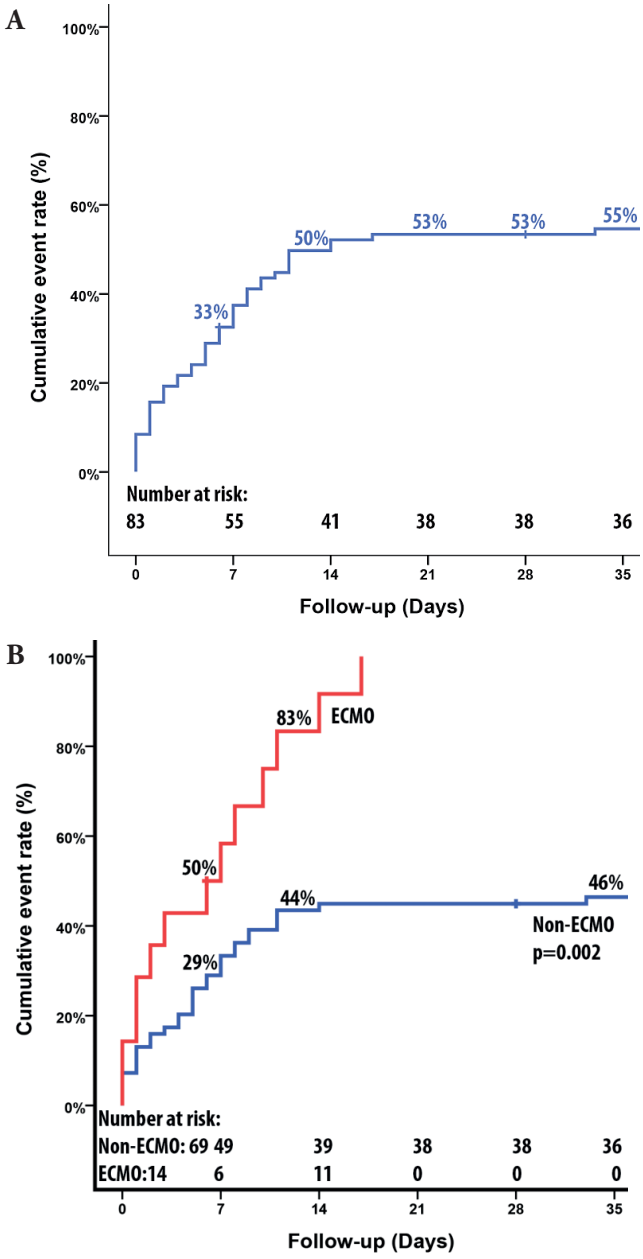


Table 2. Surgical exploration summary

	Early bleeding (n=45) n (%)
Treated conservatively	6 (13%)
Required re-exploration	39 (87%)
Time to re-exploration, median (IQR), days	5 [IQR 3-7]
Bleeding focus during re-exploration (n=39)	
- No surgical site found	17 (44%)
- End-to-side anastomosis aorta	8 (21%)
- Substernal	7 (18%)
- Diffuse bleeding	4 (10%)
- Not reported	3 (8%)
Pleural blood accumulation	9 (23%)
Treatment	
- Thoracic lavage with isotonic saline	18 (46%)
- Suture	12 (31%)
- Diathermy	5 (13%)
- Not reported	3 (8%)
- Pericardial window	1 (3%)
Second re-exploration	**9 (23%)**
- No surgical site found (x3) - End-to-side anastomosis aorta - suture - Substernal (3x) – suture (x1), diathermy (x2) - Driveline tunnel bleeding – fibrin sealant - Diaphragm fissure - suture	
Third re-exploration	**4 (10%)**
- Surgical site not found (x2) - End-to-side anastomosis aorta - suture - Small fissure peritoneum - suture	

Univariable analysis showed that ECMO preimplantation (p=0.011) and lower platelet counts directly pre- and postimplant (p=0.013, p=0.012, respectively) were associated with a higher probability for an early bleeding event (**Table 3**). A separate univariable analysis excluding patients on ECMO is included in **Supplementary Table 3**. In the multivariable analysis, ECMO preimplantation and a lower platelet count postimplant were independently associated with a higher probability for an early bleeding event (model 1, **Table 4**).

Table 3. Univariable logistic regression analysis for early bleeding

Baseline variables	OR	95% CI	p-value
Age	1.001	0.97-1.04	0.938
BMI	0.925	0.82-1.04	0.191
Gender (female)	1.364	0.49-3.80	0.552
Aetiology (nonischaemic)	1.667	0.70-4.00	0.251
Diabetes	1.795	0.42-7.72	0.432
Hypertension	0.469	0.14-1.58	0.221
CABG	4.625	0.52-41.4	0.171
IABP	0.846	0.35-2.06	0.713
ECMO	15.03	1.86-121.3	0.011*
Device (HeartMate III)	0.921	0.33-2.57	0.875
Laboratory values, preimplantation			
Platelet count 10^9/L	0.992	0.99-1.00	0.013*
Creatinine µmol/L	0.996	0.99-1.00	0.237
Haemoglobin mmol/L	0.994	0.71-1.40	0.974
CRP mg/L	1.002	0.99-1.01	0.693
INR	0.783	0.43-1.42	0.422
APTT sec	1.007	0.99-1.03	0.441
Laboratory values, postimplant			
Platelet count 10^9/L	0.985	0.97-1.00	0.012*
Creatinine µmol/L	1.000	0.99-1.00	0.356
Haemoglobin mmol/L	1.562	0.96-2.55	0.073
CRP mg/L	1.005	0.99-1.02	0.449
INR	0.531	0.16-1.73	0.293
aPTT s	1.011	0.98-1.05	0.543

*P<0.05 BMI: body mass index; CI: confidence interval; CRP: C-reactive protein; CABG: coronary artery bypass graft; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; INR: international normalized ratio; OR: odds ratio

The C-statistic of model 1 was 0.73 with a sensitivity of 82% and a specificity of 53%. Receiver operating characteristic analysis showed that the optimal cut-off value for the postimplant platelet count was 150 x10^9/L. Incorporated in the multivariable analysis (model 2), patients with a postimplant platelet count <150 x10^9/L, which is the lower limit of normal in our institution, had a 4.5 times higher probability and patients on ECMO preimplantation had a 9.6 times higher probability for an early bleeding event.

During the first year after implantation, 14 (17%) patients died and 19 (23%) underwent heart transplants. The Kaplan-Meier survival curve, stratified by early bleeding event, is presented in **Fig. 2.** Patients who experienced an early bleeding event had a significant lower survival rate at 90 days compared to patients who did not (80% vs. 97%, p=0.02). In addition, there was a significant difference in survival rate between patients with and without an early bleeding event at 1 year (75% vs 91%, log-rank p=0.04).

Table 4. Multivariable logistic regression analysis for early bleeding

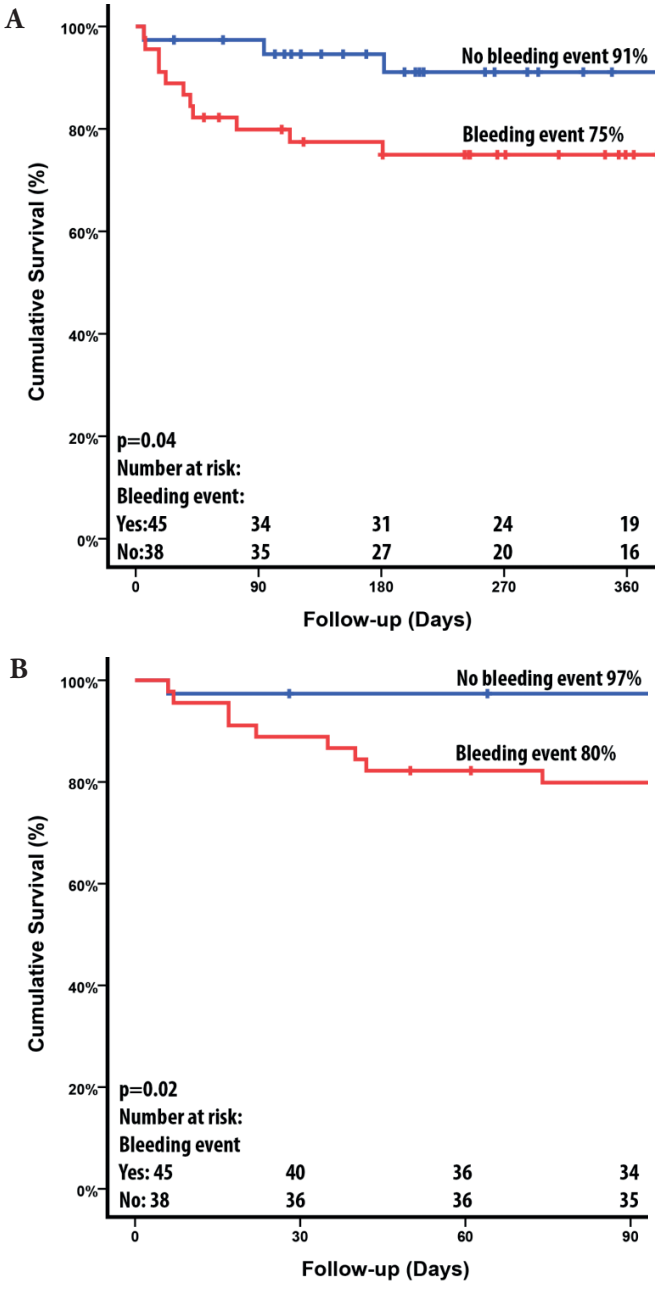
Model 1. Multivariable analysis including platelet count (continue)	OR	95% CI	p-value
Postimplant platelet count (lower)	1.01	1.00-1.03	0.04
Preimplant ECMO support	11.34	1.38-93.2	0.02
Model 2. Multivariable analysis including platelet count (dichotomized)	OR	95% CI	p-value
Postimplant platelet count <150 x10^9/L	4.46	1.57-12.7	0.005
Preimplant ECMO support	9.64	1.15-81.1	0.04

CI: confidence interval; ECMO: extracorporeal membrane oxygenation; OR: odds ratio

Discussion

This study addressed the incidence, predictors and outcome of early bleeding events requiring surgical exploration after implantation of an LVAD. This study showed that (1) the overall incidence of an early bleeding event was high after LVAD implantation, with a median time of 5 days and the majority of the events occurring within 14 days; (2) the occurrence of an early bleeding event was related to ECMO support pre-LVAD implantation and a low platelet count pre- and postimplant; (3) patients experiencing an early bleeding event had impaired survival compared to patients who did not experience this event. This result suggests that the patients previously on ECMO or with a low platelet count should be carefully monitored during the initial admission in the intensive care unit postimplant, in order for the medical team to intervene adequately and on time.

Figure 2. Kaplan-Meier survival curve by early bleeding event. **A**. Early survival by early bleeding event. **B**. First-year survival by early bleeding event.



Achieving haemostasis following LVAD implantation can be challenging, if not difficult, because of fragile tissues, coagulation disorders and extensive blood loss. In the recently published trial nonblinded randomized controlled trial comparing the HMII with the HM3, the overall bleeding rate was 33% and 39% for patients with the HM3 and the HMII, respectively, with 10% of the patients with the HM3 and 14% of those with the HMII experiencing a bleeding event that required surgery.(7) In the HMII LVAD bridge-to-transplant trial, the rate of bleeding events requiring reoperation was 31%, with 53% of patients being transfused with at least 2 units of red blood cells.(8) Finally, in the HMII vs. HeartMate XVE trial, the reoperation rate for bleeding was 30% postimplant in patients with the HMII, with 81% of the cohort requiring blood transfusions for bleeding.(2) The incidence of bleeding (55%) was higher in this study than in those mentioned previously. This finding is likely due to the fact that the present study also included patients needing ECMO support preoperatively. If we excluded the patients on ECMO from the analysis, the incidence for early bleeding would be similar to that found in the literature. However, the high risk of early bleeding events after LVAD implant in this subgroup is an important finding of the present study, especially considering the fact that the use of ECMO is increasing globally and recognition of this high-risk group is of paramount importance to decrease the mortality and morbidity of patients with have an LVAD.(9)

Although thromboembolic events and acute pump thrombosis are potentially life-threatening in patients with an LVAD, the risk of bleeding is higher than the risk of thrombosis in the early phase.(10) This situation underscores the importance of a structural approach to prevent and manage this complication. ECMO support preimplantation and a lower platelet count postimplant were independent predictors of early bleeding events after LVAD implantation. ECMO has been used with success as a bridge to an LVAD or a heart transplant.(11, 12) Nevertheless, the use of ECMO is accompanied by a high risk of complications as a consequence of heparinization and acquired coagulopathies, with 19% of the patients experiencing cannulation site haemorrhage and 20%, surgical site haemorrhage.(9) Factors including acquired von Willebrand factor deficiency, haemolysis and thrombocytopenia contribute to the bleeding risk during ECMO support.(13, 14) In addition, these conditions remain present after LVAD implantation, despite the removal of ECMO, and might be more severe due to blood loss and heparinization during surgery.(15) Recent findings have confirmed that nearly all patients with an LVAD, regardless of device, experience a loss in large von Willebrand multimers, subsequently resulting in reduced von Willebrand factor activity and an acquired form of von Willebrand deficiency, (16) also known as acquired von Willebrand syndrome. This loss in activity is observed early in the postoperative period and persists during support with an LVAD.(17, 18) Furthermore, there is an increased risk of heparin-induced thrombocytopenia and disseminated intravascular coagulation,

which all add to the burden of haematologic complications during ECMO support and the perioperative period.(14, 19) All these factors and intrinsic changes could explain the high risk of bleeding in patients bridged with ECMO compared to patients who are not bridged with an ECMO.

In this study, platelet count was the only laboratory value independently associated with an early bleeding event, with the postimplant platelet count having the highest sensitivity. In addition, we found that patients with a platelet count <150 x 10^9/L had a nearly 5-fold higher risk of an early bleeding event. The current standard of care for the monitoring of perioperative coagulation consists of platelet count, prothrombin time/INR and aPTT. The use of laboratory data obtained directly pre- and postoperatively may explain the lack of the association between prothrombin time/INR, aPTT and bleeding in our study. Longitudinal changes in these variables and their association with bleeding in patients with an LVAD have yet to be determined.

Platelet function tests, point-of-care thromboelastography- and (rotational) thromboelastometry-(ROTEM) based coagulation management have been found to significantly reduce the re-exploration rate in patients having cardiac surgery.(20) However, articles regarding their clinical use in patients on LVAD support are scarce. We are currently performing a study to investigate whether ROTEM can be used as a predictor of bleeding events after implantation of an LVAD. Furthermore, more proactive use of the echocardiographic assessment of pericardial effusions could detect a cardiac tamponade earlier on. Therefore, perioperative monitoring of platelet count and coagulation parameters in combination with frequent postoperative echocardiographic follow-up scans could be helpful for prevention and detection of a bleeding event and provide time for a planned intervention.

In a recent study, Rojas et al. reported that no postoperative bleeding was observed in 26 destination therapy patients who received an LVAD through less invasive surgery. (21) However, studies regarding less invasive surgery for LVAD implants are limited by their study design and sample size. Larger randomized studies are needed to confirm if less invasive surgery is superior to conventional surgery. In addition, formal evaluation of the efficacy and efficiency is required to determine the absolute benefit.

In the present study, an early bleeding event requiring reoperation was associated with impaired survival at 90 days and at 1 year. This result is in line with previously published data; Genovese et al. reported a significantly higher mortality rate among patients who required a reoperation 1 year after receiving an LVAD implant.

Limitations

This study has several limitations. The retrospective single-centre study design and centre-specific protocol for patient selection and management may weaken the applicability of our findings. Furthermore, data on platelet function or von Willebrand factors were not available; these data are essential in order to understand the underlying mechanisms that contribute to the higher risk of bleeding in patients on an LVAD. Future prospective research is needed to determine the relation between these factors and the risk of bleeding in patients on an LVAD. Because postoperative echocardiographic evaluation was not available systematically in all patients, assessment of the predictive value of echocardiograms and a comparison between the groups were not possible. Finally, the number of HM3 devices is low; therefore, direct comparisons between devices is of limited power. The strengths of our study include the complete follow-up, the pre- and postimplant laboratory monitoring and the multivariate models, all of which lead to a clinically useful and accurate result.

CONCLUSIONS

Early bleeding events are highly prevalent after implantation of an LVAD, especially in patients bridged with ECMO and with low platelet counts. These patients had a significantly worse survival rate compared to patients who did not experience a bleeding event. No difference was found in the rates of early bleeding events in patients with different types of LVADs.

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CHAPTER 12

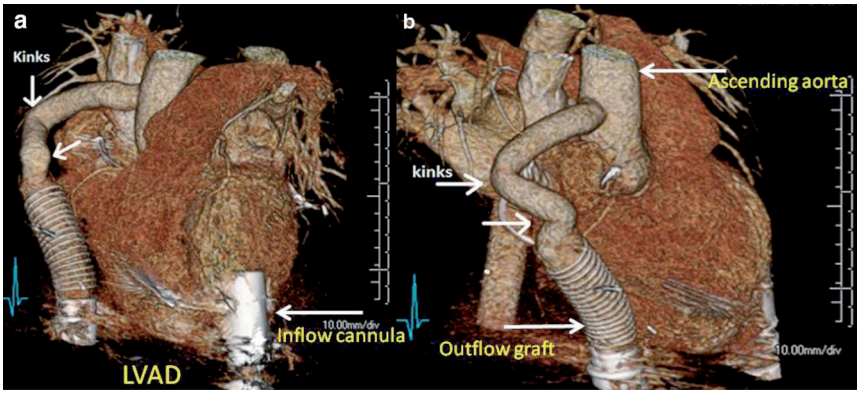
Kinking, thrombosis and need for re-operation in a patient with a left ventricular assist device.

Muslem, R. Akin, S. Manintveld, O. Caliskan, K.

Intensive Care Med. 2016;42(12):2090-1.

A 42-year-old man was re-hospitalized by acute decompensated heart failure (HF) 4 days after discharge. Physical examination revealed a continuous machinery systolic murmur at the second right intercostal space. Transthoracic echocardiogram showed a slight pericardial effusion and no signs of valve dysfunction. A CT scan showed multiple kinks in the left ventricular assist device (LVAD) outflow graft (Fig. 1). The patient underwent reoperation. At surgery, several clots around the outflow graft and mediastinum were removed, and three kinks near the excessive long outflow graft were confirmed. We performed an uneventful LVAD replacement. He was discharged the next day from ICU and 14 days later from hospital. Common complications seen in the first week after LVAD implantation are atrial or ventricular arrhythmias, respiratory failure, delirium, bleeding and renal failure. Outflow graft kinks could lead to LVAD pump thrombosis, dysfunction and relapse of HF, as in our case. This case shows that traditional physical examination, even in these highly technological medical environments, remains meaningful, despite dominant distracting sounds of a continuous-flow LVAD.

Figure 1. CT scan of the 42-year-old man with HeartMate II left ventricular assist device (LVAD) demonstrating the multiple kinking of the outflow graft (arrows) due probably to the adjusted outflow graft being too long in the primary implantation. LVADs have been increasingly used for patients with advanced heart failure (HF) with consequent increase in intensive care admission due to adverse events or as initial bridge from extracorporeal membrane oxygenation (ECMO)



CHAPTER 13

Acquired coagulopathy in patients with Left Ventricular Assist Device.

Muslem, R. Caliskan, K. Leebeek, F.W.G.

J Thromb Haemost. 2018 Mar;16(3):429-440.

Abstract

Chronic heart failure (HF) is a major emerging healthcare problem, associated with a high morbidity and mortality. Left ventricular assist devices (LVADs) have emerged as a successful treatment option for patients with end-stage HF. Despite its great benefi the use of LVAD is associated with a high risk of complications. Bleeding, pump thrombosis and thromboembolic events are frequently observed complications, with bleeding complications occur- ring in over a third of the patients. Although the design of the third-generation LVAD has improved greatly, these hemostatic complications still occur. The introduction of an LVAD into the circulatory system results in an altered hematological balance as a consequence of blood–pump interactions, changes in hemodynamics, the rheology, and the concomitant need for anticoagulation while implanted with an LVAD. The majority, if not all, LVAD patients experience a form of platelet dysfunction and impaired von Willebrand factor activity, leading to acquired coagulopathy disorders. Different diagnostic tools and treatment strategies have been reported; however, they require validation in LVAD patients. The present review focuses on acquired coagulopathies, describing the incidence, impact and underlying mechanism of acquired coagulopathy disorders in patients supported by LVADs. In addition, we will discuss diagnostic and manage- ment strategies for these acquired coagulopathies.

INTRODUCTION

Chronic heart failure (HF) is a rising global epidemic with an increasing incidence[1, 2]. It is estimated that more than 35 million people suffer from this disease worldwide [1, 2]. Heart transplantation (HTX) remains the golden standard therapy for patients who progress to end-stage HF. However, due to scarcity of donor organs, HTX is only possible in a very limited number of patients.

Though initially introduced as Bridge-to-recovery (BTR) and Bridge-to-transplantation (BTT) for patients at high risk for mortality on the HTX waiting list [3], left ventricular assist devices (LVADs) have evolved to become a common therapy for end-stage HF patients [4]. Even for patients ineligible for HTX, due to contraindications, LVADs are now used as a last resort in the form of destination therapy (DT) [5]. In the USA the rate of patient enrollment has continued at a pace exceeding 2,500 implants per year [6]. The survival of LVAD patients has improved greatly over time and is reported to be 80% and 70% at 1- and 2-year after implantation by the largest LVAD registry, the Interagency registry for mechanically assisted circulatory support (INTERMACS) [4].

Despite its great benefit, the use of LVAD is associated with a high risk for complications [4, 7]. Bleeding is the most frequent observed complication occurring in over a third of the patients [4, 8]. Besides the risk of bleeding, these patients are also at risk for thrombo-embolic events and pump thrombosis, which is associated with high mortality [4, 9]. Although the design of the third generation LVAD has improved greatly, these hemostatic complications remain high [4, 7]. The introduction of a LVAD in the circulatory system results in an altered hematological balance as a consequence of blood-pump interactions, changes in hemodynamics, the rheology, and the concomitant need for anticoagulation therapy throughout the whole period while on LVAD support. The majority, if not all, LVAD patients experience a form of platelet dysfunction and impaired von Willebrand factor activity, leading to acquired coagulopathy disorders [10, 11].

The present review focuses on acquired coagulopathies, describing the prevalence, impact, and underlying mechanism of acquired coagulopathy disorders in patients supported by LVADs. In addition, we will discuss diagnostic and management strategies for these acquired coagulopathies.

The evolution of LVADs

The first successful use of a cardiopulmonary bypass system dates back to 1953 where dr. Gibbon successfully corrected a patients atrial septal defect while on a cardiopulmonary bypass system [12]. A decade later, the first use of a pneumatically driven ventricular assist device system was reported by Dr. Debakey and his colleagues [13]. Although, this device was revolutionary, it was limited to short-term support [13]. The Novacor (World Heart Corp, Oakland, CA) left ventricular assist device was the first implantable LVAD that was used as BTT [14]. Since then a number of devices have been introduced, both para-corporeal as well as fully implantable . However, the course of advance heart failure treatment drastically changed with the introduction of the HeartMate XVE (Thoratec Corporation, Pleasanton, CA), and its approval by the Food and Drug Administration for destination therapy in 2003 [3]. With this pneumatically driven pulsatile-flow pump, LVAD therapy was now also a treatment option for patients ineligible for HTX. Though it was the most successful device up till then, it was associated with reduced durability and a high risk of bleeding, infections and thrombo-embolic events [15]. The HeartMate XVE was therefore soon followed by second and third generation devices, which were smaller, more durable, and able to provide continuous blood flow.

The HeartMate II (Abbott Laboratories, Chicago, IL), a continuous-flow LVAD with an axial rotor and mechanical contact bearings, is currently the most utilized device worldwide [4, 16]. Followed by the HeartWare HVAD (HeartWare Inc., Framingham, MA), also a continuous-flow LVAD which has a suspended rotor through a passive magnetic and hydrodynamic bearing that eliminates friction, heat, and component wear [4, 16]. The successor of the HeartMate II is the HeartMate 3 (Abbott Laboratories, Chicago, IL), a continuous-flow LVAD with a centrifugal pump containing a fully magnetically levitated rotor [17]. A new additional feature of the HeartMate 3 is the intrinsic pulse wave designed to avert stasis within the pump [18]. The HeartMate 3 has received the CE mark approval in Europe for short-term and long-term support, and is currently being studied in the U.S. for long-term support (ClinicalTrials.gov Identifier: NCT02224755). The successor of the HeartWare HVAD is the Miniaturized Ventricular Assist Device (MVAD), a smaller pump with a wide-bladed rotor design and magnetically suspended impeller. However, this device is still being investigated and is not yet not approved for clinical use in Europe and the U.S. (ClinicalTrials.gov Identifier: NCT01831544). A list of devices that are currently used is presented in **Table** 1.

Table 1. Durable continuous-flow left ventricular assist devices

Device	Type	INR range*
HeartMate II	Axial-flow	2.0–3.0
MicroMed DeBakey	Axial-flow	2.5–3.5
Jaravik 2000	Axial-flow	2.5–3.5
Circulite	Axial-flow	2.5–3.0
HeartMate 3	Centrifugal-flow	2.0–3.0
HeartWare HVAD	Centrifugal-flow	2.0–3.0
DuraHeart LVAS	Centrifugal-flow	2.0-2.5

DuraHeartTM LVAS (Terumo Heart Inc., Ann Arbor, MI, USA). HeartWare CircuLite (HeartWare, Inc. Framinham, MA, USA). Jarvik 2000 (Jarvik Heart Inc., New York, NY, USA). MicroMed DeBakey (MicroMed Technology, Inc., Houston, TX, USA). *INR ranges derived from the 2013 International Society for Heart and Lung Transplantation (ISHLT) Mechanical Circulatory Support (MCS) guidelines.

Hematological complications

Although the introduction of new devices and improved patient management has resulted in a decline in the complication rate over time, complications related to the hemocompatibility of the devices remain a significant problem [4]. The most common classification used for these complications are described by the INTERMACS registry and include bleeding, neurologic events, hemolysis, pump thrombosis, and venous or non-stroke related arterial thromboembolic events [19]. The high risk for complications is one of the reasons why LVAD therapy has not yet been expanded to patients with less severe heart failure symptoms. Reducing these complications and improving management after the occurrence of a complication could support making LVAD therapy a suitable treatment option for these patients.

