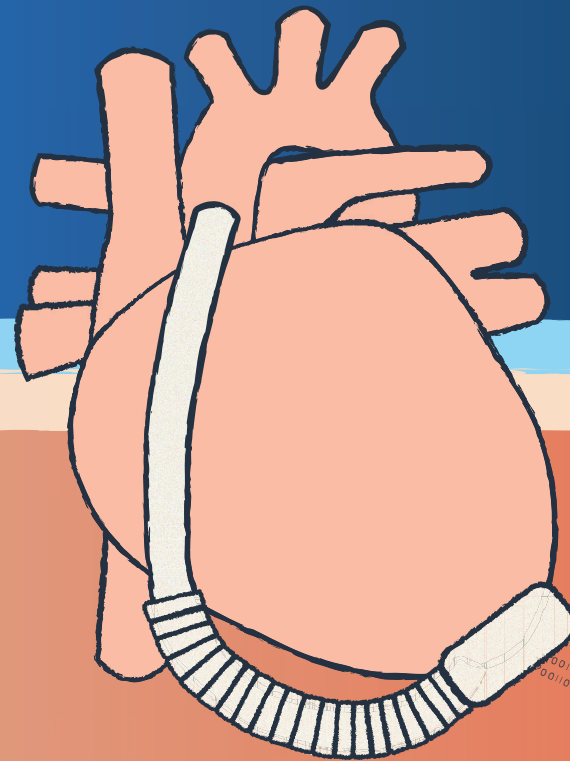


Data-driven innovation of left ventricular assist device therapy

Lieke Numan



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Data-driven innovation of left ventricular assist device therapy

Data-gedreven innovatie voor steunharttherapie
(met een samenvatting in het Nederlands)

Proefschrift

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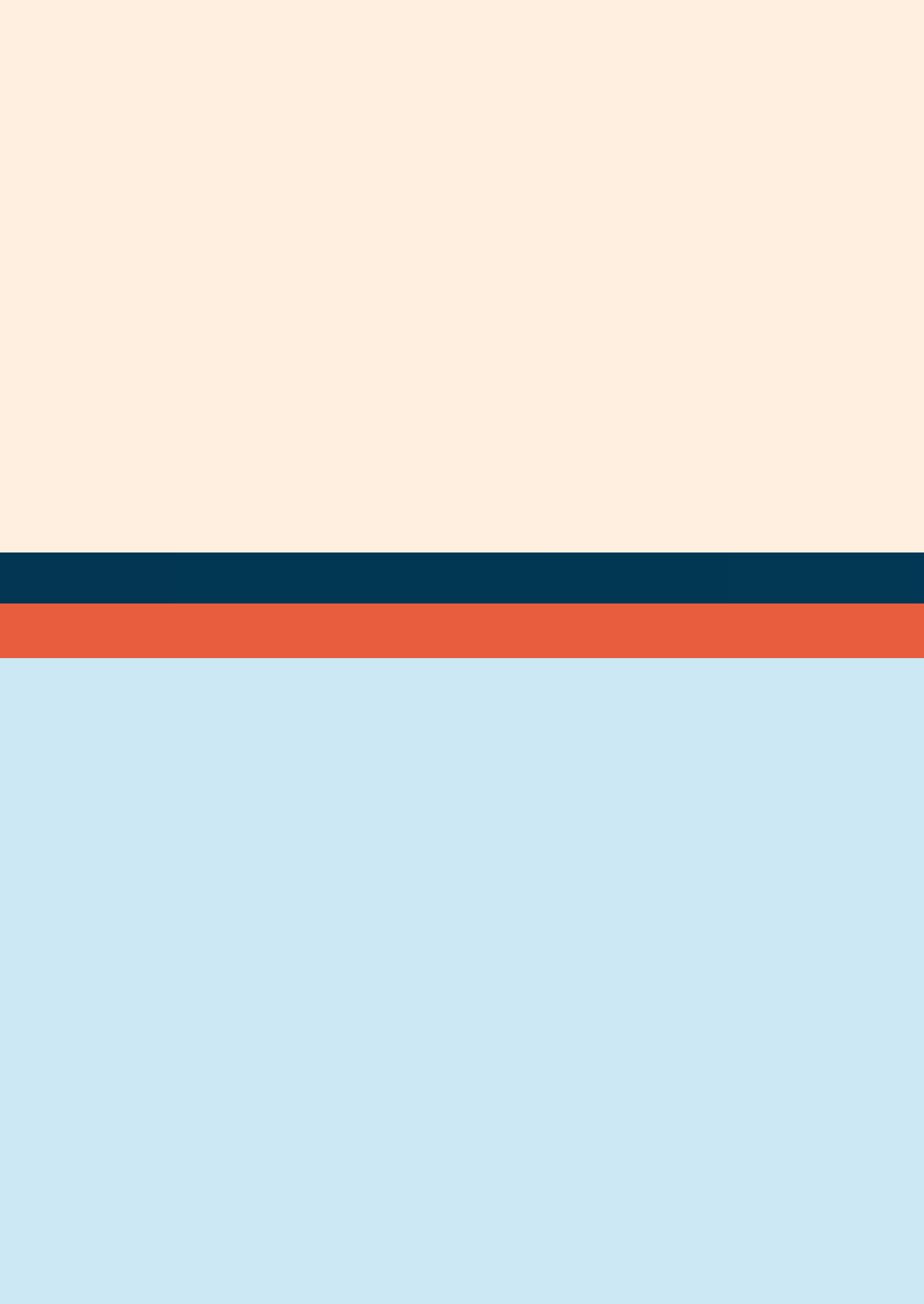
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CHAPTER 1