Bleeding is the most common complication after LVAD implantation with an incidence ranging between 20% to 60%, depending on the definition used [4, 8, 20]. In addition, it is associated with high morbidity and mortality [21, 22]. The INTERMACS defines a bleeding episode as a suspected internal or external bleeding that results in either, death, re-operation, hospitalization, or transfusion of red blood cells (≥ 4U red blood cells (RBC) within any 24-hour period during the first 7 days, or any transfusion of RBC after 7 days following implantation). Patients are at high risk for major bleeding events in the post-operative period. Approximately 20% to 30% of the patients require a surgical re-exploration early after LVAD implantation due to bleeding episodes [23, 24]. Late bleeding events include non-surgical bleedings, mainly gastro-intestinal (GI) bleeding or epistaxis [25, 26]. The mean time to first GI bleeding episode is reported

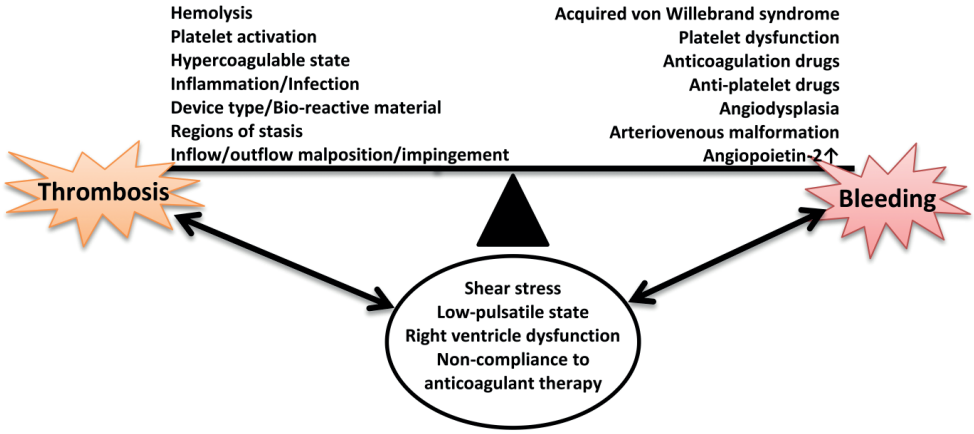
to be 88 days (95% CI, 45-131) [27]. Over time a significant increase in the event rate of GI bleedings in patients supported with a CF-LVAD compared to pulsatile devices has been reported [27-29]. In addition, patients who experience a GI bleeding are also at higher risk for thrombo-embolic events [30]. Subsequently, this all leads to a higher burden for the patient and the healthcare system.

The most frequent neurologic events observed in LVAD patients are ischemic strokes and intracranial hemorrhages. Although they are less frequently observed compared to bleeding events, the outcome after a neurologic event can be devastating. In a recent systematic review the overall neurologic event rate in 1110 LVAD patients was 9.8% with 0.08 events per patient year (EPPY) [9]. When comparing devices, ischemic stroke and intracranial hemorrhage occurred on average more in patients supported with a HeartWare device than in patients supported with a HeartMate II device (17% and 15% vs. 9% and 2%), respectively [31, 32]. The leading cause of death since the introduction of the CF-LVADs has been neurologic events, with up to 20% of the patients having a neurologic event as a primary cause of death [4, 5, 33]. Furthermore, higher mortality rates have been reported after intracranial hemorrhagic events than ischemic strokes (median mortality rate 71% vs. 31%), respectively [9]. Neurologic events severely impair the quality of life and can inhibit the patient to operate the LVAD or to life independently.

Pump thrombosis and neurologic events are the most feared complications after LVAD implantation. Pump thrombosis is categorized as suspected or confirmed pump thrombosis and results in major device malfunctioning requiring device replacement or urgent transplantation if not treated timely. The hazard for pump thrombosis is reported to peak early at 1 to 2 months and return back to a low hazard after LVAD implantation, and thereafter gradually increase over time. A low pump thrombosis rate (4%) was reported during the initial experience with CF-LVADs [5]. Subsequently, it was suggested that a more liberal anti-coagulation regimen might be beneficial in order to reduce the bleeding events [34, 35]. However, following the implementation of this less aggressive anti-coagulation regimen a higher rate of pump thrombosis was observed and confirmed by the INTERMACS registry [36, 37]. This resulted in the re-introduction of a more intense anti-coagulation therapy.

An overview of factors contributing to the risk of bleeding or thrombosis is presented in **Figure 1**. Because patients are at risk for both thromboembolic events and bleeding, a coagulopathy paradigm arises with the LVAD functioning as a double-edged sword.

Figure 1. Factors associated with thrombosis and bleeding.



Acquired coagulopathies

There are various underlying mechanisms that contribute to the risk of above mentioned hematological complications including, device hemocompatibility, use of antithrombotic therapy, GI angiodysplasias and, acquired coagulopathies, such as von Willebrand disease (VWD) or platelet dysfunction [10, 11, 25, 38, 39].

Von Willebrand Factor and Von Willebrand Disease

Although inherited VWD is a well-known cause of bleeding, acquired VWD, also known as acquired von Willebrand syndrome (AVWS), has attracted over the past couple of years the most attention with regard to a possible factor that explains the high rate of bleeding complications after LVAD implantation. Von Willebrand factor (VWF) is a multimeric large glycoprotein with 4 types of domains that serve as binding sites for; factor VIII, the glycoprotein (GP) Ibα and IIb/IIIa on platelets, the sub-endothelial matrix, and domains that interact with integrins or that mediate VWF multimerization [40-42]. The hemostatic potential of the VWF is associated with the size of the multimers, with a smaller size having less activity [43]. At sites of vascular injury endothelium cells release a vast amount of large VWF multimers. VWF in turn mediates platelet adhesion and aggregation to the sub-endothelial matrix in order to achieve hemostasis or/and formation of a platelet plug [42]. VWF especially promotes platelet aggregation in high shear stress circumstances. In addition, VWF is the carrier protein for factor VIII, thereby, protecting factor VIII from rapid proteolytic degradation [42, 44]. A disintegrin and metalloprotease with thrombospondin type 1

repeat 13 (ADAMTS13) cleaves the large VWF multimer when anchored to the sub-endothelial matrix [45]. Once cleaved, VWF is released into the circulation where it is further reduced in size by ADAMTS13 or through exposure to shear stress [45].

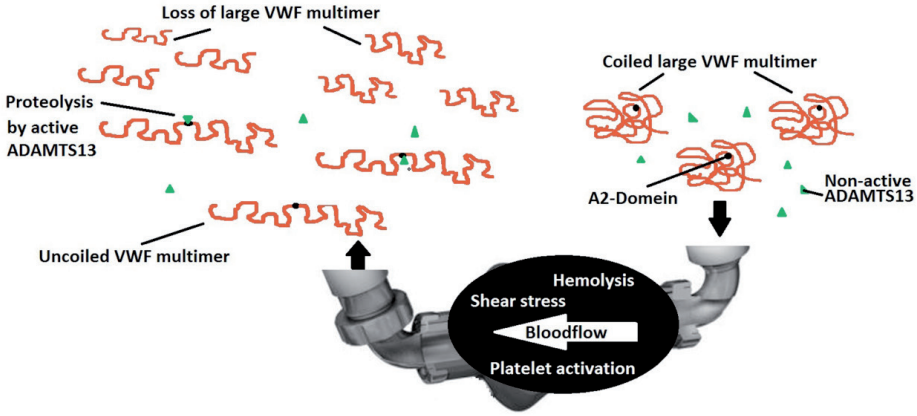
VWD is the most common inherited bleeding disorder with a prevalence that ranges between 0.6 to 1.2% in the general population [46]. VWD is subdivided into types 1, 2 and 3. The most prevalent is type 1 (70-80% of the cases), and is characterized by a quantitative deficiency of VWF. Type 2 (20% of the cases) is caused by a dysfunctional VWF molecule and further categorized in Type 2 A, B, M, and N depending on intrinsic characteristics of the VWF as a consequence of mutations in certain domains or alterations in the shape of the VWF [47], resulting in an impaired VWF function. Finally, type 3 VWD (<5% of the cases) is characterized by the absence of VWF, and subsequently also the most severe form of VWD [47]. The severity of VWD varies based on the level of residual VWF activity, which does not solely depend on the level of VWF but also on the size of the multimers. Common bleeding complications observed in patients with VWD are epistaxis, gastrointestinal (GI) bleedings, postoperative bleeding, menorrhagia and hematomas [48]. In addition, GI bleedings from angiodysplasia, which is prevalent in type 2A, type 2B and type 3 VWD, are frequently observed in elderly VWD patients [49]. These complications are due to a lower level of VWF activity and, especially seen in those individuals with a loss of large multimers, resulting in insufficient hemostasis [50]. Besides inherited VWD, different conditions and mechanisms have been described to result in an AVWS [51].

Acquired von Willebrand syndrome

AVWS has been observed in patients with a variety of conditions such as autoimmune disorders, lymphoproliferative disorders, and cardiovascular conditions, including LVAD patients [39, 52-56]. However, nearly all LVAD patients suffer from AVWS [39, 53, 55]. Identical to other cardiac conditions such as aortic stenosis (Heyde's syndrome), paravalvular leakage, or hypertrophic cardiomyopathy, patients on LVAD support have a comparable loss in VWF activity [52, 53, 57, 58]. It is thought that this loss in activity is due to an increased shear stress as a consequence of the continuous-flow pump design and cardiac conditions [57-59]. Laboratory findings show a loss of large multimers, despite an increase in VWF antigen level (Ag), reduced binding of VWF to collagen (measured by VWF:CB activity), and ristocetin cofactor activity (VWF:RCo), similar to VWD type 2A [39, 54, 55]. The ratio RCo:Ag is reduced (<0.6) due to proteolysis of VWF. This loss in VWF activity is observed early in the postoperative period after LVAD implantation, persistent during LVAD support, and resolves after LVAD explantation or heart transplantation [55, 60, 61].

Different mechanisms have been proposed to explain the development of AVWS in LVAD patients. Of these, shear stress and ADAMTS13 have been studied the most. The presence of a LVAD in the blood circulation leads to significant changes including, increased level of shear stress and lower pulse pressure. As a consequence of increased shear stress the VWF disentangles and exposes the domains A1 and A2 , which in turn promotes proteolytic cleavage by ADAMTS13, and multimeric binding to platelets GP 1bα (**Figure** 2) [62, 63]. In addition, binding of VWF multimers to platelets leads also to an increased proteolytic cleavage by ADAMTS13 [64]. This subsequently results in VWF degradation into smaller multimers and reduced VWF:CB and VWF:RCo activity. This loss in function has been reported to be present in nearly all CF-LVAD types [53, 55, 56].

Figure 2. Mechanism of acquired von Willebrand syndrome (AVWS) in left ventricular assist device (LVAD) patients. Because of the hemodynamic alterations and high shear stress situations, von Willebrand factor (VWF) uncoils and becomes more susceptible to cleavage by ADAMTS-13. This leads to a reduction of high-molecular VWF multimers (AVWS), decreased function of VWF and subsequent bleeding.



Although nearly all CF-LVAD patients suffer from AVWS, not all patients experience bleeding events. This suggests that other pathways or factors, either protective or not, are also essential in determining the risk of bleeding or thrombosis in these patients. Some studies suggest that VWF multimers also modulate angiogenesis, in which VWF is considered an inhibitor of angiogenesis [65, 66]. A loss of VWF multimers in patients with certain types of VWD or AVWS promotes angiodysplasia and arteriovenous

malformations (AVM), which is accompanied with a high risk of GI bleeding [66]. Microcirculatory changes due to loss or more weak pulsatility, and high capillary pressures in LVAD patients have also been suggested to play a concomitant role.

Lower VWF activity could stimulate VEGF-dependent vascular proliferation, initiating angiogenesis, AVMs, and subsequently, lead to GI bleedings. The finding of a higher prevalence of GI bleedings in older patients with type 2 VWD is also relevant for LVAD patients. Since an increasing number of older patients are implanted as DT therapy, the burden of bleedings is only anticipated to increase.

Furthermore, other factors such as factor XIII, serine protease granzyme, plasmin, free hemoglobin, calcium, thrombospondin-1 have been suggested to play a role in regulating VWF activity and hemostasis. Further studies have yet to determine their impact on VWF in LVAD patients.

Platelet dysfunction

Platelets have an essential role in primary hemostasis. This process is initiated through the interaction of platelets to VWF (via the GP Ib-IX-V platelet receptor), and through adhesion of platelets to the extracellular matrix (via GP Ia/IIa or VI platelet receptor) at sites of vascular injury. Subsequently, platelets are activated resulting in binding with fibrinogen, cross-linking with other platelets, and forming a platelet plug [67]. Platelet activations pathways include a variety of platelet secretion products (such as ADP and thromboxane A2), and local pro-thrombotic factors (such as collagen, thrombin, and tissue factor), leading to up-regulation and activation of glycoproteins receptors on platelets and fibrin formation. Following activation, platelet aggregation, platelet-leukocyte binding, and thrombus growth is stimulated by releasing α- and dense granules containing among others CXC chemokine ligand 4 (platelet factor 4, PF4), P-selectin, integrin's, and thrombospondin [67].

Thrombocytopenia is frequently observed in the setting of cardiopulmonary bypass or cardiac surgery due to depletion of platelets. This drop in platelet counts occurs within 72 hours and improves thereafter. Upon LVAD implantation, platelets are activated through increased shear stress, hemolysis, and contact with foreign bodies [68, 69]. Activated platelets subsequently bind to VWF or fibrinogen on the surface of the pump that is exposed to blood. This is followed by platelet aggregation, and as described above, due to platelet secretion products and pro-thrombotic factors a platelet plug is formed, which could grow extensively and occlude the device [68]. In addition, certain other conditions may predispose the patient to a hypercoagulable state, such as increased stress during systemic inflammatory responses, sepsis, or preceding episodes of infections [70, 71].

Besides AVWS, platelets dysfunction has been suggested to increase the risk of bleeding events.[10] Since primary hemostasis is initiated by VWF tethering platelets via glycoprotein membrane receptors, a dysfunction in either VWF or platelets could increase the risk for bleeding. Through increased shear stress shedding of GPIbα receptor can occur [72]. Platelet GPIbα shedding has been reported to pre-exist in CF-LVAD patients and to increase post-implantation in patients that experience a bleeding event, in contrast to patients that did not bleed, in whom a constant decrease in platelet GPIbα shedding was found [73].

Furthermore, a high rate of platelet damage and dysfunction has been observed in patients supported with a LVAD [73-75]. Steinlechner *et al.,* and more recently Baghei *et al.,* reported that platelet aggregation is significantly reduced in the majority of the patients after LVAD implantation [10, 75]. Though based on their data causality could not be established as platelet dysfunction was also present prior to LVAD implantation. Finally, in a recent publication, Mondal *et al.,* investigated a potential mechanism of platelet apoptosis in CF-LVAD patients that developed bleedings within 1-month post implantation [74]. Higher platelet reactive oxygen (ROS) generation, a decrease in total antioxidant capacity and elevated oxidized low-density lipoproteins were observed in the bleeding group, suggesting that the body's anti-oxidant capacity may not have been sufficient to combat the deleterious effects of ROS in patients that experienced a bleeding event [74]. In addition, a reduction in BCl-2 and BCl-xL (pro-survival) protein expression was evident in LVAD patients, while the translocation of Bax into the platelet mitochondria and subsequent release of cytochrome C, an essential moment that leads to downstream apoptotic events, was more prevalent in the bleeding group [74]. This suggests that there are intrinsic and extrinsic pathways, leading to platelet apoptosis, which may play a key role in developing acquired platelet dysfunction.

The use of anticoagulation, AVWS, and platelet dysfunction all contribute to increase the cumulative risk for bleeding in LVAD patients. The above mentioned pathways enable new domains for medical management strategies, which are desperately needed to prevent and reduce bleedings complications.

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a clinically significant syndrome, which is mediated by antibodies to the heparin-platelet factor 4 complex [76]. These antibodies can activate platelets and cause thrombocytopenia and thrombosis [76]. An interesting observation is that although bleeding is rare, GI bleeding is the most common type of bleeding in patients experiencing HIT [77]. Treatment includes cessation of all heparin exposure and initiation of an alternative anticoagulant.

Patients receiving LVADs often require prolonged heparin anticoagulation therapy in the perioperative period or during adverse events. In addition to the systemic heparinization, the use of cardiopulmonary bypass seems to make LVAD patients more prone to HIT. Literature regarding HIT in LVAD patients is mainly limited to case-reports. The incidence of HIT in LVAD patients has been reported to range between 4-26% [78, 79]. In addition, patients experiencing HIT did not have a decrease in the survival or an increased risk for thromboembolism [78]. However, these studies are limited by the use of different types of older generation devices.

Experience and data regarding other rare (inherited) coagulation disorders and use of LVADs are scarce and limited to case-reports and case-series [80]. Several case series on patients with a LVAD and hematologic conditions have been reported including antiphospholipid syndrome, elevated factor VIII activity, Factor V Leiden mutation, immune-mediated thrombocytopenia, lupus anticoagulant, and protein C deficiency [80] [81]. Although these case-series suggest that there is an impaired survival in patients with these coagulation disorders [80] [81], no definitive conclusion can be made due to the large variety in the underlying cause for these disorders and the small number of patients. Further research is needed to determine clinical outcomes, complication rates, and optimal medical treatment options for these patients when receiving a LVAD.

Diagnosis and management

Differences in hemocompatibility has been demonstrated between rotary pumps (HeartMate II) and centrifugal pumps (HeartWare HVAD and HeartMate 2) [82, 83]. These key differences between devices mandate tailored and up-to-date diagnostic and management protocols. In addition, more emphasis on screening and assessment for inherited or acquired coagulation disorders prior to LVAD implantation could prevent unforeseen thrombotic and bleeding complications in the perioperative period. A comprehensive discussion of anticoagulation and complication management is not covered here owing to other recent comprehensive reviews [84, 85]. In summary, because of the fear for pump thrombosis and the high risk of thrombo-embolic events, all LVAD patients receive anticoagulation and antiplatelet therapy. After the suggestion

that a more liberal anticoagulation protocol might be permissible, an increase in the pump thrombosis rate was observed, and again a more intense anticoagulation protocol has been introduced as the standard of care. The guidelines include vitamin K antagonist with an INR goal of 2.0-3.5 (Table 1), and aspirin (81-325 mg) depending on the type of device (**Table** 2) [86]. In a recent study by Nassif *et al.,* the most optimal INR based on weighted mortality of thrombosis and bleeding was 2.6. Of note, a high aspirin hyporesponsiveness rate, failure of aspirin to adequately inhibit platelet function, after LVAD implantation has been reported in a small cohort study (n=26) [87]. Though no significant associations between aspirin hyporesponsiveness and thrombo-embolic events was reported, it suggests that high platelet reactivity is present early after LVAD implantation and that standard measurement of platelet activity might not be sufficient to determine its activity.

Due to the intrinsic hematological changes after LVAD implantation and the high risk of bleeding, diagnosis of AVWS should be considered prior to the onset of bleeding events. Diagnostic laboratory test used to assess AVWS are the same as those used to assess inherited VWD and include the assessment of VWF antigen (VWF:Ag), the ability of VWF to bind to the collagen (VWF:CB), its ability to agglutinate platelets (VWF:RCo), and the ratio of VWF:RCo/VWF:Ag [51]. VWF antigen quantifies the level of VWF in the plasma, however, a high plasma level does not always indicate a high level of activity. Therefore, the ratio of activity/antigen indicates the structural or functional abnormalities of the VWF, and is often decreased in LVAD patients. In addition, VWF multimer patterns can be determined by electrophoresis and densitometry in order to quantify a loss or decrease of large multimers [51]. Furthermore, factor VIII activity (FVIII:C) should be measured. VWF propeptide level is a marker of VWF biosynthesis. In case of an increase in VWF propeptide or a decrease in VWF:Ag level, the VWF propeptide:VWF:Ag ratio will be elevated, indicating an accelerated VWF clearance from the plasma [88]. With regard to ADAMTS13 activity, additional research is required in order to determine its role in LVAD patients. Current data does not suggest that measurement of ADAMTS13 levels will be helpful [89].

An interesting, yet underappreciated topic is the measurement of platelet VWF (VWF stored in platelets). Although the importance of the contribution of platelet VWF to collagen adhesion has been demonstrated in a flow system and although it has been suggested that type 1 VWD patients response to DDAVP is better if platelet VWF is normal, literature regarding the value of platelet VWF in LVAD patients is scarce [90, 91].

Table 2. Anticoagulation and postoperative management

Early postoperative period	
Direct postoperative	Complete reversal of heparin.
First 24 h	No action required, consider acetylsalicylic acid.
Postoperative days 1–2	IV heparin or alternative anticoagulation, if no evidence of bleeding.
Postoperative days 2–3	Continue heparin, start warfarin and aspirin (81–325 mg daily) after removal of chest tubes. During LVAD support
Anticoagulation	Anticoagulation with warfarin to maintain an INR within a range as specified by each device's manufacturer is recommended (see Table 1).
Antiplatelet therapy	Chronic antiplatelet therapy with aspirin (81–325 mg daily) may be used in addition to warfarin and additional antiplatelet therapy may be added according to the recommendations of specific device manufacturers.
Early postoperative bleeding	Urgently evaluate necessity of lowering, discontinuation and/or reversal of anticoagulation and antiplatelet medications.
Gastrointestinal bleeding	Anticoagulation and antiplatelet therapy should be withheld in the case of clinically significant bleeding.
	Anticoagulation should be reversed in the setting of an elevated INR. Carefully monitoring of the device's parameters is warranted.
Neurologic event/deficit	Discontinuation or reversal of anticoagulation in the setting of hemorrhagic stroke is recommended.
Hemolysis	Hemolysis in the presence of altered pump function should prompt admission for optimization of anticoagulation and antiplatelet management and possible pump exchange.
Pump thrombosis	Heparin, GP IIb/IIIa inhibitors and thrombolytics, either alone or in combination, have been proposed as treatment options for pump thrombosis. However, the definitive therapy for pump stoppage is surgical pump exchange.

IV, intravenous; INR, international normalized ratio; modified from the 2013 International Society for Heart and Lung Transplantation (ISHLT) guidelines recommendations.

Finally, due to anticoagulant treatment with vitamin k antagonists or heparin the prothrombin time, INR, and activated partial thromboplastin time may be abnormal. However, point-of-care tests such as thromboelastometry (ROTEM :Tem International, Munich, Germany) or thomboelastography (TEG) devices, may provide us more insight with regard to the viscoelasticity of the blood and the level of platelet aggregation. Although it is frequently used during cardiac surgery, studies regarding its use in LVAD patients are scarce and current use in protocols and risk predictions models following LVAD implantation is limited. Different devices with specific features are capable of detecting platelet dysfunction and VWF deficiency, including the PFA-200 (Siemens AG, Erlangen, Germany)and Multiplate (Roche Diagnostics International, Rotkreuz, Switzerland) [92, 93]. The technical differences and detection principles are described elsewhere [92, 93]. Succinctly, through a high-shear force dynamic flow system, impedance aggregometry or viscoelastic blood property measurement, a differentiation can be made between types of platelet dysfunction, platelet activation sensitivity, and platelet aggregation. However, prospective studies are warranted to determine the role of point-of-care devices in mechanical circulatory support patients.

Traditional treatment options of bleeding in AWVS include desmopressin, VWF-containing concentrates, recombinant factor VIIa, antifibrinolytics, intravenous immunoglobin, and/or plasmapheresis [51]. The use of desmopressin has been anecdotally described to treat GI bleedings in LVAD patients. The use of desmopressin has been anecdotally described to treat GI bleedings in LVAD patients. Although the use of rFVIIa has been a remarkably safe agent for hemophiliacs, its use in LVAD patients is accompanied with a potential risk of thrombosis. Most patients are treated using VWF-containing concentrates, however its use is limited by the rapid degradation of VWF in LVAD patients [94, 95]. Preventing this rapid degradation through inhibition of VWF proteolysis by ADAMTS13 may represent a novel treatment option. An ex-vivo study using donor whole blood exposed to LVAD-like supra-physiological shear stress showed that inhibition of ADAMTS13 by doxycycline decreased VWF degradation and improved VWF function without hyper-activation of platelets [96]. In a similar manner, Rauch *et al.,* has identified an antibody (mAb508) that was able to block the VWF-ADAMTS13 interactions, resulting in an inhibition of 83±8% when used in a maximum doses [97]. Though very much promising, before its effectiveness is assessed in LVAD patients, additional research is required in order to determine both safety and feasibility of these possible treatment options, taking into account the high risk of thrombotic events.

GI bleeding is the most frequently observed bleeding event in AVWS patients, often as a consequence of arteriovenous malformation or Dieulafoy lesions [47, 66]. This is also

seen in LVAD patients [27]. Besides temporarily anticoagulation cessation during a GI bleeding episode, endoscopy and treatment of a suspected lesions is recommended in LVAD patients [27]. It has been described that preventing recurrence of GI bleeding was best obtained by prophylactic VWF concentrate in VWD patients [49]. However, targeted treatment strategies at the time of a GI bleeding is needed. This can include desmopressin, administered intravenously (0.3 μg per kilogram of body weight), intranasal (total dose, 300μg [150 μg per nostril]; in patients with body weight <50 kg, only one dose of 150 μg), or subcutaneously (0.3 μg per kilogram). Another option is the use of intravenously administered VWF/Factor VIII concentrate, or solely VWF concentrate. The aim should be to normalize the VWF:RCo activity and factor VIII activity until the GI bleeding has resolved. However, close monitoring of factor VIII and VWF levels is warranted, as different VWF concentrates have different ratios of factor VIII to VWF, leading to different levels of VWF activity and factor VIII levels in the circulation. High factor VIII levels may theoretically predispose LVAD patients to thrombotic complications. In addition, the fibrinolysis inhibitor tranexamic acid could be added to the treatment (orally 1g, 3 or 4 times daily), as it reduces mucocutaneous (re-) bleedings. Other medical treatments options for GI bleedings that has gained attention more recently include atorvastatin, thalidomide, and octreotide [98-100]. Through an anti-angiogenic pathway, thalidomide and atorvastatin reduce the rate of bleedings from AVMs and the transfusion need in VWD patients [98, 100]. Notwithstanding the observed anti-angiogenic effect of these drugs, these observations and the use of VWF (/factor VIII) concentrates need confirmation in LVAD patients through larger prospective randomized trials. These drugs have not been registered for use in LVAD patients or patients with AVWS.

Finally, a reduced pump speed does not seem to decrease VWF degradation, though this has only been quantified in a small in vivo study [101]. In addition, the finding that patients receiving third generation devices which function at a lower RPM also experience a loss in VWF activity and GI bleedings rate similar to second generation devices, suggest that lower pump speed does not add to the preservation of VWF [39, 54, 56]. Ultimately, only after device explantation or transplantation the AVWS will resolve [61].

CONCLUSION

In conclusion, in the last decade LVADs have evolved greatly and with great eager we await further developments. The increasing prevalence of heart failure and subsequently increasing use of LVADS demands tailored treatment and management strategies. Acquired coagulopathies are highly prevalent with nearly, if not all, patients experiencing AVWS. However, a definite association with bleeding events has yet to be determined. A variety of specialized techniques and assays can be used to diagnose patients with coagulopathies, though its clinical implications and consequences have to be determined in larger cohorts. In case of acquired von Willebrand syndrome is diagnosed using specific VWF assays in a bleeding LVAD patient desmopressin or VWF/factor VIII concentrates can be administered. Other promising therapies are emerging, but still require validation in LVAD patients. These complex coagulation disorders in LVAD patients require a multidisciplinary approach. Future studies focusing on these diagnostic and management therapies and assessing their safety should be a priority for cardiologist, thoracic surgeons, and hematologist.

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CHAPTER 14

Differences in the Evolution of Lactate Dehydrogenase Levels over Time Between the HeartMate II and HeartMate 3 Left Ventricular Assist Device

Muslem, R. Caliskan, K. Papageorgiou, G. Akin, S. Manintveld, O.C. Mokhles, M.M. Rohde, S. Russell, S.D. Hsu, S. Tedford, R.J. Leebeek, F.W.G. Bogers, A.J.J.C.

Submitted

Abstract

BACKGROUND: Lactate dehydrogenase (LDH) is considered a marker of haemolysis, thrombotic events and haemocompatibility in patients receiving a left ventricular assist device (LVAD). This study aimed to investigate the evolution of LDH levels over time between patients supported with a HeartMate II (HM2) or HeartMate 3 (HM3).

METHODS: A single-centered retrospective cohort was studied to evaluate all HM2 and HM3 LVAD implanted between December 2006 and April 2017. Patients were classified into two groups based on initial device. Nonlinear mixed-effects modeling was used for the analysis of repeated measurements of LDH.

RESULTS: In total, 84 patients received a LVAD (76% male, mean age 54 [43-60]), of whom 62 (74%) were HM2 and 22 (26%) HM3. Evolution of LDH ($p = 0.015$) was significantly higher for the HM2 than the HM3. The 1-year overall survival rate was 84% vs. 89% in the HM2 group compared to the HM3 group ($p=0.49$). During the first year follow-up, 3 (5%) patients had a confirmed and 8 (13%) patients had a suspected pump thrombosis in the HM2 group, whereas none of the patients in the HM3 group experienced a suspected or confirmed pump thrombosis.

CONCLUSION: Through one year, evolution of LDH was significantly higher in patients with a HM2 device compared to patients with a HM3 device, indicating lesser haemolysis and better haemocompatibility in the HM3.

INTRODUCTION

Although overall survival rates of the second generation left ventricular assist systems (LVAD) have improved significantly compared with prior devices,(1) the occurrence of thrombo-embolic events and pump thrombosis remains an important and especially morbid limitation of these devices.(1,2)

In 2014, it was reported that HM2 devices were exhibiting a rise in pump thrombosis, which can require urgent heart transplantation (HTX), device exchange, or thrombolytic therapy.(3) Although new approaches have been associated with reduced risk (e.g. stricter blood pressure management, pump speed management), pump thrombosis rate remains high.(4) In a recent trial comparing the HeartMate II (HM2), an axial-flow device, with the HeartMate 3 (HM3), a centrifugal-flow device, the pump thrombosis rate in HM2 patients was 10% at 6 months versus 0% in HM 3 patients.(2)

Although a difference in the combined end-point (free from death, disabling stroke or device exchange) has been shown between the HM2 and the HM3, driven largely by the decreased rate of device exchange for pump thrombosis, it remains unclear why HM3 devices enjoy such lower rates of pump thrombosis and device exchange compared to the HM2.(2) Haemocompatibility is a term comprising the haematological changes, blood element disruption, and the interaction between haematological elements and the pump interface.(5) It has been suggested that the HeartMate 3 has an improved haemocompatibility than previous devices. However, literature supporting this statement is scares or missing. Lactate dehydrogenase (LDH) has been known to be the most specific marker for haemolysis, pump thrombosis, and thrombo-embolic events, and could serve as a marker for haemocompatibility.(1,6)

Therefore, this study aimed to investigate the evolution of LDH over time between patients supported with a HM2 versus HM3 LVAD in order to quantify differences in pump haemocompatibility.

METHODS

Study Design

We conducted a retrospective cohort study evaluating all HeartMate II and HeartMate 3 LVAD (Abbott, Chicago, IL) implanted between December 2006 and April 2017 at the Erasmus University Medical Center, Rotterdam, the Netherlands. This study was

approved by the institutional review board of the Erasmus Medical Center (no. MEC-2017-1013).

Study outcome

The primary outcome was the assessment of longitudinal changes in LDH between the two groups. Secondary outcomes were all-cause mortality, suspected or confirmed pump thrombosis, and neurologic events.

Data collection and definitions

Patients were classified into two groups, HeartMate II (HM2) and HeartMate 3 (HM3) group, based on their initial device. Other types of durable LVADs were not implanted in our centre during the study period and therefore not included in the analysis. All data were obtained from the electronic patient records. Baseline laboratory values were collected pre-operative and during the first year of follow-up for all patients. LDH was routinely checked during follow-up. Patients were treated with LVAD as bridge-to-transplant (BTT) or destination therapy (DT). Pump thrombosis included suspected and confirmed pump thrombus and was defined according the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) adverse events definitions.(7) Neurologic events included transient ischemic attack, ischemic stroke, and haemorrhagic stroke as confirmed by a neurologist.

Statistical Analysis

Continuous parameters were expressed as median and interquartile range (IQR) or as mean and standard deviation and compared with Mann-Whitney rank sum test. Categorical parameters were expressed as number and percentage and compared by Pearson's χ^2 test or Fisher's exact test. Repeated measurements of LDH were analysed using mixed-effects models, accounting for the correlation among the measurements of each subject.

The inverse transformation was applied to the repeated measurements of LDH in order to satisfy the assumption that the residuals are normally distributed, since this assumption was violated in the original scale due to right skewness. Subject-specific trajectories of inverse LDH were allowed to be nonlinear in time, using natural cubic splines with two internal knots placed at the lower and upper quartiles of the observed follow-up times respectively. Furthermore, different average evolutions between the HM2 group and the HM3 group were specified while adjusting for the baseline characteristics age and gender. The nonlinear terms in both the fixed- and random-effects parts of the model were retained based on the corresponding likelihood ratio tests for nonlinearity (p-value: <.0001 and <.0001 respectively). Differences in the evolution of inverse LDH between

the HM2 and HM3 group were assessed using a likelihood ratio test. A Kaplan-Meier curve stratified by group was constructed for the evaluation of mortality during the first-year post-implantation. Patients were censored at time of heart transplantation. Differences in the survival during the first year pooled over strata were compared by log-rank test. Statistical significance was defined by a P-value less than 0.05. Analyses were performed using statistical software SPSS, version 20.0 for Mac (SPSS Inc., Chicago, IL) and R (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

RESULTS

Baseline characteristics

In total, 84 patients received a LVAD (76% male, median age 54 [43-60]). Of these patients, 62 (74%) patients received an axial-flow device (HM 2) and 22 (26%) a centrifugal-flow device (HM3). The baseline characteristics of the two groups are presented in **Table 1**. Patients with a HM3 were older (59 IQR [52-64] years vs. 52 IQR [43-59] years, p=0.009), had higher body-mass indices (26 IQR [22-28] kg/m^2 vs. 23 IQR [21-25] kg/m^2, p=0.015), more often implantable cardioverter defibrillator/pacemakers (86% vs. 62%, p=0.03) and were less often implanted as BTT (59% vs. 95%, p<0.001) at baseline, respectively. In addition, in the HM2 group more patients were INTERMACS class 1 (14 (23%) vs. 1 (5%), p=0.03) and the HM2 group had a higher rate of need for intra-aortic balloon pump (44% vs. 18%, p=0.03) compared to the HM3 group at baseline, respectively.

Laboratory values, including LDH, did not significantly differ at baseline, except for the estimated glomerular filtration rate (GFR), which was higher in the HM2 group (54 vs. 44 mL/min/1.73m^2, p=0.013), respectively.

Evolution of LDH

In total, 3951 repeated measurements (HM2 group: 2956, HM3 group: 995) of LDH were collected during follow-up. The mean follow-up time was 276±125 days for the HM2 group and 153±115 days for the HM3 group, respectively. The median number of measurements per subject was 43 (IQR 27 - 66) in the HM2 group and 46 (IQR 26 - 60) in the HM3 group. The individual evolution of LDH for all patients per device type is plotted in **Figure 1**. The evolutions of inverse LDH were found to be significantly different between the HM2 and HM3 groups (p=0.0015). As shown in **Figure 2**, the inverse LDH evolution over time of the HM3 group is consistently higher than the

corresponding evolution of the HM2 group with the only exception being at baseline (Wald test for difference between the intercepts of the two groups: 0.253). Implying in the original LDH scale that the evolution of the LDH is consistently lower in the HM3 group compared to the HM2 group over time.

Table 1. Baseline characteristics of the study population

	All patients (n=84)	HM2 Group (n=62)	HM3 Group (n=22)	p-value
Sex male	64 (76%)	45 (73%)	19 (86%)	0.19
Age	54 [43-60]	52 [43-59]	59 [52-64]	0.009
Body mass index	23 [21-26]	23 [21-25]	26 [22-28]	0.015
Ischemic Cardiomyopathy	40 (78%)	27 (44%)	13 (59%)	0.21
IDDM	12 (14%)	7 (11%)	5 (23%)	0.19
Hypertension	13 (16%)	10 (16%)	3 (14%)	0.78
ICD / PM	57 (68%)	38 (62%)	19 (86%)	0.03
IABP	31 (37%)	27 (44%)	4 (18%)	0.03
ECMO	13 (16%)	11 (18%)	2 (9%)	0.34
INTERMACS				0.03
• - Class I	15 (18%)	14 (23%)	1 (5%)	
• - Class II	31 (37%)	24 (39%)	7 (32%)	
• - Class III	18 (21%)	14 (23%)	4 (18%)	
• - Class ≥IV	20 (24%)	10 (16%)	10 (46%)	
Bridge-to-transplant	72 (86%)	59 (95%)	13 (59%)	<0.001
Pre-operative laboratory values				
• Lactate dehydrogenase	301 [221-442]	294 [226-445]	310 [215-449]	0.89
• eGFR CKD-EPI	50 [36-64]	54 [40-68]	44 [32-49]	0.013
• Blood Urea Nitrogen (mg/dL)	15 [10-20]	15 [9-19]	15 [12-22]	0.54
• Aspartate aminotransferase (U/L)	38 [28-86]	39 [28-88]	37 [28-66]	0.72
• Alanine aminotransferase ((U/L)	42 [24-108]	43 [24-109]	31 [23-110]	0.56
• Total bilirubine	16 [11-33]	16 [10-31]	19 [14-34]	0.36

*Continuous variables are presented as median (25-75 interquartile range); Categorical variables are presented as number (%). HM2/3, HeartMate 2/3; ECMO, Extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; IDDM, Insulin dependent diabetes mellitus; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; IABP, Intra-aortic balloon pump; ICD, Implantable Cardioverter Defibrillator; PM, Pacemaker.

Figure 1. Individual longitudinal lactate dehydrogenase evolution

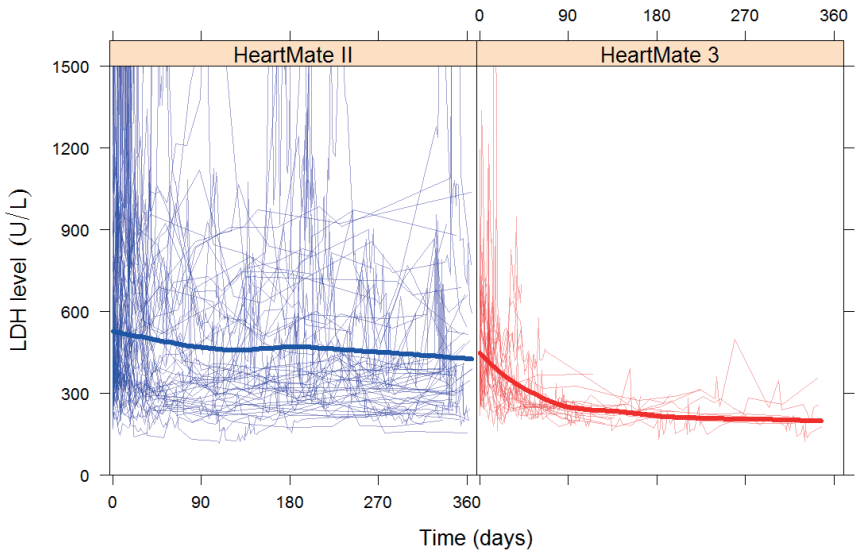
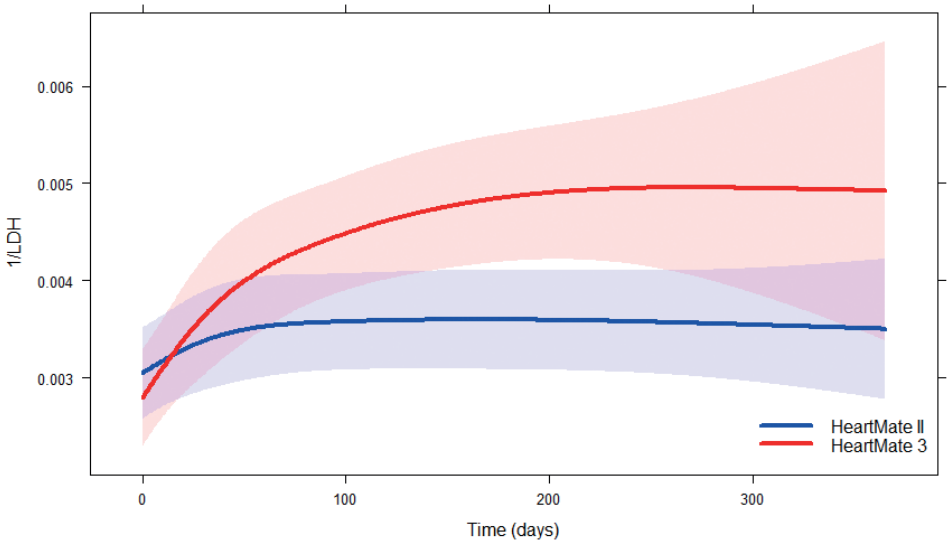


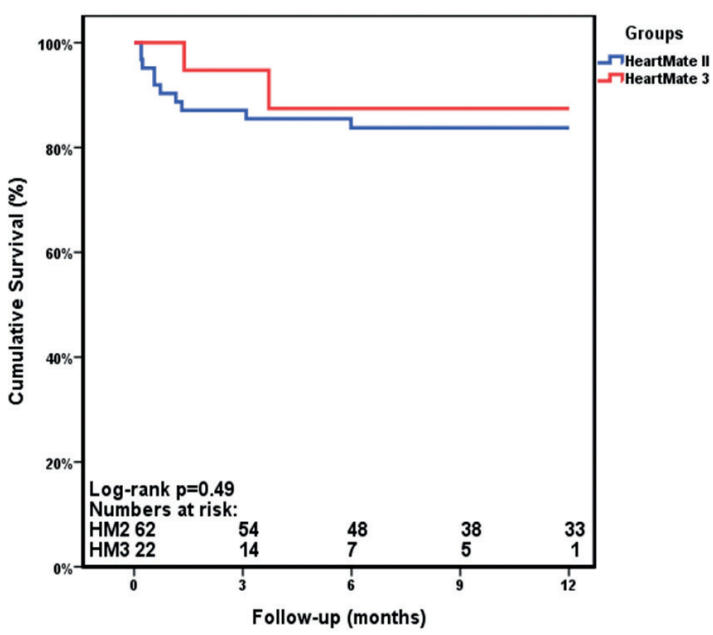
Figure 2. Inverse evolution of lactate dehydrogenase over time



Clinical course

During the first year post-implantation, 10 (16%) patients in the HM2 group underwent cardiac transplantation and 10 (16%) patients died. Two (9%) patients in the HM3 group died and none underwent cardiac transplantation (**Table 2**). The one-year overall survival rate was 84% vs. 89% in the HM2 group compared to the HM3 group (p=0.49, **Figure 3**). During the complete study period, 3 (5%) patients had a confirmed and 8 (13%) patients had a suspected pump thrombosis in the HM2 group, whereas none of the patients in the HM3 group experienced a suspected or a confirmed pump thrombosis. Although a numerical difference was observed, there was no statistically significant difference in the rate of neurologic events between the two groups (18% versus 9%, p=0.34).

Figure 3. Kaplan-Meier survival curve comparing patients with HM2 vs. HM3 LVAD.



The Kaplan-Meier survival curve shows the cumulative survival of patients with axial flow HM2 vs. patients with a centrifugal-flow HM3 device during the first year after CF-LVAD implantation.

Table 2. Clinical outcomes at one year

	All patients (n=84)	HM2 Group (n=62)	HM3 Group (n=22)
Suspected Pump thrombosis	8 (10%)	8 (13%)	0 (0%)
Confirmed Pump Thrombosis	3 (4%)	3 (5%)	0 (0%)
Neurologic event	13 (16%)	11 (18%)	2 (9%)
Cardiac transplantation	10 (12%)	10 (16%)	0 (0%)

HM, HeartMate

DISCUSSION

This study evaluated the differences in the evolution of LDH between the axial-flow HM2 and the centrifugal-flow HM3 LVAD. The evolution of LDH was significantly higher in patients with an axial-flow device than in patients with a centrifugal-flow device through the first year of follow-up, suggesting improved haemocompatibility of the HM3 device.

Haemocompatibility is a term comprising the hematological changes, blood element disruption, and the interaction between hematological elements and the pump interface.(5) This subsequently can lead to coagulopathies, such as acquired von Willebrand syndrome as well as hemolysis.(8) Although improvements in LVAD design and patient management have resulted in a lower rate of adverse events, complications related to haemocompatibility, including bleeding, stroke, and hemolysis, remain a significant problem.(7) However, our data and the recently published trial comparing the HM2 with the HM3 indicate that the centrifugal-flow devices are a step in the right direction.(2)

The difference in evolution of LDH between the two devices is thought to be due to the design of the centrifugal-flow device, which differs from its axial predecessor. The HM3 is designed to reduce shear stress through the following design alterations; the use of a magnetic bearing eliminating all friction wear, relatively large gaps located above and below the rotor to wash surfaces outside of the main flow path in order to minimize the risk of thrombogenesis and hemolysis, and finally, the use of sintered titanium in order to create texture on almost all blood containing surfaces of the pomp and to lower the thromboembolic risk.(2,9,10) The altering in design from the axial to the centrifugal-flow device also contributed to a decrease in shear stress.(9) This has been confirmed by Netuka *et al.,* who reported significant differences in the degree of von Willebrand

Factor (vWF) multimers degradation between the axial-flow and the centrifugal-flow device.(11) In addition, they suggest that the design characteristics account for this difference rather than the directional flow characteristics.(11) Despite this difference, vWF degradation still occurs in HM3 patients.(11) Difference in hemolysis and vWF has also been determined between HM2 and the HeartWare HVAD.(12) Whether haemocompatibility of HM3 is also clinically superior to other centrifugal devices is yet to be determined.

Despite the diminished rate of pump thrombosis, the neurologic event rate does not differ between the two devices.(2) Since early data suggests that there is a lower incidence of pump thrombosis in HM3 patients, one wonders if an alternative anticoagulation protocol should be considered as the use of anticoagulant medication is an important risk factor for bleeding.(13) Furthermore, given the lower LDH values in HM3, it is likely that a different cut-off value needs to be considered. However, it is unknown how alternative anticoagulation protocols might impact this observation. A LDH >2.5 times the upper limit of normal has been shown to predict thrombosis in HM2 devices.(6,14) Future studies are needed to determine the sensitivity and specificity of this value in these new devices, and in addition, determine the optimal cut-off value in order to improve clinical practise.

In our study, none of the patients implanted with a centrifugal-flow HM3 device was diagnosed with pump thrombosis, mimicking the early results from the MOMENTUM study.(2) Reducing the complication rate is of paramount importance and a constant effort has to be made to reduce the morbidity and mortality of LVAD therapy. Reducing the complication rate will not only increase the survival, but also the quality of life of the LVAD patient and the care providing partner.(15) Finally, it will also contribute in making LVAD therapy a more suitable treatment option for patients in whom currently the risk of complications and death outweighs the benefit of LVAD therapy.

This study has a several limitations, which should be taken into consideration when interpreting these results. This was a retrospective cohort study evaluating a relatively small number of patients from a single center. In addition, due to relative recent availability of HM3, fewer patients received this device, which resulted in a smaller number of observations in the HM3 group at 1 year and wider confidence intervals. Despite this discrepancy, similar numbers of LDH measurements were taken per patient and available for comparison. Furthermore, following the Dutch reimbursement of DT from 2015 onwards, the HM3 group includes more DT patients. This explains the higher age and the higher rate of implantable cardioverter defibrillator/pacemakers in the HM3 group. None of the patients in the HM3 group experienced a pump-thrombosis,

therefore no statistical test was conducted in order to quantify this difference. Lastly, we did not compare LDH values with other centrifugal flow pumps because we only implanted two types of devices in our center.

CONCLUSION

In conclusion, HM3 devices have persistently lower LDH levels than HM2 after implantation, suggestive of lower level of haemolysis, and subsequently, improved haemocompatibility compared to the HM2.

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CHAPTER 15

Differences in Lactate Dehydrogenase Levels Between the HeartWare HVAD and the HeartMate 3 Left Ventricular Assist Device.

Muslem, R. Caliskan, K. Siang, C.O. Hsu, S. Tedford, R.J.

Submitted

Abstract

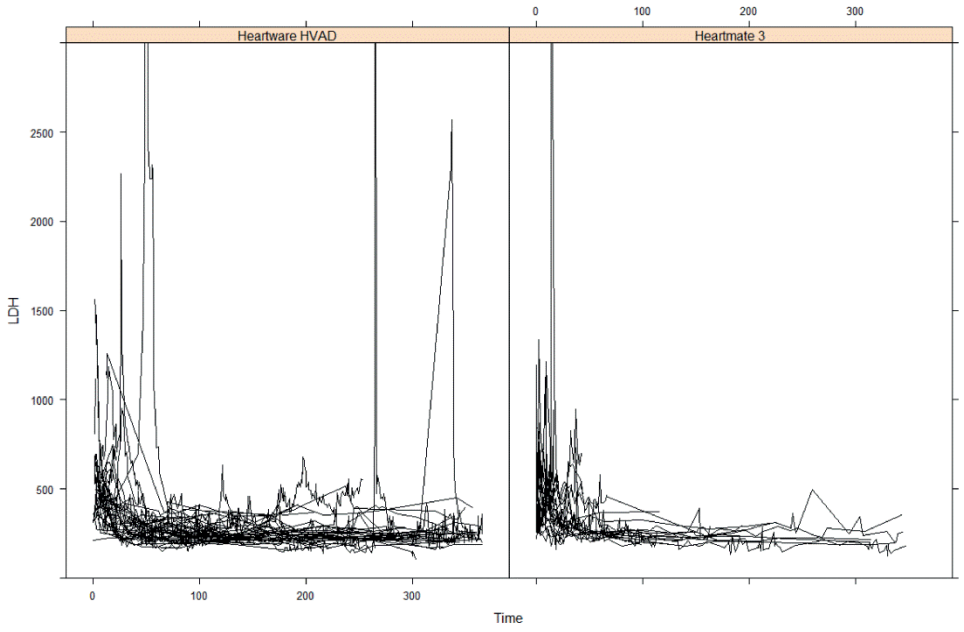
The aim of the present study was to investigate the evolution of lactate dehydrogenase (LDH) levels over time between patients supported with a HeartWare HVAD or a HeartMate 3 (HM3) left ventricular assist device (LVAD). Overall, 70 patients underwent LVAD implantation (48 HVAD and 22 HM3). In total, 2648 repeated measurements of LDH were collected during follow-up (HVAD-group:1655, HM3-group:993). The evolutions of LDH and the rate of hematological complications were not significantly different between the HVAD and the HM3 group (p=0.12, p=0.2, respectively), suggesting similar haemocompatibility of the devices.

Continuous-flow left ventricular assist devices (CF-LVADs) have revolutionized the management of patients with end-stage heart failure. Recent technological advancements have led to the introduction of several new generation devices with specific hematological characteristics. However, hematological complications remain a significant limitation of CF-LVAD support. In addition, there are limited data reported on the hematological performance of these new devices during follow-up. More often the rate of hematological complications is used to measure the hematological performance. However, this assumption is biased by a number of factors that have an impact on the complication rate, including anti-coagulant guidelines, infections, and patient-specific characteristics. Lactate dehydrogenase (LDH) is known to be the most specific marker for haemolysis, pump thrombosis, and thrombo-embolic events, and could serve as a marker for haemocompatibility.(1,2) Therefore, the aim of the present study was to investigate the evolution of LDH levels over time between patients supported with a HeartWare HVAD or a HeartMate 3 CF-LVAD in order to quantify potential differences in device haemocompatibility.

We reviewed all adult patients receiving HVAD or HM3 between August 2009 and April 2017 at two tertiary CF-LVAD centers. The primary outcome was the longitudinal change in LDH between the two groups. In order to adequately test the repeated measurements of LDH, mixed-effects models were used, accounting for the correlation among the measurements of each subject. The inverse transformation was applied to the repeated measurements of LDH in order to satisfy the assumptions of normality and homoscedasticity of the residuals. Furthermore, different average evolutions between the HVAD group and the HM3 group were specified while adjusting for the baseline characteristics age and gender. The nonlinear terms in both the fixed- and random-effects parts of the model were retained based on the corresponding likelihood ratio tests for nonlinearity (p-value: <.0001). Differences in the evolution of inverse LDH between the HVAD and HM3 group were assessed using a likelihood ratio test.

Overall, 70 patients underwent CF-LVAD implantation, of whom 48 HVAD patients and 22 HM3 patients. Mean age at implantation was 55 [IQR 49-63] years, 80% were male, 67% of the patients had non-ischemic cardiomyopathy, and 63% of the patients received their CF-LVAD as bridge-to-transplant. Furthermore, 19% of the patients were INTERMACS Class 1, 29% were Class 2, and 53% were ≥ Class 3. Baseline characteristics and laboratory data did not differ between HVAD patients and HM3 patients, except for etiology of heart failure (79% vs 41% non-ischemic p=0.002), and creatinine (132 umol/L [IQR 106-157] vs. 155 umol/L [IQR 155-200], p=0.009, respectively.

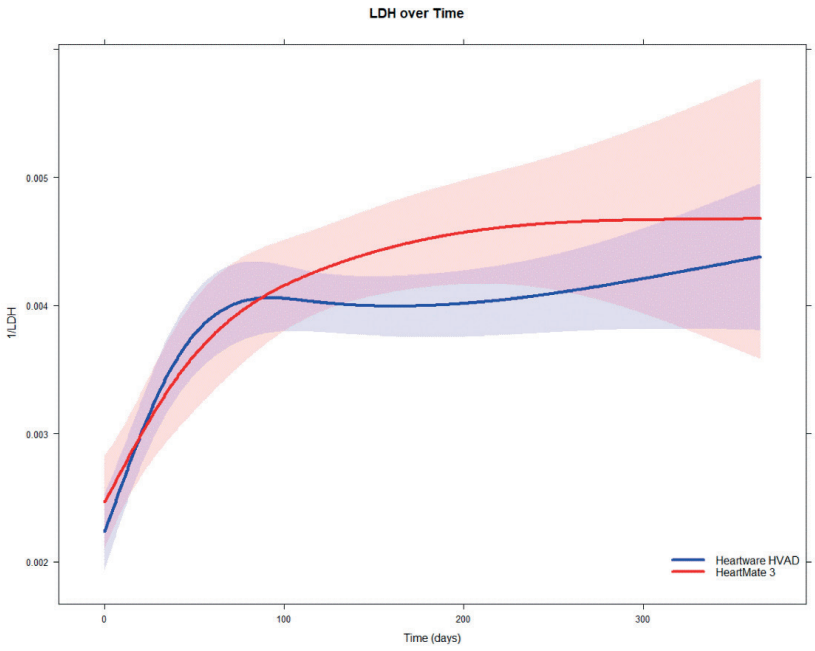
Figure 1. A. Individual longitudinal lactate dehydrogenase evolution during the first year.



In total, 2648 repeated measurements (HVAD group: 1655, HM3 group: 993) of LDH were collected during follow-up. The mean follow-up time was 250±128 days for the HVAD group and 196±121 days for the HM3 group (p=0.06), respectively. The median number of measurements per subject was 20 [IQR 13-50] in the HVAD group and 46 [IQR 26-60] in the HM3 group. The individual evolution of LDH for all patients per device type is plotted in Figure 1a. The evolutions of inverse LDH were found not to be significantly different between the HVAD and HM3 groups (p=0.12, figure 1b). As shown in Figure 1b, the inverse LDH evolution over time of the HVAD group is consistently overlapping the corresponding evolution of the HM3 group.

During the first year, 12 patients (17%) underwent heart transplantation and 14 patients (20%) died across both groups. In addition, both groups (HVAD vs. HM3) had a similar rate of disabling stroke (6% vs 9%, p=0.65), and any neurologic events (25% vs 9%, p=0.2), respectively. A higher rate of pump thrombosis was noted in the HVAD patients compared to HM3 patients (n=7 (15%) vs n=0 (0%), p=0.09), respectively. However, this did not reach significance.

Figure 1. B. Inverse evolution of lactate dehydrogenase during the first year.



Based on the individual and the grouped evolution of LDH, we report similar changes in the LDH over time in patients supported with a HVAD or HM3 CF-LVAD, suggestive of similar haemocompatability between devices. These results are in keeping with studies investigating another marker of haemocompatability, von Willebrand factor (vWF) degradation, and in particular, the degradation of high molecular weight multimers (HMWM) of vWF following CF-LVAD implantation. In both the HVAD and HM3 patients, a similar significant decrease of HMWM of vWF has been reported to occur.(3,4)

Although limited by power and not the primary focus of the study, we also found no difference in the rate of hematological complications between the two groups in this study. Because of its unmatched design and small cohort size, no additional survival comparison was appropriate.

To the best of your knowledge this is the first study to compare and differentiate between longitudinal changes of LDH in HVAD and HM3 patients. The evolution of LDH did not differ between patients supported with a HVAD or a HM3 device, suggesting similar haemocompatibility between the devices.

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CHAPTER 16

Modification of a Ventricular Assistance Device for a Hemiplegic Left ventricular assist device Patient.

Muslem, R. Yalcin, Y.C. Caliskan, K. Van der Heiden, C. Van Rhijn, H.
Bogers A.J.J.C. Manintveld, O.C.

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Abstract

Neurologic events occur in up to 18% of patients with continuous-flow left ventricular assist devices (LVAD) and is associated with significant morbidity and mortality. The current form of the LVAD equipment is not suited to serve patients who are impaired by a stroke. By creating an assistance device for the LVAD equipment, we have been able to greatly improve the quality of life and self-dependence of a hemiplegic LVAD patient.

INTRODUCTION

Since the food and drug administration approval for left ventricular assist device (LVAD) as destination therapy, the neurologic event rate has increased significantly (1). It can be hypothesized that this rise is due to the increasing age of the LVAD patients. These neurologic events are associated with significant morbidity and mortality (1, 2). Despite the risk for neurologic events there is increase in the use of LVAD therapy. This emphasizes the need for adequate rehabilitation programs and innovative solutions for patients whom are impaired after a neurologic event. These patients often rely on professional healthcare or familial support for their daily practice and assistance with their device, which eventually leads to an increase in healthcare costs. We designed an unique additional equipment for the LVAD, which makes it possible for a hemiplegic patient to be able to operate his LVAD equipment and subsequently live independently in his own home.

Case Report

We present the case of a 29 year old man on LVAD therapy who endured an ischemic infarct. He had to endure a stroke due to an embolus while on support with the Heartmate II LVAD system resulting in right sided hemiparesis. This proved to be a problem for the daily actions necessary to operate his LVAD equipment. In order to help this patient we developed an assistance device in the medical engineering department of our hospital. The assistance device can be attached to the top of the Power Module with six suction cups and consists of a piece of PVC approximately 28x12x2 cm in which several slots have been milled (Figure 1A).

It works as follows:

1. To insert/remove the batteries in the clips the patient puts the batteries upside down into the two slots on the left of the assistance device. Now he can attach or remove the clip with one hand (Figure 1B).

2. To connect the battery clip to the cable of the system controller, the clip with the battery is inserted horizontally into the slot on the right. The extra brace holds them down under the pivoting force during insertion of the cable into the clip. The cable can be released again in the same fashion (Figure 1C).

3. To be able to connect the system controller battery cables to the patient cable from the Power Module, an extra adapter is connected on top of the assistance device. This keeps the patients cable connector in place under pulling and pushing forces (e.g. inserting and detaching the contra connector from the system controller) and under rotating forces (e.g. tightening and untightening the locknut). An extra aluminum brace is attached to the front of the stud, the edge of this brace catches the rim of the connector to keep it in place when the patient detaches or connects the cables (Figure 1D).

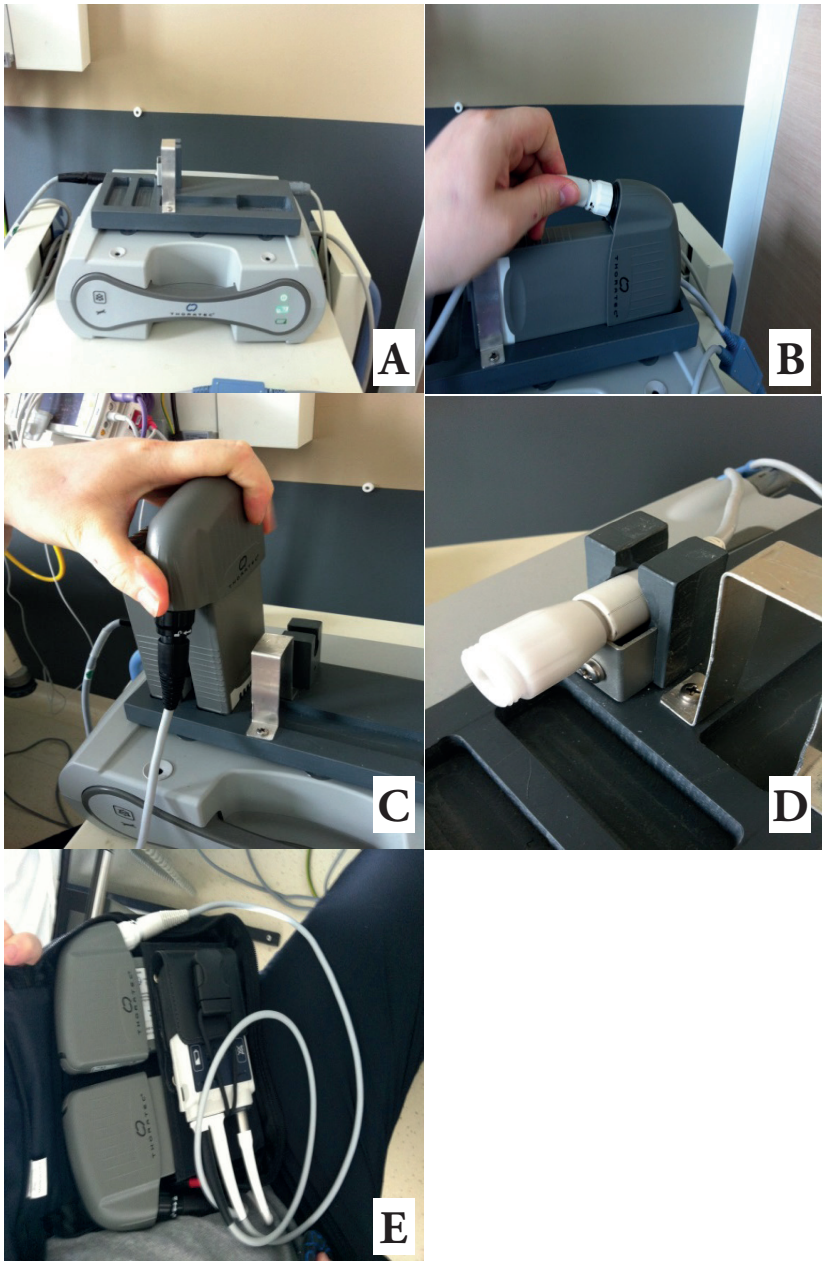
4. The manufacturer of the Heartmate LVAD system supplies several solutions to carry the batteries and system controller. This patient preferred the Consolidated Bag, which has two slots for the batteries and an elastic pouch for the system controller. However, the patient was unable to insert the system controller in this tight fitting pouch one handed. The solution was to remove the pouch and replace it with the belt attachment pouch as supplied in the Thoratec GoGear Wearable Accessories Kit. This pouch has been attached with 4 rivets to the inside of the Consolidated Bag (Figure 1E).

Finally, an approval was not required of the manufacturer, since no changes were made that would impact the device intrinsically or its performance.

Discussion

The assistance device we developed is not presented here as a one size fits all model. It shows how one can make an assistance device to enhance independence of a hemiplegic LVAD patient. The rate of neurologic events remains disturbingly high in LVAD patients and is associated with high morbidity and mortality. Patients with a neurological event often require or are dependent on extended care and regular assistance with their LVAD. Due to the custom made equipment, which can be attached by suction cups to the power module, our patient is again mobile and self-reliant. He now can connect or disconnect the cables of the LVAD with one hand. It is important to realize that this LVAD patient, with his disabilities, now manages to live independently in his own home. Although this is the first patient who has received this modified LVAD equipment, we believe that LVAD patients all over the globe could benefit from these types of innovative additional equipment after the occurrence of an event. Our case study shows that it is possible to improve the quality of life of a hemiplegic patient with a LVAD using custom made equipment.

Figure 1. Assistance device for LVAD patients
1A. The assistance device attached to the top of the Power Module with six suction cups.
1B. Inserting/removing the battery using the clips of the assistance device.
1C. Connecting/disconnecting the battery's to the system controller.
1D. Connecting/disconnecting the patients cable to the power module.
1E. Consolidated Bag customized using the Thoratex GoGear Wearable Accessories Kit.



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CHAPTER 17

Ventricular arrhythmias in patients with a continuous-flow left ventricular assist device.

Yap, S. C. Ramjankhan, F. Muslem, R. de Jonge, N. Kirkels, H. J. Akin, S. Manintveld, O. C. Birim, O. Szili-Torok, T. Caliskan, K

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Continuous-flow left ventricular assist devices (CF-LVADs) are increasingly used in the management of patients with end-stage heart failure; however, CF-LVAD support can be hampered by the occurrence of ventricular arrhythmias (VAs) (1–5). There are limited data on the temporal evolution of VA burden during long-term follow-up. The aim of the present study was to investigate the incidence, predictors, and clinical outcomes of VA in CF-LVAD patients.

We reviewed all adult patients receiving a CFLVAD between March 2006 and April 2015 in 2 large Dutch LVAD centers. The primary outcome was the occurrence of VA, defined as VA that was sustained for >30 s or was treated by an implantable cardioverter-defibrillator (ICD). Multivariate Cox regression analysis was performed to investigate predictors of late (>30 days) post-LVAD VA.

Overall, 204 patients underwent CF-LVAD implantation (mean age at implantation 49.2 ± 12.5 years, 70.6% male, 70.6% nonischemic cardiomyopathy, 58.3% ICD). The majority of patients (93.6%) received an LVAD as a bridge to heart transplantation (HTX). Eighty-five patients (41.7%) had a history of VA before LVAD implantation. During a median follow-up of 17.3 months (interquartile range: 8.1 to 29.5 months), 62 patients (30.4%) experienced post-LVAD VA. The burden of VA followed a U-shaped curve, with the highest incidence in the first postoperative month, a nadir at 15 to 18 months, and a rise after that time (Figure 1A).

Pre-LVAD VA, the presence of an ICD, the use of beta blockers, and atrial fibrillation were univariate predictors of late post-LVAD VA. In a multivariate Cox regression model, only pre-LVAD VA remained as an independent predictor of late post-LVAD VA (adjusted hazard ratio [HR]:2.13; 95% confidence interval [CI]: 1.06 to 4.27; p = 0.03) (Figure 1B).

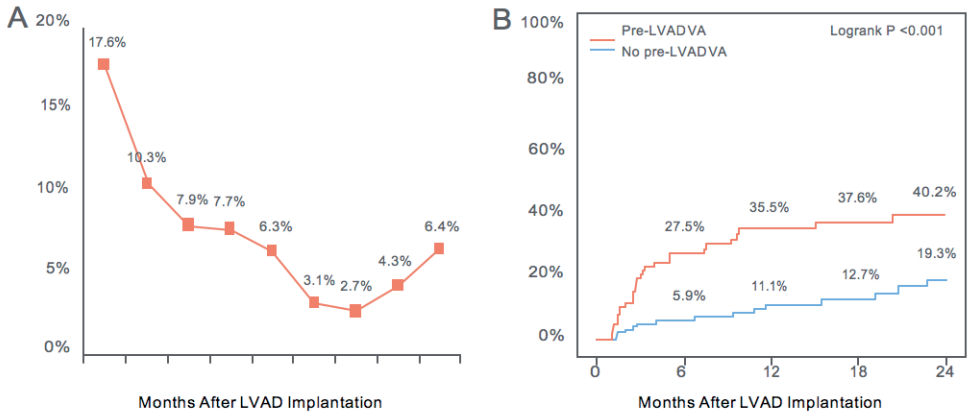
During follow-up, 88 patients (43.1%) underwent HTX and 57 patients (27.9%) died. The 1-year mortality and HTX rates were 11.8% and 18.6%, respectively. The most common mode of death was noncardiac death (52.6%), followed by cardiac death (28.1%) and death of indeterminate causes (19.3%). Post-LVAD VA was not associated with increased mortality (HR: 1.10; 95% CI: 0.63 to 1.95; p = 0.73), HTX (HR: 0.99; 95% CI: 0.63 to 1.55; p = 0.96), or the combined endpoint of HTX or death (HR: 0.98; 95% CI: 0.69 to 1.41; p = 0.93). However, 3 of 62 patients (4.8%) with post-LVAD VA had difficult to control VA that required urgent HTX.

The incidence of post-LVAD VA was 30.4% in the present study, which is in agreement with previous studies (1–5). A high early post-operative burden of VA was followed by a relatively

low VA burden after hospital discharge. However, at long-term follow-up, there appears to be increased vulnerability to VA, which could reflect incipient hemodynamic failure of appropriate LVAD support.

Pre-LVAD VA was an independent predictor of late post-LVAD VA. This is not surprising, because it reflects the presence of an arrhythmogenic substrate that is not abolished by the implantation of an LVAD. The effect of post-LVAD VA on survival rates is ambiguous in the literature (2–4). In a small study comprising 61 patients with CF-LVAD and ICDs, post-LVAD VA was an independent predictor of mortality (3). We did not find an association between post-LVAD VA and increased mortality, albeit a minority of patients with therapy-resistant VA required urgent HTX as a bail-out procedure. Our study is hampered by its retrospective design. The incidence of VA might be underestimated when VA episodes are not documented properly, especially in patients without an ICD.

Figure 1. Post-LVAD VA



(A) Incidence of post-LVAD VA depicted as the percentage of patients with VA per time interval. (B) Kaplan-Meier event curves for late (>30 days) post-LVAD VA stratified by pre-LVAD VA. LVAD = left ventricular assist device;
VA = ventricular arrhythmia.

In summary, the incidence of post-LVAD VA followed a U-shaped curve with an increase in incidence at long-term follow-up. Patients with pre-LVAD VA were more prone to develop late post-LVAD VA. Post-LVAD VA did not appear to impact survival or HTX rates; however, urgent HTX was needed in some patients with therapy-resistant VA. It is important to realize that in destination-therapy patients with therapy-resistant VA, urgent HTX will probably not be a good option.

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CHAPTER 18

The long-term durability and mechanical complications of a Continuous-flow left ventricular assist device. “An urgent call for regular inspections of the LVAD after two years.”

Muslem, R. Akin, S. Constantinescu, A.C. Manintveld, O.C. Brugts, J.J. Van der Heijden, C. Birim, O. Bogers, A.J.J.C. Caliskan, K.

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Abstract

BACKGROUND: Long-term durability and incidence of potential mechanical device failure are largely unknown. In this study, we investigated the incidence and potential predictors of mechanical device failure (MDF) in continuous flow left ventricular assist device (cf-LVAD) patients.

METHODS: We conducted a retrospective study of all cf-LVADs (type HeartMate II) implanted in our center. MDF was defined as a failure of driveline, inflow-outflow graft, electrical power, drive unit or motor failure, excluding device failure due to a biologic complication (ea. device thrombosis, hemolysis or infections).

RESULTS: A total of 69 cf-LVADs were implanted in 59 patients (median support time 344 days [IQR 149-712days], mean age 50.1±10.7 years, 75% male). MDF occurred in 9 (13%) cf-LVAD patients at a median follow-up time of 846 [IQR:708-1337] days after implantation. Freedom of MDF through the 1st, 2nd, and 3rd year after LVAD implantation was 100%, 85%, and 64%, respectively. Patients who experienced MDF, were significantly longer supported by their LVAD (median 846 [IQR: 708-1337] vs. 268 [IQR:103-481] days, p = 0.001), were more frequently re-admitted due to LVAD related technical problems (p=0.002), including a higher rate of LVAD controllers exchange (44% vs. 12%, respectively p=0.03). The main reason for MDF was a damaged or fractured driveline (n=8, 89%). In 2 patients, sudden death was related to MDF.

CONCLUSIONS: Patients needing extended cf-LVAD-support are at increasing risk for MDF. Various technical problems precede the onset of a MDF event. Periodical extensive assessment of the technical integrity of the device is indicated during long-term LVAD support.

BACKGROUND

Continuous flow left ventricular assist devices (CF-LVADs) are increasingly used in the treatment of end-stage heart failure patients in the form of bridge-to-transplantation (BTT), bridge-to-recovery, and as destination therapy (DT).(1-5) Although the use of LVAD as BTT has improved the quality of life and the survival of patients awaiting heart transplantation (HTX), HTX still remains the most successful treatment option for patients with refractory heart failure with a mean survival beyond 13-14 years.(6) Due to the extreme shortage of suitable cardiac donors and the rise of elderly patients ineligible for HTX, the use of cf-LVAD as DT is increasingly used in recent years. (1, 2) As a result, the duration of long-term mechanical support increases and device durability becomes extremely important for the long-term survival, morbidity and quality of life of patients, in particular for DT patients.(7, 8) In the REMATCH trial device failure was the leading cause of death, next to sepsis (9). Device failure can occur due to mechanical failure, driveline damage, infections or thrombosis and often requires pump replacement, which is associated with increased healthcare costs, morbidity and mortality.(8, 10-12) Previous studies have reported that the incidence of device failure and device replacement is higher from one year of mechanical support onward.(9, 11, 12) However, there is limited data on the long-term durability of current cf-LVADs and the distribution of device failure over time.

In this study, we investigated the incidence, predictors and clinical outcome of device failure in HeartMate II (formerly Thoratec Inc., currently Abbott, Chicago, IL) cf-LVAD patients beyond one year of implantation.

METHODS

Study design and patient population

We conducted a retrospective review of all patients (age ≥16 years) between December 2006 and August 2015, receiving an axial type continuous-flow HeartMate II LVAD at the Erasmus MC, Rotterdam, a tertiary referral center. Each cf-LVAD implant (primary or secondary) was separately entered into the study. The cohort of patients used in this study is derived from the local input of the EUROMACS Registry.(5) The study was approved by the institutional review board of the Erasmus MC and informed consent was signed by the patients.

Outcome definitions

The primary outcome was the occurrence of mechanical device failure (MDF). For the definition of MDF, the criteria given by Fries et al. was utilized and defined as: a mechanical problem resulting from a driveline, inflow / outflow graft damage or as a drive unit or motor failure of an implanted ventricular assist device.(13) Device failure due to a biologic complication (device thrombosis, hemolysis or infections) was excluded and is reported separately.(14) Deaths were classified as "cardiac" when a definitive cause of death related to a cardiovascular event or LVAD failure, and as "non-cardiac" when the cause of death did not relate to the cardiovascular system. Secondary outcomes were all-cause mortality, heart transplantation, LVAD replacement or explantation.

Data collection

Relevant baseline characteristics, demographics, postoperative and clinical data were collected, primarily for the EUROMACS Registry. Eventual missing data were easily retrieved from the medical records of the patients, which were stored electronically in the hospital electronic patient records. The data was obtained from reports from routine clinic visits and written correspondence from local physicians. Date of onset was recorded for all major LVAD alarms, device failure and adverse events such as, re-thoracotomy and pump thrombosis. LVAD alarms were collected by the LVAD technician (CvdH) for clinical purposes during regular clinical visits. The device failure was confirmed independently by the cardiologists (KC, SA). Subsequently, data were processed anonymously. All cases of device failure were extensively revised to determine the characteristics of the patient, onset, diagnostic tests used, treatment and treatment outcome.

Statistical analysis

Categorical variables are represented by frequencies and percentages. Continuous data are presented as mean ± standard deviation or as median and interquartile range [25^{th} to 75^{th} percentile]. Continuous variables were compared using paired or independent t-test, Mann-Whitney U-test or Wilcoxon's test when appropriate. When comparing frequencies between groups, the Chi-square or Fisher's exact test was used, where appropriate. Statistical analyses were performed using SPPS version 21(IBM corporation, Armonk, NY). All test were two-tailed. All p-values between 0.05 and 0.10 were considered to be a statistical trend and a p-value <0.05 was considered statistically significant.

Table 1. Baseline characteristics of study population at LVAD implantation.

	Total population (n=69)	Mechanical device failures (n=9)	Non-mechanical device failures (n=60)	p-value
Demographics				
Age at implantation, Years	50.1±10.7	47.4±14.2	50.5±10.2	ns
Male gender	52 (75)	7 (78)	45 (75)	ns
BSA, m^2	1.9±0.21	1.9±0.18	1.9±0.21	ns
BMI, kg/m^2	23.0±3.7	22.9±3.4	22.6±3.8	ns
Etiology				
• Non-ischemic CMP	37 (54)	3 (33)	34 (57)	ns
• Ischemic CMP	32 (46)	6 (67)	26 (43)	
Co-morbidities at Baseline				
• Myocardial infarct	30 (44)	6 (67)	24 (40)	ns
• PCI	26 (38)	4 (44)	22 (37)	ns
• CABG	4 (6)	2 (22)	2 (3)	0.08
• ICD	42 (61)	4 (44)	38 (63)	ns
• Hypertension	12 (17)	1 (11)	11 (18)	ns
• Diabetes mellitus	4 (6)	1 (11)	3 (5)	ns
• TIA / CVA	6 (9)	-	6 (10)	ns
• COPD	3 (4)	-	3 (5)	ns
Pre-operative status				
INTERMACS class				ns
• I	14 (20)	2 (22)	12 (20)	
• II	15 (22)	4 (44)	11 (18)	
• III	19 (28)	3 (33)	16 (27)	
• IV	12 (17)	-	12 (20)	
• V-VII	9 (13)	-	9 (15)	
Inotropic support	54 (78)	9 (100)	45 (75)	ns
IABP	27 (39)	5 (56)	22 (37)	ns
ECMO	13 (19)	2 (22)	11 (18)	ns

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean ± standard; ns, not significant (p>0.05); BSA, body surface area; BMI, body mass index; CMP, cardiomyopathy; PCI, percutaneous coronary intervention; CABG, Coronary artery bypass graft; TIA, transient ischemic attack; CVA, ischemic cerebrovascular accident; COPD, Chronic Obstructive Pulmonary Disease; Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS); IABP, Intra-aortic balloon pump; ECMO, Extracorporeal Membrane Oxygenation.

RESULTS

Baseline characteristics

A total of 69 CF-LVADs were implanted in our center between December 2006 and August 2015 in 59 patients (mean age at implantation 50.1±10.7 years, 75% male, 54% non-ischemic cardiomyopathy). All patients received their LVAD initially as a BTT. Seventy-eight percent of the patients required intravenous inotropic agents, 39% had an intra-aortic balloon pump and 19% were supported by an ECMO, pre-implantation. MDF occurred in 9 patients, of whom 7 had lead fractures. Their baseline characteristics did not differ significantly when grouped into MDF and Non-MDF groups (Table 1).

Clinical outcomes and the epidemiology of mechanical device failure

During a median follow-up (FU) duration of 344 days [IQR 149-712 days], 9 (13%) patients reached the endpoint MDF. Overall, 12 (17%) patients died and 26 (38%) patients underwent heart transplantation during the follow-up period (**Table 2**). MDF accounted for 17% of the deaths. Outcomes stratified by groups are presented in **Figure 1.** Three (4%) patients had their LVAD exchanged because of pump thrombosis, and one patient experienced cardiac recovery and subsequently the LVAD was explanted (**Figure 2.)** Competing endpoints up to 60 months after LVAD implantation are presented in **Figure 3**.

Figure 1. Flow-chart. LVAD, left ventricular assist device.

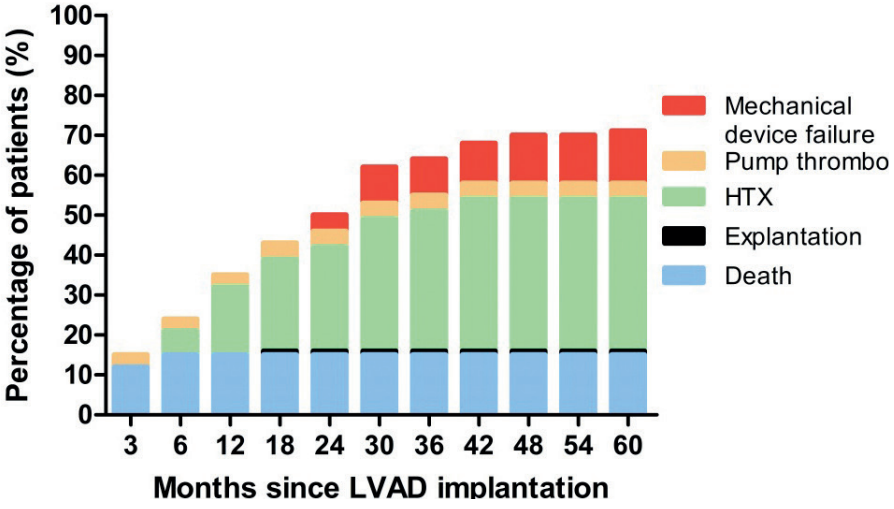


Figure 2. The rise of mechanical failure.

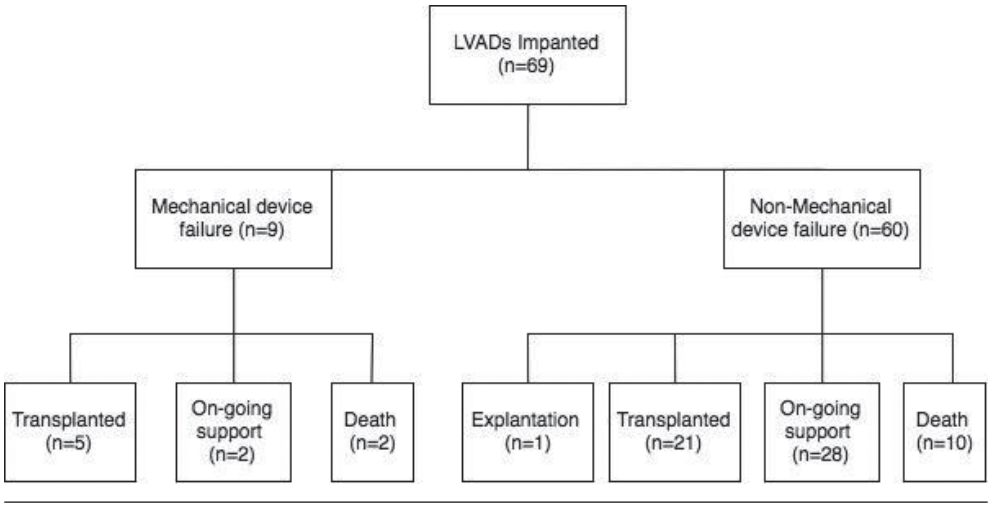
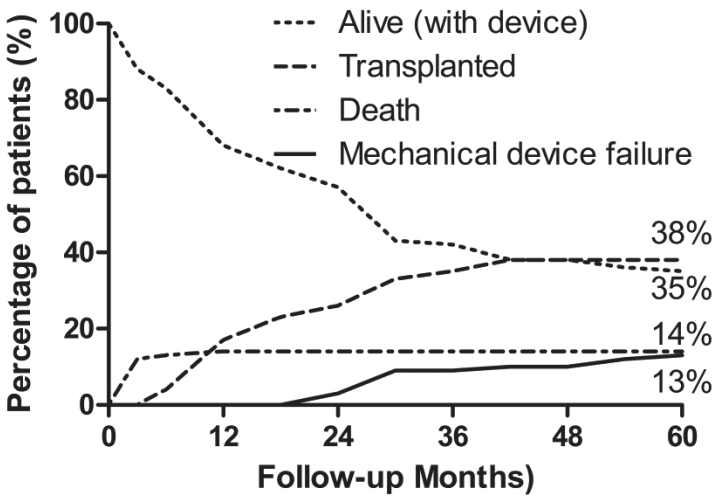


Figure 3. Competing endpoints after cf-LVAD implantation.



MDF occurred at a minimum of 649 days with a median time of 846 days [IQR 708-1337 days] after implantation. In addition, patients who experienced MDF were significantly longer supported by their LVAD compared to the Non-MDF group, median 846 days [IQR 708-1337 days] versus 268 days [IQR 103-481 days], p = 0.001, respectively (**Table 2**). The incidence in the first, second and third year was 0%, 13% and 38%, respectively. Event-free survival through the 1st, 2nd, and 3rd year after LVAD implantation for MDF was 100%, 85%, and 64%, respectively. The total incidence rate (IR) was 0,11 MDF per patient year. In **Figure 4** the cumulative percentage of patients free from technical problems preceding the onset of MDF is presented, censored for death and HTX.

Table 2. Follow-up after LVAD implantation.

	Total population (n=69)	Mechanical Failures (n=9)	Non-mechanical device failures (n=60)	p - value
Follow-up, days	344 [149 - 712]	846 [708-1337]	268 [103 - 481]	0,001
BMI difference at last FU*	+2.0±3.0	+2.0±2.5	+2.1±3.2	ns
NYHA class at last FU*				ns
• I	30 (51)	8 (89)	22 (44)	
• II	19 (32)	1 (11)	18 (36)	
• III	8 (14)	-	8 (16)	
• IV	2 (3)	-	2 (4)	
Clinical outcome				
• Death	12 (17)	2 (22)	10 (17)	ns
• Heart transplantation	26 (38)	5 (56)	21 (35)	ns
• LVAD explantation	1 (1)	-	1 (2)	ns
Re-thoracotomy	34 (49)	5 (56)	29 (48)	ns
• Early (<30 days)	28 (41)	3 (33)	25 (42)	ns
Re-admission reason				
• Cardiac deterioration	5 (7)	2 (22)	3 (5)	ns
• LVAD-related	36 (52)	9 (100)	27 (45)	0.002

*Only patients included that were discharged. Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean ± standard deviation or median [IQR (interquartile range 25th, 75th percentile)]. ns, not significant (p>0.05); NA, not applicable

Onset of mechanical device failure, diagnosis and treatment

The number of patients with any cf-LVAD alarms was higher in the MDF group, mainly due internal driveline damages. Seventy-eight percent of the patients in the MDF group experienced a red LVAD alarm versus 3% in the Non-MDF group (p<0.001, **Table 3**). Likewise, more patients had their LVAD controllers exchanged (p=0.03) and had a damaged or fractured driveline in the MDF group compared to the Non-MDF group (p<0,001). There was no difference in the re-admission frequency due to progression of heart failure. In addition, the frequency of any or early (<30 days) re-thoracotomy after LVAD implantation did not differ significantly between the two groups.

Table 3. Overview of technical problems in advance of mechanical device failure.

	Total population (n=69)	Mechanical device failures (n=9)	Non-mechanical device failures (n=60)	p - value
LVAD parameters at last FU*				
• Pump Speed, rpm	9058 (319)	9155 (240)	9040 (331)	ns
• Pump flow, L/m	5.0 (1.0)	5.0 (0.73)	4.9 (1.0)	ns
• Pulse index	5.7 (1.0)	5.6 (0.68)	5.7 (1.1)	ns
• Pump power, Watts	5.7 (0.9)	6.0 (0.65)	5.6 (0.9)	ns
Any LVAD Alarm	23 (33)	9 (100)	14 (23)	0,001
• Red alarm	9 (13)	7 (78)	2 (3)	0,001
• Yellow alarm	4 (6)	1 (11)	3 (5)	ns
• Other	10 (15)	1 (11)	9 (15)	ns
Driveline damage	12 (17)	8 (89)	4 (7)	<0.001
• Internal damage • External damage	7 5	7 1	- 4	
Battery lead damage	14 (20)	3 (33)	11 (18)	ns
Battery defect	3 (4)	2 (22)	1 (2)	ns
LVAD controller exchange	11 (16)	4 (44)	7 (12)	0.03
LVAD exchange	10 (15)	7 (78)	3 (5)	0.001
• due to mechanical failure	7 (10)	7 (78)	-	
• due to pump thrombosis	3 (4)	-	3 (5)	

*Only patients included that were discharged. Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean ± standard deviation. ns, not significant (p>0.05);

An overview of the 9 patients with MDF (age at implantation 47.4±14.2, 78% male, 67% Ischemic cardiomyopathy) is given in **table 4**. Furthermore, three out of nine MDF patients (2 pre-MDF and one post-MDF) were treated with benzodiazepines during their LVAD-support. Two (22%) of these patients died suddenly outside the

hospital, one at home and one in a nursing home. The primary reason for MDF was a driveline fracture. In three (33%) patients the LVAD alarms or pump speed drops were position-dependent. In all patients, a history of technical problems before the occurrence of MDF was present. No traumatic event could be recalled in all the MDF patients. All the patients except for one, presented themselves with red alarms, low-flow alarms, temporary pump stop or a combination of the aforementioned.

In four patients, the driveline fracture was detected with abdomen x-ray (**Figure 5**). LVAD replacement was necessary in 6 patients (86%) and one patient had his external driveline repaired by the manufacturer. All patients that were re-admitted to the hospital due to the occurrence of MDF survived until discharge. Two (22%) of these patients are still on LVAD-support after LVAD-replacement, and 5 (56%) patients underwent heart transplantation 109, 166, 244, 660, and 985 days after experiencing MDF.

Figure 4. Percentage of patients free from mechanical failure or technical problems.

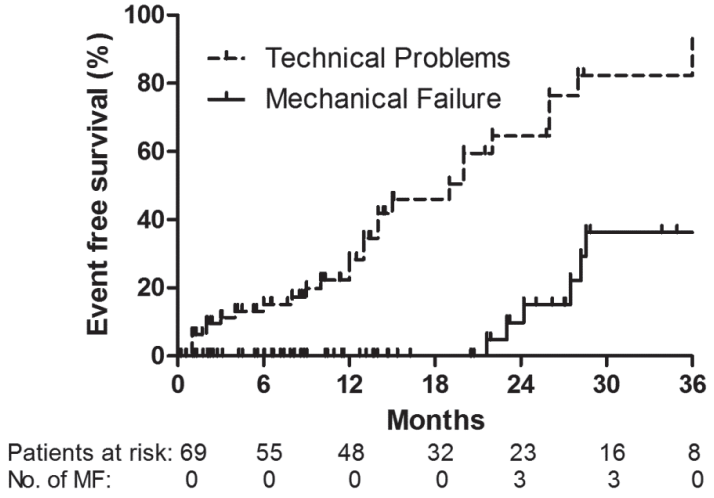


Figure 5A X-ray of internal part of the driveline of a 54-year-old male (Patient no. 7 in table 3), who received a LVAD because of progressive heart failure, which originated from a myocarditis. Twenty-six months after LVAD implantation he experienced low voltages. Initially it was thought to be a software problem and his controller was exchanged. However, he presented himself, 29 months after LVAD implantation, with a pump stop during the night, which was position dependent. X-ray of the internal part of the driveline showed irregularities in the C-shape section. Because of the pump stop and the irregularities of the driveline, his LVAD and driveline was exchanged.

Figure 5B Driveline damage externally observed

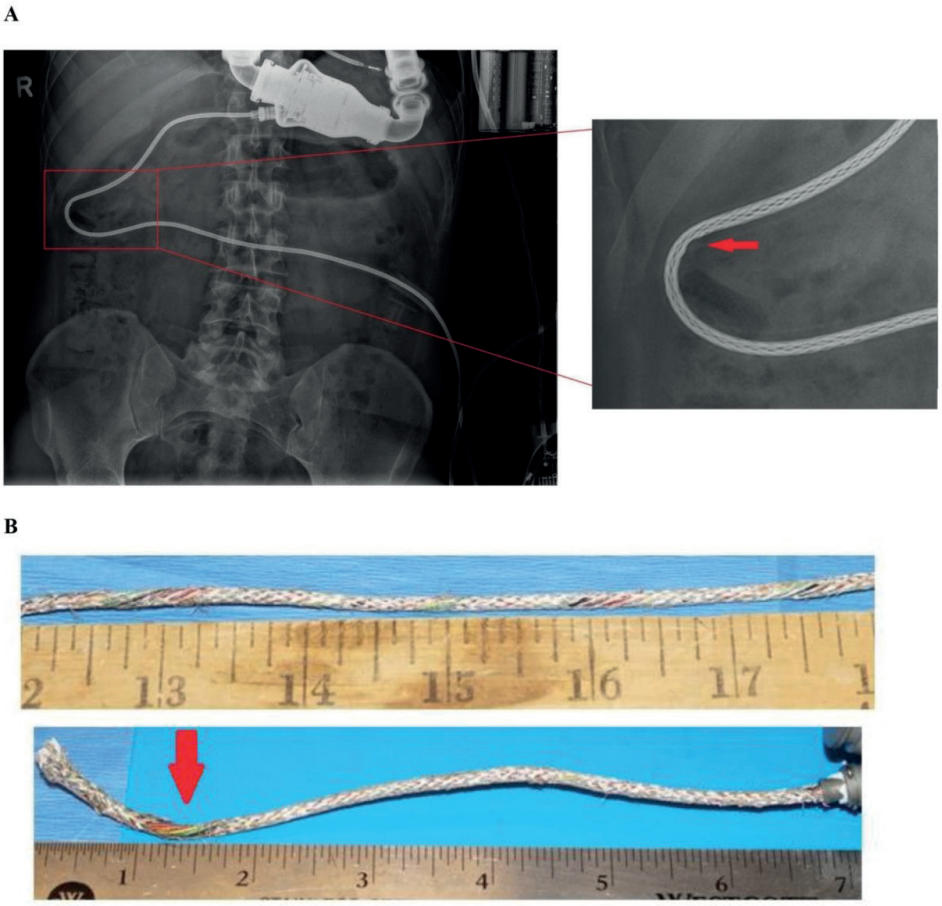


Table 4. Detailed overview of patients with Mechanical device failure.

	1	2	3	4	5	6	7	8	9
Age (Years)	42	43	16	41	58	57	64	54	52
Gender	Male	Male	Male	Female	Female	Male	Male	Male	Male
Etiology	Ischemic	Non-ischemic	Non-ischemic	Ischemic	Ischemic	Ischemic	Ischemic	Non-ischemic	Non-ischemic
Year of Implant	2008	2009	2010	2010	2010	2010	2011	2013	2013
Time to event, days	1454	824	846	726	1693	1219	691	857	649
Total support time, days	1620	1809	955	1386	1693	1219	935	921	998
Outcome	HTX	HTX	HTX	HTX	Death	Death	HTX	On-going support	On-going support
Follow up									
Re-thoracotomy	No	No	Yes	Yes	No	Yes	No	Yes	Yes
NYHA class**	I	I	I	I	I	II	I	I	I
BMI increase***	5.7	0.4	0.3	1.2	6.8	0.6	1.6	1.1	0.5
Technical problems (months post implantation)	Battery exchange (35) DL fracture(48)	Alarms (26) Contr. Exchange (26) Red alarms (27) DL damage(27)	Battery lead (20) and driveline damage (28)	High flow (4) High flow (7) Battery Lead (20) and DL damage(23)	Pump speed drops (14) Battery lead (16,46) DL damage(52) LVAD failure (56)	Red Alarm (10) battery defect (20) patient lead damage (36) LVAD failure (40)	Contr. to hot (1) DL loose (8) Contr. Reset (20) DL fracture (22)	Low voltage (26) Contr. Exchange (29) DL damage(29)	Low flow(19) Contr. exchange(22) Assumed DL fracture(22)
Presentation	Position dependent red alarms and pump speed drops	Red alarms	Pump speed drops and red alarms	Pump speed drops to 2200 rpm and power increase to 10 Watt	Alarms and pump speed drops	Yellow alarms	Position dependent red alarms and pump speed drops	Position dependent pump speed drops, low flow and red alarms	Red and low flow alarms

Diagnostic modality	Inspection controller X-ray: no sign of DL fracture	X-ray: Isolation material damage of the DL	X-ray and Inspection external DL	X-ray: DL damage in the abdominal area	Autopsy	Autopsy	X-ray: potential wire twist or fracture near the pump.	X-ray: DL damage	X-ray: no evident point of damage
Assumed location drive-line fracture	Oxidated, powerbase lead due to fluid, pump shutdown	Near the entrance point of the DL in the LVAD pump	External DL damage near connector and 10 cm near the DL exit	Internal part of the DL	Near the LVAD pump	Battery lead damage	Internal near abdominal wall	Internal curve of DL	Internal part of the DL
Parts replaced.	LVAD exchanged	Contr. + LVAD exchanged	External DL welded	LVAD exchanged	-	-	Contr. + LVAD exchanged	Contr. + LVAD exchanged	Contr. + LVAD exchanged

* Interagency Registry for Mechanically Assisted Circulatory Support at implantation; ** NYHA class at last follow-up; *** BMI increase at last follow-up vs. baseline; **** Controller Exchange; DL; Driveline, Batt; Battery

Discussion

In this study we describe the rate, associated factors, clinical presentation and outcome of mechanical device failure in continuous-flow left ventricle assist device patients. MDF is a serious complication seen at mid-term follow-up of cf-LVAD patients, jeopardizing the long-term outcome. Patients with apparently futile, however cumulative technical problems over time were more prone to experience MDF, which often requires invasive surgery and LVAD replacement. The incidence of technical problems rises over time, comparatively like the incidence of MDF. MDF occurred at a median FU time of 846 [708-1337] days after implantation. The majority of the patients with MDF presented with red LVAD alarms and concomitant temporary pump stop. Seventeen percent of the deaths was due to MDF. However, if patients reached the hospital on time, then they could be treated successfully. Through timely connection to an ungrounded cable or staying on batteries, further electrical shortcut could be prevented and semi-urgent LVAD exchange or external repair of de driveline could be conducted.

Current developments and the rise of Mechanical Device Failure.

Studies have reported an increase in survival of patients on mechanical circulatory support (MSC) since the use of cf-LVADs.(15) The two-year survival in the HeartMate II DT trial improved from 58% in the early trial experience to 63% for the midtrial group.(16) Also, the INTERMACS analysis of 2011 showed that cf-LVADs are superior to pulsatile pumps for DT and with the approval of the HeartMate II cf-LVAD for DT, the number and proportion of devices implanted as DT progressively increased. The DT already represent nearly half of the long-term MCS device strategy in the USA.(1) These developments lead to an increase of patients who are supported by a cf-LVAD for longer than 2 years. However, due to the fact that these patients are not eligible for transplantation, they have no other treatment options in the case of cardiac deterioration or severe adverse events, in contrast to the BTT patients. Therefore, device durability is extremely important for this group of patients. Up to now, the most common cause of device failure was pump thrombosis (10, 11, 17). However, we report a cohort with a higher incidence of device failures requiring LVAD replacement originating from a mechanical problem (13%) in contrast to a biological problem (4%). This is supported by the major clinical trial; HeartMate II Destination Therapy.(18) Eight percent of the pump replacements in the CF-LVAD patients was in this trial due to mechanical device failure and 2% due to biological problems. In a recent study, Stulak and colleagues reported on driveline damages (incidence 3.9%) and durability of driveline repair. (19) In contrast to our study with mainly internal driveline fractures requiring device exchange, they reported on damages to the external portion of the driveline, which could be managed in the majority of the patients through driveline repair with good durability.

(19) An explanation for the overall higher incidence of MDF in our cohort could be the fact that most studies describe the survival of patient up to two years. However, in our study the majority (67%) of MDF occurred after two years and 33% occurred even three years after LVAD implantation. Furthermore, a relatively high percentage of patients (17%) had a damaged driveline in our study, which is an important cause for MDF.

Factors associated with device durability

It has been reported that the durability and functionality of LVADs is influenced by multiple factors, including anatomical constraints, patient complications, device design and manufacturer.(17) The most common cause of MDF in our study was due to a damaged driveline, which is also described elsewhere.(8, 12) In addition, factors as support time, LVAD alarms and controller exchanges seem to be associated with device durability and predict MDF. On the other hand, an uncontrolled level of anxiety could lead to inadvertent damages to the DL. In our cohort limited data was available on anxiety levels in order to further quantify this. All the patients in the MDF group had improved functional status at time of event and had gained some weight. Increased body size has been mentioned as a risk factor for driveline fractures because of the constant pulling of the cable.(12) In combination with improved functionality, it could be hypothesized that an increased weight and activity has an additive effect on the risk of developing driveline damage and eventually mechanical device failure. Further research has yet to prove these hypotheses.

Survival

In the REMATCH trial, LVAD failure was the second most frequent cause of death (17%) among device-supported patients and they reported a device failure probability of 35% at 24 months.(4) Our study is in line with the reported frequency of LVAD failure as cause of death (17%). However, contrary to the REMATCH trial, in our study only 6 patients (9%) had a device failure due to any problem at 24 months. Kirklin *et al,* already reported that patients, who undergo transplantation, potentially avoid an unfavorable LVAD outcome.(15) This "censoring" of patients at time of transplantation introduces considerable uncertainty about long-term device complications and device failure. This uncertainty affects mostly the DT patients, due to the fact that they do not have transplantation as a rescue option. Therefore, further research is needed, which addresses only the DT patients and investigates the long-term device complications and true survival of these patients.

Analogy

As history repeats itself, it has proven multiple times, the use of any medical device is accompanied by the risk of failure. Examples include the Bjork-Shiley valves or the Riata ICD leadsIn a study conducted by de Mol *et al.,* 7 of the 24 electively explanted Bjork-shiley valves showed a defect in at least one strut, while there were no indications for a valve defect before explanting the valve.(20) Their findings supported the hypothesis that because of the devastating consequences of a strut fracture the true incidence of fractures can remain undetected. This also applies to mechanical circulatory support devices, with regard to the driveline. Although, the follow-up of cf-LVAD patients are very strict. It has to be emphasized that MCS devices are designed to only last for a limited amount of time. Unawareness of the state (internal or external) of the driveline may therefore lead to fatal cases that could have been prevented. Both, device characteristics as human errors can increase the risk of malfunctioning. (17, 20) Luckily, manufacturers keep modifying their devices over time, which has led to a significantly decline in the incidence of lead failures (21). These two lead revisions included; changes to the external connector bend relief at the controller (June 2007), and changes to the internal pump-end bend relief (December 2010) (21). The HeartMate II is worldwide the most implanted LVAD, it has been of paramount importance for the treatment of end-stage heart failure and a stepping stone for the success of MCS. However, the journey toward the ideal LVAD is still long and therefore, careful assessments of technical integrity of the device during follow-up is needed to ensure patients' safety.

Clinical implications: an urgent call for periodical technical inspections of the device.

Although the introduction of the CF-LVAD had an positive impact on the survival of end-stage heart failure patients, neglecting it limitations can lead to devastating events. Mechanical device failure is an arising problem for patients who are surpassing the boundaries of mechanical circulatory support. Consequently, device durability has become extremely important to patients living with mechanical circulatory devices. We report MDF as main reason for death after the second year of LVAD-support and a MDF incidence of 38% during the third year after implantation. Therefore, periodical and intensive examination of the LVADs driveline and its technical integrity is indicated. Pamboukian and colleagues reported that through a formalized long-term management strategy, an intensive surveillance protocol and better patient selection leads to an improved two-year survival.(22) We add to this that there should be more emphasis on controlling the driveline on the long-term. It is reported that often the damage on the driveline occurs at a "weak" place, the feed through of the driveline to the pump body. (12) We observed also driveline damages mainly in the internal part of the driveline, especially the C-shape part (see Figure 5A). The duration of LVAD-support, history of technical problems and the presence of driveline damage should be considered to

determine if the performance of regular x-ray is justified. Especially in patients with increased weight and physical activity, a low-threshold should be taken in to account.

Limitations of the study

This study has several limitations, which should be taken into account in the final interpretation of the data. This is a single-center study and is partly confined by its retrospective design. The data was collected from the hospitals electronic medical records. Therefore, the data depends on documented events. Also, the number of cases and patients with LVAD-support duration larger than 3 years were limited. Finally, our findings were restricted to HeartMate II and may not be applicable to patients supported with other types of cf-LVADs.

CONCLUSION

In conclusion, the incidence of mechanical device failure increases with time and CF-LVAD recipients with an extended LVAD-support time, a history of technical problems or damaged driveline are more prone to experience mechanical device failure. Mechanical device failure can be managed successfully if patients reach the hospital in time. We expect improvements that will increase the durability of devices and the survival of patients. New technical improvements are used in the driveline of the HeartMate III to improve its longevity. Further research has to show if this adds to the reliability and durability of the cf-LVAD.

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CHAPTER 19

Summary and conclusion
Samenvatting en conclusie

SUMMARY AND CONCLUSION

Left ventricular assist device (LVAD) therapy has emerged as a viable treatment option for patients with advanced heart failure, regardless of eligibility for heart transplantation (HTX). However, it is still limited by severe complications and suboptimal long-term clinical outcomes. This thesis aimed to contribute to the current body of evidence and experiences with continuous flow-LVADs in the new era of advanced heart failure therapy. Furthermore, we investigated clinical outcomes, complications, and the impact of LVAD on end-organ function. In addition, an effort was made to predict these end-points in order to improve the selection criteria for LVAD therapy and current clinical practice.

Main findings

In **Chapter 2,** we present a general overview of the current literature, the history and evolution of LVADs over time, and the current selection criteria for LVAD therapy. Great progress has been made in the development of long-term mechanical circulatory devices. LVADs have been reduced in size and shifted from pulsatile devices to continuous flow magnetic levitated small intra-pericardial devices with improved complication profiles. A clear transition is noted in the indication for LVAD therapy, with the majority of the patients currently being implanted as destination therapy. Furthermore, the published literature regarding mortality and morbidity following LVAD implantation is summarized in this chapter, concluding that the survival of LVAD patients has improved greatly over time. However, although the overall incidence of complications is decreasing, they remain a huge burden on the patient and the caregiver. The most common and severe complications following LVAD implantation include bleeding, infection, stroke, renal dysfunction, and right-sided heart failure (RHF). Several risk scores have been developed to predict mortality and to identify patients who are at risk for complications, though their use in the clinic is limited because of the rather small derived populations.

Right heart failure

In **Chapter 3 and 4** we identified the impact of early right heart failure (RHF) on mortality and derived and validated a novel risk score for early RHF after LVAD implantation in the largest LVAD registry of Europe, the European Registry for Patients with Mechanical Circulatory Support (EUROMACS). Eligible patients (n=2988) were

randomly divided into derivation (n=2000) and validation (n=988) cohorts. There is a wide range in the reported incidence rate in the literature, partly due to the lack of a universal definition of RHF. We used 3 components to define RHF, similar to those used in the large international registries, consisting in the requirement of mechanical right ventricular (RV) support via a RV assist device or extracorporeal membrane oxygenator, pharmacological support via the use of continuous intravenous inotropic support, or pulmonary vasodilators such as inhaled NO, resulting in a RHF incidence in the derivation cohort of 22%. In addition, patients with RHF had a significantly lower 1-year (53% versus 71%) and 2-year (45% versus 58%) survival compared with patients without RHF, emphasizing the need for a preoperative tool to correctly identify patients at risk for RHF. We examined a large set of potential preoperative predictors and after multivariable regression analysis generated a risk score using the relative magnitude of the exponential regression model coefficients of independent predictors. This resulted in a risk score, incorporating 5 variables (Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) class, severe right ventricular dysfunction on echocardiography, ratio of right atrial/pulmonary capillary wedge pressure, hemoglobin content, and use of multiple inotropes). In line with published data, we quantified that patients with an advanced INTERMACS score (class 1-3), indicating sicker and decompensating patients with threatening secondary organ failure, had a nearly 5-fold increase in the incidence of evident RHF. Furthermore, pre-operative RV dysfunction on echocardiography was associated with higher rates of early RHF. Though echocardiographic assessment of RV function is readily available, there is potential for high variability in the visual scoring of the RV function. Nevertheless, we firmly believe that visual assessment of RV dysfunction is simple but robust, and therefore of great additional value. The use of multiple inotropes had the greatest weight in predicting post-LVAD RHF among all 5 predictors. This might reflect, in fact, the biventricular origin of hemodynamic instability. Subsequently, one can hypothesize that patients on multiple inotropes might benefit from temporary RV circulatory support before LVAD implantation. However, randomized studies are needed to investigate if temporary RV circulatory support is superior to expanding inotropic or vasopressor support, and subsequently, determine the outcome following LVAD implantation.

Considering that RHF is associated with high mortality and morbidity, it has a huge impact on patients selected for LVAD therapy. The EUROMACS-RHF risk score outperformed previously published scores and known individual echocardiographic and hemodynamic markers of RHF and may be useful for tailored risk-based clinical assessment and management of patients with advanced HF evaluated for LVAD therapy. The pre-operatively determined risk could be important in the decision process,

preoperative preparation, timing of surgery, and should be included in the informed consent of the patients and the family.
Severe tricuspid regurgitation is associated with an impaired right ventricle function and increases the risk for mortality. In **Chapter 5** we reviewed the literature and provided a contemporary overview of outcomes in patients who underwent LVAD surgery with or without concomitant tricuspid valve surgery (TVS). In addition, we sought to determine whether LVAD and concomitant TVS would be superior to isolated LVAD implantation in patients with tricuspid regurgitation prior to LVAD implantation. We conclude that there is no significant difference in early and late mortality, early and late RHF, acute kidney failure, hospital stay, and RVAD implantation between patients receiving isolated LVAD implantation versus LVAD and concomitant TVS. The interpretation of these results is two-fold. One could argue that there is no benefit in concomitant TVS during LVAD implantation. However, patients treated with concomitant TVS were sicker at baseline (patients who received concomitant TVS had higher creatinine, bilirubin, and central venous pressure), suggesting that concomitant TVS improves the survival of these patients with tricuspid regurgitation to a similar level as patients without tricuspid regurgitation. Complicating matters, significant tricuspid regurgitation can reduce to insignificant tricuspid regurgitation after optimizing loading conditions. In addition to the published literature which is heterogeneous and conflicting, we do not suggest that all patients with tricuspid regurgitation should receive concomitant TVS at the time of LVAD implantation. However, considering the equipoise for TVS during LVAD implantation following our study, we emphasize that there is a need for additional clinical trials identifying selection criteria's for TVS at the time of LVAD implantation.

Imaging of the LVAD

In **Chapter 6** and **7** we examine the novel use of conventional imaging technics in LVAD patients. The evaluation of LV shape, function and intra-cardiac blood flow in patients with a LVAD may be challenging due to impaired image quality by standard transthoracic echocardiography. However, standard transthoracic echocardiography continues to be the main imaging method for evaluating LVAD patients. In **Chapter 6** we were able to show that routine use of a contrast agent was safe when used in patients supported by a third generation LVAD, and that it enhanced the diagnostic accuracy of transthoracic echocardiography in these patients. In this prospective study, we examined 14 patients supported with a HeartMate 3, whom all underwent standard echocardiography and contrast echocardiography. The contrast was well tolerated by all patients without any side effects. In addition, we were able to determine that contrast echocardiography significantly improved the visualization of the endocardial borders

of the LV. The American Society of Echocardiography and the European Association of Echocardiography have recognized the clinical value of contrast echocardiography and issued position papers providing guidelines. It has become clear that contrast echocardiography is a safe imaging modality, that may provide improved image quality or information that cannot be obtained by standard echocardiography in stable and in critically ill patients.

There is currently no gold standard test available for the detection of the exact site of infection or to monitor the response to treatment of LVAD infections. In addition, prompt diagnosis of LVAD-related infections can be particularly challenging in cases involving pump or cannula infections, pocket infections or deep sternal wound or mediastinal infections. In **Chapter 7** we reviewed the current evidence in the literature and described our experience using ^{18}F-FDG PET/CT for the diagnosis and management of LVAD infections. The literature regarding this topic was extremely scarce, with only 47 cases published in total. Nonetheless, it could be concluded that the discriminative capability of ^{18}F-FDG PET/CT in detecting infections of LVAD components is exceptionally good, with the largest case-series reporting a sensitivity of 100% and a specificity of 80%. This is in line with our observations where we found a sensitivity and specificity of 100%. Furthermore, the ^{18}F-FDG PET/CT imaging provided accurate information on the localization and extent of LVAD-specific or –related infections. The next challenge is to determine the optimal timing to perform the ^{18}F-FDG PET/CT scan. In our relatively small cohort, the ^{18}F-FDG PET/CT was able to rule out the presence of an infection even in an early postoperative period (3–6 weeks). Larger studies are needed to determine the optimal timing to perform an ^{18}F-FDG PET/CT in case of ongoing suspicion of LVAD-specific infections.

LVAD and Renal function

Acute kidney injury (AKI) has been identified as a risk factor for mortality after general cardiac surgery. Subsequently, LVAD patients are also at risk for developing AKI post-operatively. However, inconsistent results have been reported regarding the incidence of AKI and the impact of AKI on mortality after LVAD implantation. Therefore, we conducted a retrospective, multicenter cohort study, and investigated the incidence of AKI, as defined by the AKI criteria proposed by the Kidney Disease: Improving Global Outcome (KDIGO) group, corresponding risk factors, and the impact of AKI on mortality and renal function during the first year after LVAD implantation (**Chapter 8**). The overall criteria for AKI were met in the majority of the patients (70%), with an incidence of 45% AKI stage I, 9% AKI stage II, and 16% AKI stage III. In addition,

we identified the need of inotropic support and an estimated glomerular filtration rate (eGFR) <30 ml/min per 1.73 m^2 as independent predictors of AKI and subsequent increase in severity. Furthermore, factors independently associated with mortality included AKI stage ≥II and an eGFR<60 ml/min per 1.73 m^2, suggesting that sicker patients with impaired renal function before LVAD implantation are at highest risk for developing AKI and more advanced AKI stages. In addition, they are also prone to have higher mortality rates at 1 year after LVAD implantation. Furthermore, patients with no AKI or AKI stage I had significantly improved renalfunction at1year after implantation compared with baseline, whereas those with AKI Stage II and III did not have any significant improvement in renal function. This could be due to the intrinsic renal damage in these patients prior to LVAD implantation because of pre-existing heart failure or due to the AKI in the perioperative period, which seems to be irreversible in these patients. This is mainly important considering the fact that LVADs are increasingly implanted in older patients, with frequently an impaired renal function, subsequently resulting in a higher risk of AKI and a higher risk for mortality. Therefore, preventing AKI should be a main goal following LVAD implantation in order to reduce morbidity and mortality following LVAD implantation.

AKI is based on creatinine and similar to blood urea nitrogen (BUN), both are an important indicators of the renal condition. Creatinine, BUN, and proteinuria have been identified as independent predictors of cardiovascular and all-cause mortality in the general population. However, current risk scores that predict mortality in LVAD patients only include creatinine or BUN. Subsequently, data on proteinuria measurements are currently not used in LVAD patients. Therefore, in **Chapter 9**, we assessed whether proteinuria could be of additional value in classifying patients into risk groups for worse outcome. We evaluated the association of proteinuria prior to LVAD implantation in relation to mortality and the need for renal replacement therapy (RRT) during the first year of follow-up. A retrospective, multicenter cohort study was conducted including 173 patients, who had urine dipstick performed within 7 days prior to LVAD implantation. Proteinuria was defined as trace or higher. Twenty-four percent of the patients had pre-operative proteinuria. These patients with proteinuria had a significant lower 1-year survival compared to patients without proteinuria (52% vs 78%, p<0.001) and required more often RRT (32% vs 15%, p=0.02). In addition, this was confirmed in the multivariate cox-regression analysis where proteinuria was identified as an independent predictor of mortality with an adjusted hazard ratio of 2.09 (95 confidence interval, 1.10-3.80, p=0.02), and for the need of RRT during the first year (adjusted hazard ratio, 2.23; 95% confidence interval, 1.13–4.84; p= 0.02). In addition, stratification based on renal function and proteinuria differentiated patients in a low-, intermediate-, and high-risk groups for the composite endpoint of mortality

or RRT. Therefore, we conclude that proteinuria, which was present in a quarter of all tested LVAD patients, is associated with worse outcome in all-cause mortality and a higher need of RRT. In addition, the concomitant presence of proteinuria in patients with an impaired renal function significantly worsens their outcome. One explanation for this increased risk is attributed to chronic renal venous congestion, which is a known cause of renal damage ("cardiorenal syndrome"), consequently resulting in an increase in proteinuria. The higher rate of right ventricular assist device requirement in the proteinuria group seems to confirm that patients with proteinuria have more severe chronic RV dysfunction prior to LVAD implantation. Due to the increased risk of patients with proteinuria for mortality and need of renal replacement therapy, we suggest that the measurement of proteinuria should be used as an additional tool in the pre-operative risk stratification of patients selected for LVAD therapy.

An important observation, shown in both studies, was the association of age with renal function and mortality. Since patients with advanced age are more frequently referred for LVAD implantation due to ineligibility for HTX, we ought to evaluate the effect of age on renal function and mortality in patients implanted with an LVAD, in **Chapter 10**. Patients were stratified according to the age groups <45, 45–54, 55–64, and ≥65 years old. Older age adversely affected renal function as well as survival 1-year post-implantation. Furthermore, older patients had a lower mean eGFR before LVAD implantation, as well as at all time points after LVAD implantation compared to younger patients. In addition, older patients were less likely to experience an improvement in their renal function following LVAD implantation. It has been suggested that the lack of improvement in renal function in LVAD patients may be related to the number of comorbidities, to renovascular disease or to the development of cardiorenal syndrome. This could explain the lack of improvement of renal function in older patients, since older patients are more likely to have more comorbidities and compromised renal function secondary to heart failure, which seems irreversible in the long-term.

Based on our data, patients aged ≥60 years and with an eGFR <55 mL/min per 1.73 m2 are at high risk for mortality, and therefore need more consideration prior to LVAD implantation. In addition, improvement of the current risk models is needed in order to accurately determine and to inform the clinician which of these patients will benefit from an LVAD implantation. This is especially relevant because of the rise in destination therapy patients, who are deemed not suitable for cardiac transplantation, and subsequently are dependent on their LVAD for circulatory support. Informing these patients of their risk factors that might impair their quality of life or even result in death after implantation is of paramount importance. These patients could determine based

on their values if they consider the risk acceptable, and subsequently the decision to implant an LVAD should be a shared decision.

Hematological changes after LVAD implantation

Although the introduction of new devices and improved patient management has resulted in a decline in the complication rate over time, complications related to the haemocompatibility of the devices remain a significant problem. The most common complications include bleeding, neurologic events, hemolysis, pump thrombosis and venous or non-stroke-related arterial thromboembolic events.

Bleeding is the most common complication after LVAD implantation, especially in the postoperative period. An early bleeding may delay recovery and extend the period of hospitalization and even be life-threatening when it leads to hemodynamic instability. In addition, the abundant use of transfusions may lead to sensitization, RHF, and a longer listing time for HTX. In **Chapter 11**, we conducted a single-center retrospective cohort study and investigated the incidence, predictors, and clinical outcome of early bleeding events requiring thoracic surgical-exploration or transfusion in the postoperative period following LVAD implantation. We observed that almost half of the patients experienced an early bleeding (47%) within a median time of 6 days [IQR1-9]. Furthermore, a quarter of the patients required two or more surgical re-exploration. No difference was found in the rates of early bleeding events in patients with different types of LVADs. In addition, we identified thrombocytopenia ($<150x10^9$/L), and the need of an extracorporeal membrane oxygenator (ECMO) pre-implantation as independent predictors of an early bleeding event. These patients who experienced an early bleeding event also had a significantly worse 90-day survival rate compared to patients who did not. This result suggests that the patients preoperatively on ECMO or with a low platelet count should be carefully monitored during the initial admission in the intensive care unit post-implant, in order for the medical team to monitor and timely intervene.

Recent studies suggest that less invasive surgery is the key to a lower rate of postoperative bleeding events. However, these studies are limited by their small sample size and single center design. Larger randomized studies are needed to confirm if less invasive surgery is superior to conventional surgery. In addition, formal evaluation of the efficacy and efficiency is required to determine the absolute benefit.

Although the risk of bleeding is a predominant phenomenon after LVAD implantation, thrombosis in the early postoperative period may occur. In **Chapter 12,** we present an

unusual cause of pump thrombosis, which occurred 4 days after discharge. The patient was re-hospitalized due to acute decompensated heart failure while on LVAD support. Physical examination revealed a continuous machinery systolic murmur at the second right intercostal space. Additional imaging, by means of a CT-scan, showed multiple kinks in the LVAD outflow graft, which was successfully replaced surgically. This case points at rare problems that attending physicians should be aware of in treating patients on LVAD.

In **Chapter 11** we identified ECMO and thrombocytopenia as independent predictors of early postoperative bleeding events. ECMO has been used with success as a bridge to an LVAD or a heart transplant. Nevertheless, the use of ECMO is accompanied by a high risk of complications as a consequence of heparinization and acquired coagulopathies. Factors including acquired von Willebrand factor deficiency (VWD), hemolysis and thrombocytopenia contribute to the bleeding risk during ECMO support. In addition, these conditions remain present after LVAD implantation. The introduction of an LVAD into the circulatory system results in an altered hematological balance as a consequence of blood–pump interactions, changes in hemodynamics, the rheology, and the concomitant need for anticoagulation while implanted with an LVAD. The majority, if not all, LVAD patients experience a form of platelet dysfunction and impaired von Willebrand factor (VWF) activity, leading to acquired coagulopathy disorders. In **Chapter 13** we reviewed the literature and focused on acquired coagulopathies, describing the incidence, impact and the underlying mechanism of acquired coagulopathy disorders in patients supported by LVADs. In addition, we discussed the diagnostic and management strategies for these acquired coagulopathies. Inherited VWD is a well-known cause of bleeding. However, the acquired VWD, also known as acquired von Willebrand syndrome (AVWS), has attracted the most attention over the past couple of years with regard to a possible factor that explains the high rate of bleeding complications after LVAD implantation. The VWF is a multimeric large glycoprotein and the hemostatic potential of the VWF is associated with the size of the multimers, with a smaller size having less activity. The function of VWF is extensively described in **Chapter 12**, In brief, VWF mediates the platelet adhesion and aggregation to the sub-endothelial matrix in order to achieve hemostasis and form a platelet plug at sites of vascular injury. A disintegrin and metalloprotease with thrombospondin type 1 repeat 13 (ADAMTS-13) cleaves the large VWF multimer when anchored to the subendothelial matrix. Once cleaved, VWF is released into the circulation, where it is further reduced in size by ADAMTS-13 or through exposure to shear stress.

Recent findings have confirmed that nearly all patients with an LVAD, regardless of device, experience a loss in large von Willebrand multimers, subsequently resulting in

reduced VWF activity and an acquired form of VWD, the AVWS. It is thought that this loss in activity is due to an increased shear stress as a consequence of the continuous-flow pump design and cardiac conditions. Laboratory findings show a loss of large multimers, despite an increase in VWF antigen level (Ag), reduced binding of VWF to collagen (measured by VWF:CB activity) and ristocetin cofactor activity (VWF:RCo). This loss in VWF activity is observed early in the postoperative period after LVAD implantation, persistent during LVAD support, and resolves after LVAD explantation or heart transplantation. Different mechanisms have been proposed to explain the development of AVWS in LVAD patients. Of these, shear stress and ADAMTS-13 have been studied the most. The presence of an LVAD in the blood circulation leads to significant changes, including increased level of shear stress and lower pulse pressure. As a consequence of increased shear stress the VWF disentangles and exposes the domains A1 and A2, which in turn promotes proteolytic cleavage by ADAMTS-13 and multimeric binding to platelets GP 1bα, also leading to an increased proteolytic cleavage by ADAMTS-13. This subsequently results in VWF degradation into smaller multimers and reduced activity. Although nearly all LVAD patients suffer from AVWS, not all patients experience bleeding events. Therefore, a definite association with bleeding events has yet to be determined. This also suggests that other pathways or factors, either protective or not, are also essential in determining the risk of bleeding or thrombosis in these patients.

Traditional treatment options for bleeding in aWVS include desmopressin, VWF-containing concentrates, recombinant (r) Factor VIIa, antifibrinolytics, intravenous immunoglobin, and plasmapheresis. The use of desmopressin has been anecdotally described for treatment of gastrointestinal bleeding in LVAD patients. In addition, several novel treatment options are emerging. However, their safety and effectiveness have yet to be determined in LVAD patients, taking into account the high risk of bleeding and thrombotic events.

The introduction of new generation devices has improved the survival of LVAD patients greatly. However, the occurrence of thrombo-embolic events and pump thrombosis remains an important limitation. The new centrifugal-flow HeartMate 3 (HM3) device proved itself superior to his predecessor the axial-flow HeartMate II (HMII), mainly due to a decrease in the rate of device exchange and pump thrombosis in the HM3 patients. However, it remains unclear why the HM3 devices enjoyed such lower rated of pump thrombosis and improved haemocompatibility. In addition, the HeartWare HVAD is the most used LVAD in Europe. However, no comparison has been made between the HM3 and the centrifugal-flow HeartWare HVAD regarding differences haemocompatibility. Lactate dehydrogenase (LDH) has been known to be the most

specific marker for hemolysis, pump thrombosis, and thromboembolic events, and could serve as a marker for haemocompatibility. In **Chapter 14** and **15,** we studied the evolution of LDH over time between patients supported with a HMII versus HM3 LVAD, and between patients supported with a HM3 versus HeartWare HVAD in order to quantify differences in device haemocompatibility. Nonlinear mixed-effects modeling was used for the analysis of repeated measurements of LDH. The evolution of LDH was significantly higher in patients with an axial-flow HMII device than in patients with a centrifugal-flow HM3 device, suggesting improved haemocompatibility of the HM3 device. In addition, we observed similar changes in LDH over time in patients supported with the centrifugal-flow HM3 device and the centrifugal-flow HeartWare HVAD, suggesting similar haemocompatibility. This differences between second generation and third generation devices is thought to be caused by the design of the pumping mechanism of the LVAD. Second generation devices are axial-flow devices, in contrast to third generation devices, which are centrifugal-flow devices. The new devices are designed to reduce shear stress through the following design alterations; the use of a magnetic bearing eliminating all friction wear, relatively large gaps located above and below the rotor to wash surfaces outside of the main flow path in order to minimize the risk of thrombogenesis and hemolysis, and finally, the use of sintered titanium in order to create texture on almost all blood containing surfaces of the pomp and to lower the thromboembolic risk. This altered design has been reported to result in lower VWF degradation. Despite the diminished rate of pump thrombosis in the HM3 patients, the neurologic event rate does not differ from that of the HMII patients. Therefore, we are far from the perfect LVAD. Persistent effort has to be made to improve the design of LVADs and to reduce the complication rate in order to reduce the morbidity and mortality of LVAD therapy. The high risk of complications is one of the reasons why LVAD therapy has not (yet) been expanded to patients with less severe heart failure symptoms. Reducing these complications and improving management after the occurrence of a complication could support making LVAD therapy a suitable treatment option for these patients.

Neurologic events are disturbingly high in LVAD patients and are associated with high morbidity, as well as devastating outcomes. In **Chapter 16,** we present an innovative assisting device for a hemiplegic LVAD patient who was impaired by a stroke and unable to operate his LVAD. We showed how one can make an assistance device to enhance the independence of a hemiplegic LVAD patient to such an extent that the patient now lives independently in his own home. The message we wanted to convey is that in the case of a neurologic event, despite it being accompanied with severe morbidity, innovative methods should be addressed in order to improve the independence and quality of life of these LVAD patients.

Long-term complications

Though initially introduced as short-term support, the LVAD has evolved to a durable long-term mechanical circulatory support device. In addition, as a consequence of the increase in patients receiving an LVAD as destination therapy, the device durability has become extremely important, due to the fact that the life of destination therapy patients depend on the durability of the LVAD. Furthermore, the quality of life of these patients is dependent the complications that occur on the long-term. Following bleeding and infections, ventricular arrhythmias (VA) are one of the most commonly reported adverse events. It is known that the burden of VA is highest in the early postoperative phase, however, there is limited data on the temporal evolution of VA burden during long-term follow-up and its clinical consequence. In **Chapter 17**, we studied in this multicenter retrospective study, the incidence, predictors, and clinical outcomes of VA in LVAD patients. One-third of the patients experienced VA in our study. The burden of VA followed a U-shaped curve, with the highest incidence in the early postoperative phase, lowest at 15 to 18 months, and a rise again hereafter. Furthermore, pre-LVAD VA was an independent predictor of late post-LVAD VA. This is not surprising as it reflects the presence of an arrhythmogenic substrate which is not abolished by the implantation of an LVAD. In general, VA can be treated appropriately with antiarrhythmic drug therapy and implantable cardioverter defibrillator (ICD) therapy. However, a small proportion of patients may develop resistant VA, which may cause hemodynamic compromise despite the presence of LVAD support. Overall, post-LVAD VA does not seem to be associated with higher mortality and heart transplantation rates.

It has been reported that the durability and functionality of LVADs are influenced by multiple factors, including anatomical constraints, complications, device design, and even the specific manufacturer. However, there is limited data on the long-term durability of current LVADs and the distribution of device failure over time. In **Chapter 18**, we described the rate, associated factors, clinical presentation, and outcome of device failure in LVAD patients. We defined device failure as a mechanical problem resulting from the driveline, inflow/outflow graft, or as a drive unit or motor failure of the LVAD, in short mechanical device failure (MDF). The prevalence of MDF increased over time, with the median time to MDF being greater than two years. Patients with apparently futile, however, cumulative technical problems over time were more prone to experience MDF. In addition, the majority of the patients with MDF presented with red LVAD alarms and concomitant temporary pump stop. Furthermore, seventeen percent of the deaths were due to MDF. However, if patients reached the hospital on time, then they could be treated successfully. Treatment included semi-urgent LVAD exchange or external repair of the driveline.

Though patients with more than 10 years of LVAD support has been described in the literature and we have witnessed this also in our clinic, this is rather exceptional. Therefore, neglecting the limitations of LVADs could lead to devastating events, which is a serious problem for patients who are currently surpassing the boundaries of mechanical circulatory support. Considering the increasing incidence of MDF following LVAD implantation, we recommend periodical and intensive examination of the LVADs driveline and its technical integrity. The duration of LVAD support, history of technical problems, and the presence of driveline damage should guide the clinician in determining whether additional imaging is justified. Finally, the longer a patient is supported with an LVAD the more suspicious clinicians have to be for MDF.

Future perspective

In the last decade LVADs have evolved greatly and with great eager we await further developments. The growing population of patients with heart failure will result in the extension of the linear trend that has been noted in the rate of LVAD implants. The rate of LVAD implantation has surpassed the rate of heart transplantation, with currently more LVADs implanted as destination therapy than bridge to transplantation. This has led to an acceleration in the developments of LVADs and contributed to our understanding of important underlying mechanisms of complications. However, there is still very much that we have to learn regarding the optimal selection criteria's, support time, additional beneficial treatments, medications, and long-term outcomes of LVAD therapy. In addition, we expect the indications for LVAD therapy to be expanded. LVAD as a bridge to recovery or as rescue therapy has been sporadically described in the literature. However, future clinical trials are needed to determine the feasibility of these indications. In addition, better models that predict survival and discriminate between HF patients that might benefit from LVAD therapy are needed to improve outcomes.

Technical advancements have led to more durable devices, resulting in improved clinical outcomes. However, there is still room for progress. Future devices are expected to be smaller, include remote monitoring, and be fully implantable, eliminating the driveline. We anticipate that devices will be able to automatically accommodate to the patient's physical activity. The lack of pulsatility in the second generation devices has been associated with several adverse effects, including arteriovenous malformations and aortic insufficiency. The first step to overcome this problem has been introduced in the third generation devices. The HeartMate III and HeartWare MVAD have been equipped with the ability to modulate pump speed (intermittent lower-speed pump operation) generating an intrinsic pulsatile flow. The evidence-based benefit of this function has

yet to be fully clarified. Likewise, ongoing research in the pharmacological or cell-based therapy groups to improve myocardial recovery rates have yet to be further elaborated.

Though LVADs have been proven superior to optimal medical therapy for advanced HF patients. Living with an LVAD can be extremely challenging, stressful, and hazardous, considering the constant risk of complications. Therefore, appropriate examinations of the physical and especially the psychological condition of the patient are essential in order to ensure optimal chances for a good quality of life while on LVAD support. Especially in destination therapy patients, if they are not enjoying the journey, they probably won't enjoy the destination.

Finally, before allowing the concept that life ends when the brain dies, the heart has symbolized life for centuries and it still does for many people. In patients with an LVAD the function of the heart is artificially supported. Therefore, care at the end of life of LVAD patients can be very conflicting for caregivers. Family members and caregivers of the patients are in need of advice and clinicians should be aware of their responsibilities in this phase. Because, for the patient and the family, it only ends when the pump is switched off and the heart stops beating.

Conclusion

This dissertation contributes to the knowledge regarding clinical outcomes and complications following LVAD implantation. We introduced a novel risk score that contributes to identifying high-risk patients for early RHF. In addition, we determined that concomitant tricuspid valve surgery at the time of LVAD implantation did not increase the risk for early RHF or mortality.

We identified several predictors for acute kidney injury, early bleeding events, early mortality following LVAD implantation, and determined the impact of these events on survival during LVAD support. Furthermore, several factors associated with renal function and late mortality were identified and could be used as selection criteria for LVAD therapy.

We concluded that acquired coagulopathies are highly prevalent with nearly, if not all, patients experiencing acquired von Willebrand syndrome. However, a definite association with hematological complications has yet to be determined. Furthermore, we showed that new generation LVADs show improved haemocompatibility compared to second generation devices.

Although, the rate of early and long-term complications remains too high, the survival of LVAD patients has improved greatly over time and LVAD therapy has become an accepted treatment option for patients with advanced HF. Our results underline the importance of careful monitoring of patients after LVAD implantation irrespective of time. Higher expectations are being set for future generation devices. It is anticipated that these advancements will improve the outcomes in LVAD patients. Finally, with this dissertation we hoped to set the path for the next step towards improving the clinical care of patients with advanced heart failure requiring LVAD therapy.

SAMENVATTING EN CONCLUSIE

Steunharten om de linkerkamer van het hart te ondersteunen, ook wel '*left ventricular assist device*' (LVAD) genoemd, zijn uitgegroeid tot een reëel alternatief voor harttransplantatie (HTX) naast optimale medicamenteuze therapie in patiënten met eindstadium hartfalen. Deze therapie is echter nog niet optimaal vanwege de ernstige complicaties en de suboptimale klinische resultaten op de lange termijn. Het doel van dit proefschrift was om een bijdrage te leveren aan de huidige literatuur en kennis met betrekking tot LVADs in een nieuw tijdperk van eindstadium hartfalentherapie. Daarnaast hebben wij klinische resultaten, complicaties en de invloed van LVAD-ondersteuning op de functie van verschillende organen onderzocht. Eveneens hebben wij deze eindpunten getracht te modeleren en te voorspellen, om daarmee de huidige selectiecriteria voor LVAD-therapie en de huidige klinische praktijk te verbeteren.

In **Hoofdstuk 2** presenteerden wij een algemeen overzicht van de huidige literatuur, de geschiedenis en de evolutie van LVADs. Grote vooruitgangen zijn geboekt in de ontwikkeling van het mechanisch steunhart. Het apparaat is veranderd van een groot pulsatiel apparaat naar een klein intra-pericardiaal apparaat waarbij de pomp zweeft in een magnetisch veld. Het complicatieprofiel is hierdoor gunstiger. Daarnaast heeft er ook een duidelijke verschuiving plaatsgevonden in de indicatiestelling voor LVAD-therapie, waarbij een LVAD in het merendeel van de patiënten momenteel geïmplanteerd wordt als '*destination therapy*', een laatste redmiddel voor patiënten met eindstadium hartfalen. Zelfs als deze patiënten niet in aanmerking komen voor een HTX.

Tevens is de gepubliceerde literatuur over sterfte en morbiditeit na LVAD-implantatie in dit hoofdstuk samengevat. Hierbij wordt geconcludeerd dat de overleving van LVAD-patiënten in de loop der tijd sterk is verbeterd en de algehele incidentie van complicaties afneemt. LVAD gerelateerde complicaties, echter, nemen nog steeds een enorme ziektelast voor de patiënt en familie met zich mee. De meest voorkomende en ernstige complicaties na implantatie van een LVAD omvatten bloedingen, infecties, beroerten, nierfalen en rechtszijdig hartfalen (RHF). Er zijn verschillende risicoscores ontwikkeld om de mortaliteit en het risico op complicaties te voorspellen. Deze risicoscores worden echter nog beperkt toegepast in de kliniek.

Rechter hartfalen

In **Hoofdstuk 3** en **4** is de impact van vroeg RHF op mortaliteit geïdentificeerd. Daarnaast is er een nieuwe risicoscore voor vroeg RHF na LVAD-implantatie ontwikkeld en gevalideerd in het grootste LVAD-register van Europa: het Europese register voor patiënten met mechanische circulatie ondersteuning (EUROMACS).

Binnen de literatuur bestaat een grote variatie in gerapporteerde RHF-incidentie. Dit is deels te verklaren door het ontbreken van een universele definitie van RHF. Om RHF te definiëren pasten wij drie criteria toe, overeenkomend met de criteria die in de grote internationale registers worden gebruikt, bestaande uit mechanische rechterhartkamer (RV) ondersteuning middels een RV steunhart of middels extracorporale membraan oxygenatie, farmacologische ondersteuning middels continue intraveneuze inotrope ondersteuning of pulmonaire vasodilatoren zoals geïnhaleerd NO. Patiënten werden willekeurig verdeeld in een studiecohort (n = 2000) en een validatiecohort (n = 988). Dit resulteerde in een RHF-incidentie in de studiecohort van 22%. Patiënten met RHF hadden een significant lagere 1-jaars en 2-jaars overleving vergeleken met patiënten zonder RHF. Dit benadrukt de behoefte om patiënten met een verhoogd risico op RHF voorafgaande aan de operatie te kunnen identificeren. Om deze reden onderzochten wij een groot aantal potentiële preoperatieve voorspellers en genereerden wij, na multivariabele regressieanalyse, een risicoscore aan de hand van de relatieve grootte van de exponentiële regressiemodelcoëfficiënten van onafhankelijke voorspellers. Dit resulteerde in een risicoscore van 9,5 punten, bestaande uit vijf preoperatieve variabelen: (1) *Interagency Registry voor Mechanisch Ondersteunde Circulatory Support* (INTERMACS) klasse, (2) ernstige rechterventrikeldisfunctie op echocardiografie, (3) verhouding tussen rechter boezemdruk en de pulmonale capillaire druk, (4) hemoglobinewaarde en (5) het gebruik van meerdere intropica. In overeenstemming met al eerder gepubliceerde literatuur hebben wij berekend, dat patiënten met een gevorderde INTERMACS-score (klasse 1-3) die dus zeer ziek zijn en in wie secundair orgaan falen dreigt, een bijna vijfvoudig verhoogd risico hebben op evident RHF hebben. Daarnaast was peroperatieve RV-disfunctie op echocardiografie geassocieerd met een hogere incidentie van vroeg RHF. Hoewel echocardiografische beoordeling van de RV-functie direct beschikbaar is, is er mogelijk tussen onderzoekers een grote variabiliteit in de visuele beoordeling van de RV-functie. Desondanks dat is de visuele beoordeling van de RV eenvoudig maar ook robuuste manier om de RV-functie in kaart te brengen en daarom van grote toegevoegde waarde. De behoefte aan meerdere soorten inotropica had de grootste voorspellende waarde voor vroeg RHF. Dit zou in feiten een afgeleide kunnen zijn van beiderzijds hartfalen dat de oorzaak is van de hemodynamische instabiliteit in deze patiënten. Om deze reden zou kunnen worden verondersteld dat patiënten met meerdere soorten

inotropica baat zouden kunnen hebben bij tijdelijke mechanische RV-ondersteuning vóór LVAD-implantatie. Gerandomiseerde studies zijn echter nodig om te onderzoeken, of tijdelijke mechanisch ondersteuning van de circulatie superieur is aan het ophogen van medicatie.

Gezien het feit dat RHF geassocieerd is met een hoge mortaliteit en morbiditeit, heeft RHF een enorme invloed op patiënten die zijn geselecteerd voor LVAD-therapie. De EUROMACS-RHF-risicoscore had een betere voorspellende waarde dan eerder gepubliceerde scores en bekende echocardiografische en hemodynamische markers voor RHF. De risicoscore kan van toegevoegde waarde zijn bij het bepalen van het individuele risico op RHF in patiënten met gevorderd HF die geëvalueerd worden voor LVAD-therapie. Het preoperatieve vastgestelde risico kan belangrijk zijn gedurende de preoperatieve voorbereiding en de timing van de operatie. Daarnaast kunnen de patiënt en de familie het eventuele risico op RHF meenemen in hun afweging tot LVAD-therapie.

Ernstige tricuspidalisklep insufficiëntie, lekkage van de hartklep gelegen tussen de rechterboezem en rechterkamer is geassocieerd met een verminderde rechterventrikelfunctie en een verhoogd risico op mortaliteit. In **Hoofdstuk 5** bespreken we de literatuur en presenteren we een overzicht van de resultaten bij patiënten die LVAD-chirurgie ondergingen met of zonder gelijktijdige correctie van de tricuspidalisklep (Tricuspid valve surgery, TVS). Wij onderzochten of LVAD-implantatie in combinatie met TVS (LVAD+TVS) een superieur resultaat gaf aan enkel LVAD-implantatie bij patiënten met preoperatief tricuspidalisklep lekkage. Wij concludeerden, dat er geen significant verschil is in vroege en late mortaliteit, vroeg en laat RHF, acuut nierfalen, ziekenhuisverblijf en de behoefte aan mechanische RV-ondersteuning tussen patiënten die enkel LVAD-implantatie waren ondergaan versus patiënten met LVAD+TVS. De interpretatie van deze resultaten is tweevoudig. Men zou kunnen betogen dat gezien er geen verschil in uitkomst is ongeacht TVS, dus dat er geen voordeel is van gelijktijdige TVS tijdens LVAD-implantatie. Patiënten die tijdens hun LVAD-implantatie gelijktijdig TVS zijn ondergaan waren echter zieker bij aanvang (TVS patiënten hadden hogere creatinine, bilirubine en centraal veneuze druk waarden). Dit suggereert dat gelijktijdige TVS de overleving van deze patiënten verbetert tot een vergelijkbaar niveau met patiënten die een LVAD-implantatie hebben ondergaan zonder tricuspidalisklep lekkage bij aanvang. Hoewel er equipoise is voor TVS tijdens LVAD-implantatie is er echter nog grote onzekerheid, gezien de heterogeniteit van de gepubliceerde literatuur, of alle patiënten met tricuspidalisklep lekkage gelijktijdig TVS moeten ondergaan op het moment dat de LVAD wordt geïmplanteerd. Aanvullend klinisch onderzoek is nodig om patiënten

met tricuspidalisklep lekkage die baat zouden hebben bij een TVS gedurende de LVAD-implantatie, te identificeren.

Beeldvorming van de LVAD

In **Hoofdstuk 6** en 7 onderzochten wij het gebruik van conventionele beeldvormingstechnieken bij LVAD-patiënten. De evaluatie van intra-cardiale bloedstromen en vorm en functie van de linkerhartkamer (LV) bij patiënten met een LVAD is een uitdaging, vanwege de verminderde beeldkwaliteit van de huidige standaard echocardiografie. Standaard transthoracale echocardiografie is en blijft echter de belangrijkste beeldvormingsmethode voor de evaluatie van LVAD-patiënten. In **Hoofdstuk 6** toonden wij aan dat routinematig gebruik van een contrastmiddel veilig was in patiënten die werden ondersteund met een LVAD en dat het de diagnostische nauwkeurigheid van transthoracale echocardiografie bij deze patiënten verbetert. In dit prospectieve onderzoek onderzochten wij 14 patiënten die ondersteund werden met een HeartMate III en daarnaast standaard echocardiografie en contrast-echocardiografie ondergingen. Het contrast werd goed verdragen door alle patiënten en er traden geen bijwerkingen op. Bovendien konden wij vaststellen dat contrast-echocardiografie de visualisatie van de endocardiale grenzen van de LV significant verbeterde. De *American Society of Echocardiography* en de *European Association of Echocardiography* erkennen de klinisch toegevoegde waarde van contrast-echocardiografie. Hiermee is contrast-echocardiografie erkend als een veilige beeldmodaliteit die een verbeterde beeldkwaliteit en meer informatie kan bieden. Welke anders niet verkregen zou kunnen worden door standaard echocardiografie bij stabiele en zieke patiënten met een LVAD.

Er is momenteel geen gouden standaardtest beschikbaar om de exacte plaats van infecties in LVAD-patiënten te detecteren of om de respons op de behandeling van LVAD-infecties te vervolgen. Bovendien kan een snelle diagnose van LVAD-gerelateerde infecties bijzonder lastig zijn in het geval van een pomp-, canule- of pocketinfectie, een diepe sternale wond of een mediastinale infectie. In **Hoofdstuk 7** hebben wij het huidige bewijs in de literatuur besproken en onze ervaring beschreven met ^{18}F-FDG PET/CT voor de diagnose en behandeling van LVAD-infecties. De literatuur over dit onderwerp was uiterst schaars, met in totaal slechts 47 casussen. Desondanks kan worden geconcludeerd dat het onderscheidende vermogen van ^{18}F-FDG PET/CT bij het detecteren van infecties van LVAD-componenten buitengewoon goed is, waarbij de grootste casusreeksen een gevoeligheid van 100% en een specificiteit van 80% rapporteerden. Dit is in lijn met onze waarnemingen, waarbij wij een sensitiviteit en specificiteit van 100% vonden. Daarnaast leverde de ^{18}F-FDG PET/CT-beeldvorming

accurate informatie op over de locatie en omvang van LVAD-specifieke of -gerelateerde infecties. De volgende uitdaging is om de optimale timing te bepalen voor het uitvoeren van de ^{18}F-FDG PET/CT-scan. In ons relatief kleine cohort was de ^{18}F-FDG PET/CT in staat om de aanwezigheid van een infectie uit te sluiten, zelfs in een vroege postoperatieve periode (3-6 weken). Verdiepende studies zijn nodig om de optimale timing te bepalen voor het uitvoeren van een ^{18}F-FDG PET/CT in het geval van voortdurende verdenking op LVAD-specifieke infecties.

LVAD en nierfunctie

Acuut schade aan de nier (*Acute kidney injury*, AKI) is geïdentificeerd als een risicofactor voor mortaliteit na algemene hartchirurgie. LVAD-patiënten lopen ook het risico om postoperatief AKI te ontwikkelen. Er zijn echter inconsistente resultaten gemeld met betrekking tot de incidentie van AKI en de impact van AKI op mortaliteit na LVAD-implantatie. Daarom hebben wij in **Hoofdstuk 8** een retrospectieve, multicenter cohortstudie uitgevoerd en de incidentie van AKI, overeenkomstige risicofactoren voor AKI en de impact van AKI op mortaliteit en nierfunctie gedurende het eerste jaar na implantatie van een LVAD onderzocht.

De meerderheid van de patiënten (70%) ervaarden enig stadium van AKI, met een incidentie van 45% AKI stadium I, 9% AKI stadium II en 16% AKI stadium III. Verder identificeerden wij de behoefte aan inotrope ondersteuning en een geschatte glomerulaire filtratiesnelheid (eGFR) <30 ml/min per 1,73 m^2 als onafhankelijke voorspellers van AKI en een toename in AKI stadium. Daarnaast constateerden wij dat AKI stadium ≥II en een eGFR <60 ml/min per 1,73 m2 onafhankelijk geassocieerd zijn met mortaliteit. Dit suggereert dat ziekere patiënten met een verminderd nierfunctie voorafgaand aan LVAD-implantatie het hoogste risico lopen op het ontwikkelen van AKI en verder gevorderde AKI stadia. Bovendien hebben deze patiënten een lagere 1-jaars overleving na LVAD-implantatie. Patiënten die geen AKI of AKI stadium I hebben ervaren, toonden een significant verbetering van hun nierfunctie 1 jaar na implantatie vergeleken met voor de implantatie. Terwijl patiënten met AKI stadium II en III geen significante verbetering in nierfunctie lieten zien. Dit kan te wijten zijn aan de intrinsieke schade aan de nieren bij deze patiënten voorafgaand aan LVAD-implantatie, mede vanwege het reeds langer bestaande hartfalen of vanwege het feit dat de AKI in de perioperatieve periode ontstond, die bij deze patiënten onomkeerbaar blijkt te zijn. Dit is vooral belangrijk gezien het feit dat LVADs in toenemende mate worden geïmplanteerd in oudere patiënten met vaak een gestoorde nierfunctie. Ditresulteert vervolgens in een hoger risico op AKI en een

hoger risico op mortaliteit. Daarom zou het voorkomen van AKI een belangrijk doel moeten zijn na LVAD-implantatie om morbiditeit en mortaliteit te verminderen.

AKI is gebaseerd op creatinine, en net als ureum (*Blood Urea Nitrogen*, BUN) zijn beide een belangrijke indicator voor de functie van de nier. Creatinine, BUN en proteïnurie zijn geïdentificeerd als onafhankelijke voorspellers van mortaliteit in de algemene bevolking. Huidige risicoscores die de mortaliteit bij LVAD-patiënten voorspellen, omvatten echter alleen creatinine of BUN. Hierdoor wordt de informatie, gehaald uit proteïnurie-metingen, momenteel niet gebruikt bij LVAD-patiënten. Daarom hebben wij in **Hoofdstuk 9** onderzocht of proteïnurie van toegevoegde waarde kan zijn bij het classificeren van patiënten in risicogroepen op slechtere uitkomsten na LVAD-implantatie. Wij evalueerden de associatie van proteïnurie voorafgaand aan de LVAD-implantatie in relatie tot mortaliteit en de noodzaak tot dialyse (*Renal Replacement Therapy*, RRT) gedurende het eerste jaar na implantatie. Een retrospectieve, multicenter cohortstudie werd uitgevoerd met 173 patiënten, bij wie binnen zeven dagen voorafgaand aan de implantatie de urine met een urinedipstick was getest. 24 procent van de patiënten had preoperatieve proteïnurie. Patiënten met proteïnurie hadden een significant lagere 1-jaars overleving en waren vaker afhankelijk van RRT in vergelijking met patiënten zonder proteïnurie. Dit werd bevestigd in de multivariate analyse, waarbij proteïnurie werd geïdentificeerd als een onafhankelijke voorspeller van mortaliteit en van RRT gedurende het eerste jaar na LVAD-implantatie. Stratificatie op basis van nierfunctie en proteïnurie differentieerde patiënten in een lage-, tussen- en hoog risicogroep voor het samengestelde eindpunt van sterfte of RRT. Patiënten met een slechte nierfunctie en proteïnurie, hadden een significant verhoogd risico op het samengestelde eindpunt van sterfte of RRT ten opzichte van patiënten die alleen een slechte nierfunctie hadden zonder proteïnurie. Hiermee tonen wij aan dat de aanwezigheid van proteïnurie niet alleen geassocieerd is met een slechtere uitkomst na LVAD-implantatie maar ook dat de aanwezigheid van proteïnurie bij patiënten met een gestoorde nierfunctie hun uitkomst aanzienlijk verslechtert. Een verklaring voor dit verhoogde risico wordt toegeschreven aan chronische veneuze congestie in de nier, een bekende oorzaak van schade aan de nieren (“cardiorenaal syndroom”), resulterend in een toename van proteïnurie. De hogere behoefte van mechanische ondersteuning van de RV in de proteïnuriegroep lijkt te bevestigen dat patiënten met proteïnurie ernstiger chronische RV-disfunctie hebben voorafgaand aan LVAD-implantatie. Vanwege het verhoogde risico van patiënten met proteïnurie op mortaliteit en de noodzaak tot dialyse, concluderen wij dat proteïnurie gebruikt kan worden als extra hulpmiddel bij de preoperatieve risicostratificatie van patiënten die zijn geselecteerd voor LVAD-therapie.

Een belangrijke observatie, bevestigd in beide studies, was de associatie tussen leeftijd en nierfunctie en tussen leeftijd en mortaliteit. In **Hoofdstuk 10** hebben wij deze associaties bij patiënten met een LVAD geëvalueerd. Patiënten werden gestratificeerd volgens de leeftijdsgroepen <45, 45-54, 55-64 en ≥65 jaar. Wij observeerden dat een oudere leeftijd een nadelige invloed had op de nierfunctie en de overleving op 1 jaar na LVAD-implantatie. Oudere patiënten hadden een slechtere nierfunctie vóór LVAD-implantatie, evenals op alle tijdstippen na LVAD-implantatie in vergelijking met jongere patiënten. Hiernaast toonden oudere patiënten minder vaak een herstel van hun nierfunctie na implantatie van een LVAD ten opzichte van jongere patiënten. De bestaande comorbiditeiten zoals andere renovasculaire aandoeningen of de ontwikkeling van het cardiorenale syndroom zouden het gebrek aan verbetering van de nierfunctie bij oudere patiënten kunnen verklaren.

Gebaseerd op onze gegevens hebben patiënten met de leeftijd ≥60 jaar en met een eGFR <55 ml / min per 1,73 m^2 een verhoogd risico op mortaliteit. Daarom dient er meer aandacht te zijn voor deze groep voorafgaand aan de LVAD-implantatie. Daarnaast zijn er nieuwe risicomodellen nodig die de clinicus nauwkeurig kan informeren omtrent het risicoprofiel van de patiënt en of de patiënt baat zal hebben bij een LVAD-implantatie. Dit is met name relevant vanwege het toenemende aantal patiënten die een LVAD ontvangen als destination therapie. Deze patiënten zijn afhankelijk van hun LVAD voor ondersteuning van de bloedsomloop. Complicaties, zoals het afhankelijk worden van dialyse kunnen de kwaliteit van leven van deze patiënten aanzienlijk verminderen. Het informeren van deze patiënten over de risicofactoren die de kwaliteit van hun leven kunnen schaden of zelfs overlijden tot gevolg kunnen hebben na LVAD-implantatie is daarom van groot belang. Deze patiënten moeten hun risicoprofiel op complicaties en overlijden mee kunnen nemen in hun afwegingen en met de arts tot de beslissing komen of een LVAD-implantatie de juist keuze is.

Hematologische veranderingen

Hoewel de introductie van nieuwe typen LVADs en de ontwikkelingen in de zorg van patiënten met een LVAD hebben geleid tot een afname van de complicaties, blijven complicaties met betrekking tot de hemocompatibiliteit van de apparaten een aanzienlijk probleem. De meest voorkomende complicaties zijn bloedingen, neurologische complicaties, hemolyse, pomptrombose en veneuze of niet-beroerte-gerelateerde arteriële trombo-embolische complicaties.

Een bloeding is de meest voorkomende complicatie na implantatie van een LVAD, met name in de postoperatieve periode. Een vroege bloeding kan het herstel vertragen, de ziekenhuisopname verlengen en zelfs levensbedreigend zijn als het leidt tot hemodynamische instabiliteit. Bovendien kan het overvloedige gebruik van transfusies leiden tot sensitisatie, RHF en een langere wachttijd voor een harttransplantatie.

In **Hoofdstuk 11** hebben wij een single-center, retrospectieve cohortstudie uitgevoerd en de incidentie, predictoren en de klinische uitkomst onderzocht van bloedingen die thoracale chirurgische exploratie of transfusie vereisten in de postoperatieve periode na LVAD-implantatie. Wij stelden vast dat bijna de helft van de patiënten een vroege bloeding (47%) ervaart binnen een mediane tijd van 6 dagen. Bovendien behoefde een kwart van de patiënten twee of meer chirurgische re-exploraties. Er werd geen verschil gevonden in de percentages vroege bloedingen bij patiënten met verschillende typen LVADs. Daarnaast identificeerden wij trombocytopenie ($<150x10^9$/L) en de noodzaak van ECMO pre-implantatie als onafhankelijke voorspellers van een vroege bloeding. Patiënten met een vroege bloeding hadden ook een significant slechtere overleving na 90 dagen in vergelijking met patiënten zonder een bloeding. Dit resultaat suggereert dat de patiënten die ECMO-ondersteuning nodig hebben of de patiënten die een laag aantal bloedplaatjes hebben zorgvuldig moeten worden vervolgd tijdens de eerste opname op de intensive care-unit na implantatie van de LVAD, zodat het medische team adequaat en tijdig kan ingrijpen bij een verdenking op een bloeding.

Recente studies suggereren dat minder invasieve chirurgie de sleutel is tot een lager aantal postoperatieve bloedingen. Deze studies worden echter beperkt door hun kleine steekproefomvang en studieontwerp. Grotere gerandomiseerde studies zijn nodig om te bevestigen of minder invasieve chirurgie superieur is aan conventionele chirurgie. Daarnaast is een formele evaluatie van de werkzaamheid en efficiëntie vereist om het absolute voordeel te bepalen.

Ondanks dat het risico op bloedingen met name verhoogd na implantatie van een LVAD, kan een pomptrombose ook voorkomen. In **Hoofdstuk 12** presenteerden wij een ongewone oorzaak van een pomptrombose die 4 dagen na ontslag optrad. De patiënt werd opnieuw opgenomen in het ziekenhuis als gevolg van acuut gedecompenseerd hartfalen, ondank het feit dat de patiënt mechanisch werd ondersteund door zijn LVAD. Lichamelijk onderzoek toonde een continue, systolische souffle bij de tweede intercostaal ruimte rechts. Aanvullende beeldvorming, door middel van een CT-scan, toonde meerdere knikken in de LVAD-uitstroomcanule, die met succes chirurgisch werd vervangen. Met deze casestudie benadrukken wij de ongewone presentaties van LVAD patiënten waarop clinici behoed dienen te zijn. Voorzichtigheid is geboden, omdat deze

patiënten zich asymptomatisch, gedecompenseerd of op manieren kunnen presenteren die wij nog niet kennen.

In **Hoofdstuk 11** identificeerden wij ECMO behoefte en trombocytopenie als onafhankelijke voorspellers van vroege postoperatieve bloedingen. ECMO is met succes gebruikt als brug naar LVAD-ondersteuning en harttransplantatie. Desalniettemin gaat het gebruik van ECMO gepaard met een hoog risico op complicaties als gevolg van heparinisatie en verworven coagulopathieën. Factoren waaronder verworven von Willebrand-factor-deficiëntie (VWD), hemolyse en trombocytopenie dragen bij aan het risico op bloedingen tijdens ECMO-ondersteuning. Bovendien blijven deze aandoeningen aanwezig na LVAD-implantatie. De introductie van een LVAD in de bloedsomloop resulteert in een veranderd hematologisch evenwicht ten gevolge van bloed-pomp-interacties, veranderingen in de hemodynamiek, de reologie en de bijkomende behoefte aan anticoagulantia van LVAD-patiënten. De meerderheid, zo niet alle LVAD-patiënten, ervaren een vorm van bloedplaatjesdysfunctie en een aangetaste von Willebrand-factor (VWF) -activiteit, leidend tot verworven coagulatiestoornissen. In **Hoofdstuk 13** bespreken wij de literatuur en hebben wij ons gericht op verworven coagulopathieën, waarbij de incidentie, impact en het onderliggende mechanisme van verworven coagulopathieën in LVAD-patiënten beschreven zijn. Daarnaast benoemen we diagnostische en managementstrategieën voor deze verworven coagulopathieën. Erfelijke VWD is een bekende oorzaak van bloedingen. Echter, de verworven VWD, ook wel bekend als het verworven von Willebrand-syndroom (aVWS), heeft de afgelopen jaren de meeste aandacht getrokken met betrekking tot een mogelijke factor die de hoge mate van bloedingscomplicaties na implantatie van een LVAD kan verklaren. De VWF is een groot glycoproteïne multimeer en het potentiële hemostatische effect van het VWF is positief gecorreleerd met de grootte van deze multimeren. De functie van VWF wordt uitgebreid beschreven in **Hoofdstuk 13**. In het kort, VWF medieert de bloedplaatjesadhesie en aggregatie met de sub-endotheliale matrix om hemostase te bewerkstelligen en een plaatjesprop te vormen op de plaats van een vasculaire verwonding. Een desintegrine en metalloprotease met trombospondine type 1, lid 13 (ADAMTS-13) splitst het grote VWF-multimeer wanneer het verankerd is aan de sub-endotheliale matrix. Eenmaal gesplitst, komt VWF vrij in de bloedsomloop, waar het verder wordt verkleind door ADAMTS-13 of door blootstelling aan een verhoogde druk.

Recente bevindingen hebben bevestigd dat bijna alle patiënten met een LVAD, ongeacht het apparaat, een verlies ervaren in de concentratie van grote von Willebrand-multimeren, welke vervolgens resulteert in verminderde VWF activiteit en dus tot een verworven vorm van von Willebrand tekort, de aVWS. Aangenomen wordt dat dit

verlies aan activiteit te wijten is aan een verhoogde druk als gevolg van het ontwerp van de pomp en de cardiale conditie. Laboratoriumbevindingen tonen een verlies van grote multimeren, een verhoging van het VWF-antigeenniveau (Ag), een verminderde binding van VWF aan collageen (gemeten door VWF: CB-activiteit) en ristocetine-cofactoractiviteit (VWF: RCo). Dit verlies van VWF-activiteit wordt vroeg in de postoperatieve periode waargenomen, is persistent tijdens LVAD-ondersteuning en verdwijnt na LVAD-explantatie of harttransplantatie. Verschillende mechanismen zijn geopperd die de ontwikkeling van aVWS inLVAD-patiënten trachten te verklaren. Hiervan is het mechanisme van de wisselwerking tussen een verhoogde druk en het enzym ADAMTS-13 het meest bestudeerd. De aanwezigheid van een LVAD in de bloedsomloop leidt tot significante veranderingen, waaronder een verhoogde vloeistofdruk en een lagere polsdruk. Als gevolg van een toegenomen vloeistofdruk ontvouwt het VWF zich en stelt hierbij bepaalde domeinen bloot. Dit bevordert vervolgens proteolytische splitsing door ADAMTS-13 en binding aan bloedplaatjes. Dit resulteert in de afbraak van VWF in kleinere multimeren en een verminderde activiteit. Hoewel bijna alle LVAD-patiënten aan aVWS lijden, ervaren niet alle patiënten een bloeding. Een definitieve associatie met een bloeding dient daarom nog bewezen te worden. Dit suggereert ook dat andere factoren, al dan niet beschermend, ook essentieel zijn voor het bepalen van het risico op bloedingen of trombose bij deze patiënten.

Traditionele behandelingsopties voor een bloeding in patiënten met een aWVS zijn desmopressine, VWF-bevattende concentraten, recombinante (r) factor VIIa, antifibrinolytica, intraveneuze immunoglobulines en plasmaferese. Het gebruik van desmopressine is anekdotisch beschreven voor de behandeling van gastro-intestinale bloedingen bij LVAD-patiënten. Daarnaast zijn er verschillende nieuwe behandelingsopties in opkomst. De veiligheid en effectiviteit van deze behandelopties moeten echter nog worden bepaald bij patiënten met een LVAD.

De introductie van een nieuwe generatie LVADs heeft de overleving van LVAD-patiënten enorm verbeterd. Het optreden van trombo-embolische complicaties en pomptrombose blijft echter een belangrijk probleem. De nieuwe HeartMate 3 (HM3) LVAD met een centrifugale bloedstroom bleek superieur te zijn aan zijn voorganger, de axiale flow HeartMate II (HMII), voornamelijk als gevolg van een afname van het aantal LVAD-vervangingen en pomptrombose bij de HM3-patiënten. Het blijft echter onduidelijk waarom de HM3-patiënten een lager aantal pomptrombose en een verbeterde hemocompatibiliteit ervaarden. De HeartWare HVAD is naast de Heartmate de meest gebruikte LVAD in Europa. Er is echter geen vergelijking gemaakt tussen de HM3 en de HeartWare HVAD met betrekking tot verschillen in hemocompatibiliteit. Van lactaatdehydrogenase (LDH) is bekend dat het de meest specifieke marker is voor

hemolyse, pomptrombose en trombo-embolische complicaties. Het dient dan ook als een marker voor hemocompatibiliteit. In **Hoofdstuk 14** en **15** onderzochten wij de evolutie van LDH gedurende het eerste jaar na LVAD-implantatie in patiënten ondersteund met een HMII versus een HM3 LVAD en tussen patiënten ondersteund met een HM3 versus een HeartWare HVAD om verschillen in de hemocompatibiliteit van de apparaten te kwantificeren. Middels een non-lineair mixed-effects model werd getracht de evolutie van LDH over tijd te projecteren. De evolutie van LDH was significant hoger over tijd in patiënten met een axiaal flow HMII LVAD dan in patiënten met een centrifugaal HM3 LVAD. Dit duidt op een verbeterde hemocompatibiliteit van het HM3 LVAD. Wij observeerden geen verschil in LDH over tijd tussen patiënten die ondersteund werden met een centrifugaal HM3 LVAD of een centrifugaal HeartWare HVAD, hetgeen duidend op vergelijkbare hemocompatibiliteit tussen deze typen LVADs. Het verschil tussen de tweede en de derde generatie apparaten wordt waarschijnlijk veroorzaakt door het verschil in ontwerp van de pompmechanisme van de LVADs. Tweede generatie LVADs zijn apparaten met een axiaal pompmechanisme. Apparaten van de derde generatie, daarentegen, hebben een centrifugaal pompmechanisme. Over deze nieuwe LVADs is een lagere VWF-afbraak gerapporteerd, duidend op een verbeterde hemocompatibiliteit. Ondanks het verminderde aantal pomptrombose bij de HM3-patiënten, verschilt de hoeveelheid neurologische complicaties niet van die van HM2-patiënten. Daarom zijn wij nog ver verwijderd van de perfecte LVAD. Het ontwerp van LVADs tracht verbeterd te blijven worden om complicaties te verminderen. Het hoge risico op complicaties is een van de redenen waarom LVAD-therapie nog niet is uitgebreid naar patiënten met minder ernstige symptomen van hartfalen. Het verminderen van de complicaties en het verbeteren van het management na het optreden van een complicatie zou kunnen helpen om LVAD-therapie een geschikte behandelingsoptie voor deze patiënten te maken.

Ongeacht de type LVAD, komen neurologische complicaties verontrustend vaak voor en zijn deze naast een hoge morbiditeit ook geassocieerd met dramatische uitkomsten. In **Hoofdstuk 16** presenteren wij een innovatief hulpmiddel voor een hemiplegische LVAD-patiënt die geïnvalideerd was door een beroerte en daardoor niet in staat was om zijn LVAD te bedienen. Wij hebben laten zien hoe een simpel hulpmiddel de onafhankelijkheid van een hemiplegische LVAD-patiënt zodanig kan verbeteren dat de patiënt nu zelfstandig in zijn eigen huis kan wonen. De boodschap die wij hoopten over te brengen is dat in het geval van invalidatie door een neurologische complicatie innovatieve methoden moeten worden bedacht om de onafhankelijkheid en de kwaliteit van leven van de LVAD-patiënt te verbeteren.

Lange-termijn complicaties

Hoewel LVADs aanvankelijk werden geïntroduceerd als apparaten voor kortdurende ondersteuning, heeft het zich ontwikkeld tot een duurzame behandeling. Als gevolg van de toename van patiënten die een LVAD als destination therapie ontvangen, is de duurzaamheid van het apparaat zeer belangrijk geworden. Voor destination therapie LVAD patiënten is hun levensduur mede afhankelijk van de duurzaamheid van de LVAD. Bovendien is de kwaliteit van leven van deze patiënten ook afhankelijk van complicaties die zich voordoen op de lange termijn. Na bloedingen en infecties zijn ventriculaire aritmieën (VA) een van de meest gemelde complicaties. Het is bekend dat de incidentie van VA het hoogst is in de vroege postoperatieve fase. Echter is er weinig bekend over de incidentie van VA op de lange termijn en de klinische gevolgen hiervan. In **Hoofdstuk 17** bestudeerden wij in een multicenter retrospectief onderzoek de incidentie, voorspellers en klinische uitkomsten van VA bij LVAD-patiënten. Een derde van de patiënten ervaarde een VA. De incidentie van VA volgde een U-vormige curve, met de hoogste incidentie in de vroege postoperatieve fase, het laagst bij 15 tot 18 maanden met vervolgens weer een toename van de incidentie. Daarnaast hadden patiënten met VA voor LVAD-implantatie een verhoogd risico op VA na LVAD implantatie. Dit is niet verrassend omdat het de aanwezigheid van een aritmogeen substraat weergeeft dat niet wordt opgeheven door de implantatie van een LVAD. Over het algemeen kunnen VA behandeld worden met antiaritmische medicatie en implanteerbaar cardioverter defibrillator (ICD)-therapie. Een klein deel van de patiënten kan echter een moeilijk te behandelen VA ontwikkelen, welke een hemodynamische instabiliteit kan veroorzaken, ondanks de aanwezigheid van de LVAD. Desondanks hebben patiënten die VA ervaren niet een hoger risico op overlijden.

Er is gerapporteerd dat de duurzaamheid en functionaliteit van LVADs wordt beïnvloed door meerdere factoren, waaronder anatomische beperkingen, complicaties, ontwerp van het apparaat en zelfs de specifieke fabrikant. Er is echter weinig bekend over de duurzaamheid van de huidige LVADs op de lange termijn en de incidentie van mechanisch falen van de LVAD over tijd. In **Hoofdstuk 18** hebben wij de incidentie, geassocieerde factoren, de klinische presentatie en de uitkomst van het mechanische falen van de LVAD onderzocht. Wij definieerden mechanisch falen als een mechanisch probleem uitgaande van de aandrijflijn, instroom canule, uitstroom canule, aandrijfmotor of als gevolg van een motorstoring van de LVAD, afgekort tot mechanisch falen van het apparaat ("*Mechanical device failure*" MDF). De prevalentie van MDF nam gedurende de follow-up toe, waarbij de mediane tijd tot MDF meer was dan twee jaar. Patiënten met schijnbaar niet ernstige, echter cumulatieve technische problemen, hadden na verloop van tijd meer risico op MDF. De meerderheid van de patiënten

met MDF presenteerden zich met een rood LVAD-alarm en een tijdelijke pompstop. Daarnaast was MDF de oorzaak van overlijden in zeventien procent van de sterfgevallen. Wanneer patiënten echter op tijd het ziekenhuis bereiken, kunnen ze succesvol worden opgevangen en behandeld. De behandeling omvatte semi-urgente LVAD-uitwisseling of externe reparatie van de aandrijflijn.

In de literatuur worden enkele patiënten die langer dan 10 jaar ondersteund zijn middels een LVAD beschreven. Echter is dit eerder een uitzondering dan de norm. Daarom zou het negeren van de beperkingen van LVADs kunnen leiden tot ernstige complicaties, al dan niet fataal zijn. MDF is met name een probleem dat zich voor doet bij patiënten die de grenzen van mechanische ondersteuning overschrijden. Gezien de toenemende incidentie van MDF na implantatie van een LVAD, adviseren wij om periodiek en intensief onderzoek te doen naar de aandrijflijn van LVADs en zijn technische integriteit. De duur van LVAD-ondersteuning, de geschiedenis van technische problemen en de aanwezigheid van schade aan de aandrijflijn moeten de clinicus helpen bij het bepalen of aanvullende beeldvorming gerechtvaardigd is. Tot slot, des te langer een patiënt wordt ondersteund met een LVAD, des te meer een arts bedacht dient te zijn op MDF.

Toekomstperspectief

In het laatste decennium zijn LVADs enorm geëvolueerd en met grote belangstelling wachten wij verdere ontwikkelingen af. De groeiende populatie van patiënten met hartfalen zal resulteren in de verlenging van de lineaire trend die is opgemerkt in het aantal LVAD-implantaties. Op het moment worden er al meer LVADs geïmplanteerd dan dat er harttransplantaties worden verricht. Dit heeft geleid tot een versnelling in de ontwikkeling van LVADs en bijgedragen aan ons begrip over onderliggende mechanismen van ernstige LVAD gerelateerde complicaties. Er valt echter nog veel te leren met betrekking tot de optimale selectiecriteria, ondersteuningsduur, aanvullende gunstige behandelingen, medicijnen tijdens LVAD-ondersteuning en de langetermijnresultaten van LVAD-therapie. Daarnaast verwachten wij dat de indicatie voor LVAD-therapie wordt uitgebreid. LVAD als een brug naar cardiaal herstel of als reddingtherapie is al sporadisch beschreven in de literatuur. Er is echter meer klinische onderzoek nodig om de uitkomsten van deze indicaties te kwantificeren. Daarnaast zijn er nieuwe modellen nodig die beter HF-patiënten kunnen identificeren die mogelijk baat zouden kunnen hebben bij LVAD-therapie.

Technische ontwikkelingen hebben geleid tot duurzamere LVADs, resulterend in verbeterde klinische resultaten. Er is echter nog steeds ruimte voor verbetering.

Toekomstige LVADs zullen naar verwachting kleiner zijn, hemodynamisch informatie kunnen leveren op afstand en volledig implanteerbaar zijn waardoor de aandrijflijn wordt geëlimineerd. Wij verwachten dat in de toekomst LVADs zich automatisch kunnen aanpassen aan de fysieke activiteit van de patiënt. Het ontbreken van pulsatiliteit bij de tweede generatie LVADs is in verband gebracht met verschillende nadelige effecten, waaronder arterioveneuze malformaties en aorta-insufficiëntie. De eerste stap om dit probleem op te lossen is geïntroduceerd in de derde generatie LVAD. De HeartMate III en HeartWare MVAD zijn uitgerust met de mogelijkheid om de pompsnelheid aan te passen en een intrinsieke pulsatiele bloedstroom te genereren. Of deze functie daadwerkelijk bijdraagt aan verminderde malformaties en/of aorta-insufficiëntie dient nog volledig te worden onderzocht. Evenzo zal aanvullend onderzoek in de toekomst moeten aantonen of medicamenteuze therapie bijdraagt aan het herstel van cardiaal weefsel tijdens LVAD-ondersteuning.

Ondersteuning middels een LVAD is bewezen superieur te zijn aan optimale medicamenteuze therapie in de behandeling van patiënten met eindstadium hartfalen. Leven met een LVAD kan echter zeer uitdagend, stressvol en gevaarlijk zijn gezien het constante risico op complicaties. Daarom zijn onderzoeken naar de fysieke en met name de psychische conditie van de patiënt essentieel om optimale kansen op een goede kwaliteit van leven te verzekeren na LVAD-implantatie. Met name in de destination therapie patiënten dient hier extra aandacht voor te zijn zodat ze ook kunnen genieten van hun reis.

Tot slot, voordat het concept “het leven eindigt wanneer het brein sterft” werd geaccepteerd, heeft het hart het leven eeuwenlang gesymboliseerd en dat doet het nog steeds voor velen. Bij patiënten met een LVAD wordt de functie van het hart kunstmatig nagebootst. Daarom kan zorg aan het einde van het leven van LVAD-patiënten zeer conflicterend zijn voor zorgverleners. Familieleden en zorgverleners van de patiënten hebben advies nodig en artsen dienen zich in deze fase bewust te zijn van hun verantwoordelijkheden, omdat het voor de patiënt en het gezin pas eindigt als de pomp is uitgeschakeld en het hart stopt met kloppen.

Conclusie

Dit proefschrift draagt bij aan de kennis over klinische uitkomsten en complicaties na implantatie van een LVAD. Wij introduceerden een nieuwe risicoscore die bijdraagt aan het identificeren van hoog risicopatiënten voor vroeg RHF. Daarnaast hebben wij vastgesteld dat gelijktijdige behandeling met een tricuspidalisklep ten tijde van LVAD-implantatie het risico op vroeg RHF of mortaliteit niet verhoogde. Wij identificeerden verschillende voorspellers voor acute schade aan de nier, vroege bloedingscomplicaties, vroege mortaliteit en beschreven de impact van deze complicaties op de overleving van LVAD-patiënten. Bovendien werden verschillende factoren die geassocieerd zijn met nierfunctie en late mortaliteit, geïdentificeerd, die gebruikt zouden kunnen worden als selectiecriteria voor LVAD-therapie.

Wij concludeerden dat verworven coagulopathieën zeer veel voorkomen en dat bijna, zo niet alle, LVAD-patiënten het verworven von Willebrand-syndroom ervaren. Echter, een definitieve associatie tussen verworven von Willebrand-syndroom en hematologische complicaties moet nog worden vastgesteld. Verder toonden wij aan dat de nieuwe generatie LVADs een verbeterde hemocompatibiliteit vertonen in vergelijking met de tweede generatie LVADs.

Hoewel het aantal vroege en lange-termijn complicaties te hoog blijft, is de overleving van LVAD-patiënten in de loop der tijd sterk verbeterd en is LVAD-therapie een geaccepteerde behandelingsoptie geworden voor patiënten met eindstadium hartfalen. Onze resultaten onderstrepen het belang van zorgvuldige monitoring van patiënten na implantatie van een LVAD, ongeacht de tijd. Er worden hogere eisen gesteld aan toekomstige LVADs. Verwacht wordt dat de uitkomsten in LVAD-patiënten zullen blijven verbeteren.

Tot slot hopen wij met dit proefschrift een weg te banen voor de volgende stap naar verbetering van de klinische zorg voor patiënten met eindstadium hartfalen.

CHAPTER 20

Dankwoord/Acknowledgements
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Erasmus MC department:	Cardiothoracic Surgery
Research school:	Cardiovascular Research School (COEUR)
PhD period:	Oktober 2016 – Oktober 2018
Title thesis:	"A New Era in Advanced Heart Failure Therapy." Left Ventricular Assist Devices.
Promotors:	A.J.J.C. Bogers
Co-promotor:	K. Caliskan

ACADEMIC EDUCTION

2012-2015	Bachelor of Science in Medicine, Erasmus MC, Rotterdam, The Netherlands
2015-2019 (expected)	Master of Science in Medicine, Erasmus MC, Rotterdam, The Netherlands
2015-2019 (expected)	Clinical Research Master, NIHES, Rotterdam, The Netherlands

PhD Training	**Year**	**Workload**
General courses		
Research Integrity	2016	0,3
Scientific Writing in English for Publication, NIHES, Rotterdam, The Netherlands	2016	2
Principles of Research in Medicine, NIHES, Rotterdam, The Netherlands	2015	0,7
Principles of Epidemiologic Data-analysis, NIHES, Rotterdam, The Netherlands	2015	0,7
Fundamentals of Epidemiology, Harvard School of Public Health, Boston, USA	2016	2,5
Society and Health, Harvard School of Public Health, Boston, USA	2016	2,5
In-depth courses		
Study design, NIHES, Rotterdam, The Netherlands	2015	4,3
Biostatistical methods I: Basic principles, NIHES, Rotterdam, The Netherlands	2015	5,7
Biostatistical methods II: classical regression models, NIHES, Rotterdam, The Netherlands	2015	4,3
Pharmaco-epidemiology and drug safety, NIHES, Rotterdam, The Netherlands	2015	1,9
Methods of clinical research, NIHES, Rotterdam, The Netherlands	2016	0,7
Clinical trials, NIHES, Rotterdam, The Netherlands	2016	0,7
Clinical epidemiology, NIHES, Rotterdam, The Netherlands	2016	5,7
Advanced Topics in Clinical Trials, NIHES, Rotterdam, The Netherlands	2016	1,9
Advanced Analysis of Prognosis Studies, NIHES, Rotterdam, The Netherlands	2016	0,9
Arrhythmia Research Methodology, COEUR, Rotterdam	2016	1,5
Heart Failure Research, COEUR, Rotterdam	2016	1,5
Repeated measurements NIHES, Rotterdam, The Netherlands	2017	1,9
Congenital Heart Disease Part I, COEUR, Rotterdam	2017	1
Intensive care I & II, COEUR, Rotterdam	2017	0,5

Oral presentation		
American College of Cardiology, Washington (2 presentations)	2017	1,2
International Society of Heart and Lung Transplantation, San Diego (2 presentations)	2017	1,2
European Society of Cardiology, München (2 presentations)	2018	1,2

Poster presentation		
International Society of Heart and Lung Transplantation, Washington	2016	0,6
American College of Cardiology, Washington (4 posters)	2017	2,4
International Society of Heart and Lung Transplantation, Washington (5 posters)	2017	3,0
Heart Valve Society, New York, USA	2018	0,6

Teaching		
Supervising 2nd year medical students in writing a systematic review	2017	0,6
Lectures COEUR course Congenital Heart Disease: Introducing a new era in advance heart failure trough VADs.	2017	0,6
Lectures VECTOR course Heart Failure: From Heart failure to LVAD.	2017	0,6
Supervising 4th year medical students in writing a thesis	2018	0,6

International conferences		
International Society of Heart and Lung Transplantation, Washington D.C., USA	2016	1,5
American College of Cardiology 66th annual meeting, Washington D.C., USA	2017	1,5
International Society of Heart and Lung Transplantation, San Diego, USA	2017	1,5
Heart Valve Society, New York, USA	2018	1,5

Grants / Prizes	
Gert-Jan Mulder Baltimore Scholarschip	
Award Best Moderated Poster 0 European Society of Cardiology Congress (München)	
Total workload (ECTS)	59,8

LIST OF PUBLICATIONS

1. **Muslem R**, Veen KM, Soliman OI, Caliskan K, Kolff MEA, Dousma D, Manintveld OC, Birim O, Bogers AJJC, Takkenberg JJM.
Left Ventricular Assist Device Implantation With and Without Concomitant Tricuspid Valve Surgery: a Systematic Review and meta-analysis.
Eur J Cardiothorac Surg. 2018 Oct 1;54(4):644-651. doi: 10.1093/ejcts/ezy150.

2. **Muslem R,** Caliskan K, van Thiel R, Kashif U, Akin S, Birim O, Constantinescu AA, Brugts JJ, Bunge JJH, Bekkers JA, Leebeek FWG, Bogers AJJC.
Incidence, predictors and clinical outcome of early bleeding events in patients undergoing a left ventricular assist device implant.
Eur J Cardiothorac Surg. 2018 Jul 1;54(1):176-182. doi: 10.1093/ejcts/ezy044.

3. **Muslem R,** Yalçin 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. 2018 Feb 6. doi: 10.1097/MAT.0000000000000752. [Epub ahead of print]

4. **Muslem R,** Caliskan K, Leebeek FWG.
Acquired coagulopathy in patients with left ventricular assist devices.
J Thromb Haemost. 2018 Mar;16(3):429-440. doi: 10.1111/jth.13933. Epub 2018 Jan 22. Review.

5. **Muslem R,** Caliskan K, Akin S, Sharma K, Gilotra NA, Constantinescu AA, Houston B, Whitman G, Tedford RJ, Hesselink DA, Bogers AJJC, Russell SD, Manintveld OC.
Acute kidney injury and 1-year mortality after left ventricular assist device implantation.
J Heart Lung Transplant. 2018Jan;37(1):116-123. doi: 10.1016/j.healun.2017.11.005.Epub 2017 Nov 6.

6. **Muslem R,** Caliskan K, Akin S, Yasar YE, Sharma K, Gilotra NA, Kardys I, Houston B, Whitman G, Tedford RJ, Hesselink DA, Bogers AJJC, Manintveld OC, Russell SD.
Effect of Age and Renal Function on Survival After Left Ventricular Assist Device Implantation.
Am J Cardiol. 2017Dec15;120(12):2221-2225. doi: 10.1016/j.amjcard.2017.08.045. Epub 2017 Sep 20.

7. **Muslem R,** Akin S, Constantinescu AA, Manintveld O, Brugts JJ, van der Heiden CW, Birim O, Bogers AJJC, Caliskan K.
Long-Term Mechanical Durability of Left Ventricular Assist Devices: An Urgent Call for Periodic Assessment of Technical Integrity.
ASAIO J. 2018 Jul/Aug;64(4):521-528. doi: 10.1097/MAT.0000000000000679.

8. Schinkel AFL, Akin S, Strachinaru M, **Muslem R,** Soliman OII, Brugts JJ, Constantinescu AA, Manintveld OC, Caliskan K.
Safety and feasibility of contrast echocardiography for the evaluation of patients with HeartMate 3 left ventricular assist devices.
Eur Heart J Cardiovasc Imaging. 2018 Jun 1;19(6):690-693. doi: 10.1093/ehjci/jex177.

9. Soliman OII, Akin S, **Muslem R,** Boersma E, Manintveld OC, Krabatsch T, Gummert JF, de By TMMH, Bogers AJJC, Zijlstra F, Mohacsi P, Caliskan K; EUROMACS Investigators.
Derivation and Validation of a Novel Right-Sided Heart Failure Model After Implantation of Continuous Flow Left Ventricular Assist Devices: The EUROMACS (European Registry for Patients with Mechanical Circulatory Support) Right-Sided Heart Failure Risk Score.
Circulation. 2018 Feb 27;137(9):891-906. doi: 10.1161/CIRCULATIONAHA.117.030543. Epub 2017 Aug 27.

10. **Muslem R,** Caliskan K, Akin S, Sharma K, Gilotra NA, Brugts JJ, Houston B, Whitman G, Tedford RJ, Hesselink DA, Bogers AJJC, Manintveld OC, Russell SD.
Pre-operative proteinuria in left ventricular assist devices and clinical outcome.
J Heart Lung Transplant. 2018 Jan;37(1):124-130. doi: 10.1016/j.healun.2017.07.011. Epub 2017 Jul 15. Erratum in: J Heart Lung Transplant. 2018 Apr;37(4):535.

11. Akin S, **Muslem R,** Constantinescu AA, Manintveld OC, Birim O, Brugts JJ, Maat APWM, Fröberg AC, Bogers AJJC, Caliskan K.
18F-FDG PET/CT in the Diagnosis and Management of Continuous Flow Left Ventricular Assist Device Infections: A Case Series and Review of the Literature.
ASAIO J. 2018 Mar/Apr;64(2):e11-e19. doi: 10.1097/MAT.0000000000000552.

12. Yap SC, Ramjankhan F, **Muslem R,** de Jonge N, Kirkels HJ, Akin S, Manintveld OC, Birim O, Szili-Torok T, Caliskan K.
Ventricular Arrhythmias in Patients With a Continuous-Flow Left Ventricular Assist Device.
J Am Coll Cardiol. 2016 Jul 19;68(3):323-325. doi: 10.1016/j.jacc.2016.05.016.

13. **Muslem R,** Akin S, Manintveld O, Caliskan K.
Kinking, thrombosis and need for re-operation in a patient with a left ventricular assist device.
Intensive Care Med. 2016 Dec;42(12):2090-2091. doi: 10.1007/s00134-016-4337-0. Epub 2016 Apr 7.

14. Levolger S, van Vledder MG, **Muslem R,** Koek M, Niessen WJ, de Man RA, de Bruin RW, Ijzermans JN.
Sarcopenia impairs survival in patients with potentially curable hepatocellular carcinoma.
J Surg Oncol. 2015 Aug;112(2):208-13. doi: 10.1002/jso.23976. Epub 2015 Aug 12.

15. **Muslem, R**. Caliskan, K. Papageorgiou, G. Akin, S. Manintveld, O.C. Mokhles, M.M. Rohde, S. Russell, S.D. Hsu, S. Tedford, R.J. Leebeek, F.W.G. Bogers, A.J.J.C.
Differences in the Evolution of Lactate Dehydrogenase Levels over Time Between the HeartMate II and HeartMate 3 Left Ventricular Assist Device.
Submitted.

16. **Muslem, R**. Caliskan, K. Siang, C.O. Hsu, S. Tedford, R.J.
Differences in Lactate Dehydrogenase Levels Between the HeartWare HVAD and the HeartMate 3 Left Ventricular Assist Device.
Submitted

Book chapters

1. **Muslem, R**. Caliskan, K. Bogers, A.J.J.C. "Left ventricular assist devices, welcome to the new era in advanced heart failure therapy." Book chapter 2017 Cardiovascular NCVC Jakarta

2. **Rahatullah Muslem**, Mohammed Ouhlous, Sakir Akin and Abd Alla Fares. Tricuspid valve disease – a computed tomographic assessment. Practical Manual of Tricuspid Valve Disease. Editors O. I. Soliman & F.J. ten Cate

ABOUT THE AUTHOR

Rahat Muslem was born on November 22nd, 1991 in Peshawar, Pakistan. After going back and forth between Afghanistan and Pakistan, he and his family came to the Netherlands in 1998. He graduated from the Arentheem College at Arnhem in 2011, and started this academic career in the same year at the University of Amsterdam (The Netherlands) where he studied Biomedical Science. It was during this period that he became familiar with clinical research.

Motivated to combine clinical research with medicine, he started medical school at the Erasmus University Rotterdam, The Netherlands in 2012. Subsequently, in his second year of medicine he became acquainted with Dr. K. Caliskan and research in the field of end-stage heart failure, which eventually resulted in this thesis. In 2015, Rahat was accepted by the Netherlands Institute of Health Sciences (NIHES) to combine his Master in Medicine with a Master of Science in Clinical Research. During this program he received additional training inter alia in statistical methods, study design and fundamentals of research. Furthermore, as part of the program he studied in depth courses in Epidemiology and Statistics at the Harvard School of Public health in Boston, Massachusetts, USA during the summer in 2016.

In 2016 he was granted with a scholarship by the Gert-Jan Mulder stichting to study abroad. This enabled him to collaborate with the department of Cardiology and Cardiovascular surgery at the Johns Hopkins Hospital, Baltimore, Maryland. USA, where he successfully worked for 6 months on several multi-center studies.

Parallel to the double Master's degree he started his PhD at the department of Cardiothoracic Surgery under the supervision of Professor A.J.J.C. Bogers and Dr. Caliskan.

In Oktober 2017 he started with his medical internships, which he expects to complete in Juli 2019.

In January 2018 Rahat was elected as the chairmen of KEIHAN, a non-profit organization with the aim to contribute in strengthening the basis for development and self-sufficiency through knowledge and improved health care for citizens of Afghanistan.

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This thesis aimed to contribute to the current body of evidence and experiences with Left Ventricular Assist Devices in the new era of advanced heart failure therapy, which is characterized by mechanical circulatory support. In the last decade LVADs have evolved greatly and with great eager we await further developments. The growing population of patients with heart failure has resulted in an exponential increase in the rate of LVAD implantations worldwide. In addition, technical advancements have led to more durable devices, resulting in improved clinical outcomes. However, only recently great progress has been made in this field. Through this thesis we hoped to set the path for the next step towards improving the clinical care of patients with advanced heart failure.