General introduction and thesis outline

Heart failure (HF) is a pandemic affecting 1-2% of adults and represents a growing economic burden.(1)(2) It is a clinical syndrome caused by a structural abnormality or dysfunction of the heart, leading to inadequate cardiac output during rest or activity.(3) For patients with advanced HF, where treatment (medication, cardiac synchronization and/or implantable cardioverter defibrillator) is insufficient, heart transplantation is the gold standard in selected patients.(4) Due to a growing population of patients with advanced HF and a permanent shortage of donor hearts, left ventricular assist devices (LVADs) are increasingly used as a therapy for patients with end-stage HF. Patients receive an LVAD as a bridge to heart transplantation (BTT), destination therapy (DT) or bridge to decision (BTD), although treatment strategy may change over time. Patients eligible for long-term mechanical support such as LVAD therapy are classified using the Interagency Registry for Mechanically Assisted Circulatory support (INTERMACS) profiles. (5) The classification system ranges from INTERMACS 1, a critical “crash and burn” situation to INTERMACS 7, where mechanical circulatory support (MCS) or heart transplantation is not (yet) indicated. Patients with a lower INTERMACS score have a worse survival when compared to patients with a higher score.(6)

Table 1: Interagency Registry for Mechanically Assisted Circulatory support (INTERMACS) classification, modified from (5).

Profile	Time frame for intervention
Profile 1: Critical cardiogenic shock, “crash and burn” Patient with life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypoperfusion, often confirmed by worsening acidosis and/or lactate levels.	Definitive intervention needed within hours.
Profile 2: Progressive decline, “sliding on inotropes” Patient with declining function despite intravenous inotropic support, may be manifest by worsening renal function, nutritional depletion, inability to restore volume balance.	Definitive intervention needed within few days.
Profile 3: Stable on inotropes or inotrope-dependent, “dependent stability” Patient with stable blood pressure, organ function, nutrition, and symptoms on continuous intravenous inotropic support, but demonstrating repeated failure to wean from support due to recurrent symptomatic hypotension or renal dysfunction.	Definitive intervention elective over a period of weeks to few months.
Profile 4: Resting symptoms, “frequent flyer” Patient can be stabilized close to normal volume status but experiences daily symptoms of congestion at rest or during activities of daily life. Doses of diuretics generally fluctuate at very high levels. Consider more intensive management and surveillance.	Definitive intervention elective over a period of weeks to few months.
Profile 5: Exertion intolerant, “housebound” Comfortable at rest and with activities of daily life but unable to engage in any other activity, living predominantly within the house. Patient are comfortable at rest without congestive symptoms, but may have underlying refractory elevated volume status, often with renal dysfunction.	Variable urgency, depends upon maintenance of nutrition, organ function and activity.
Profile 6: Exertion limited, “walking wounded” Patient without evidence of fluid overload is comfortable at rest, and with activities of daily living and minor activities outside the home but fatigues after the first few minutes of any meaningful activity.	Variable, depends upon maintenance of nutrition, organ function and activity.

Table 1: CONTINUED.

Profile	Time frame for intervention
Profile 7: Advanced NYHA III, “placeholder” A placeholder for more precise specification in future, this level includes patients who are without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion.	Transplantation or circulatory support may not currently be indicated

LEFT VENTRICULAR ASSIST DEVICE

LVADs unload the left ventricle (LV) by pumping blood from the LV towards the aorta. The pump consists of an inflow cannula located in the LV, an impeller and an outflow graft coupled to the aorta. The pump is connected via a driveline that exits the body at the lower abdomen to an external controller and two batteries (figure 1). Currently, most patients are supported with a HeartMate 3 (HM3, Abbott, Chicago, IL, USA) or HeartWare (HVAD, Medtronic, Minneapolis, MN, USA), which was recently withdrawn from the global market.(7)

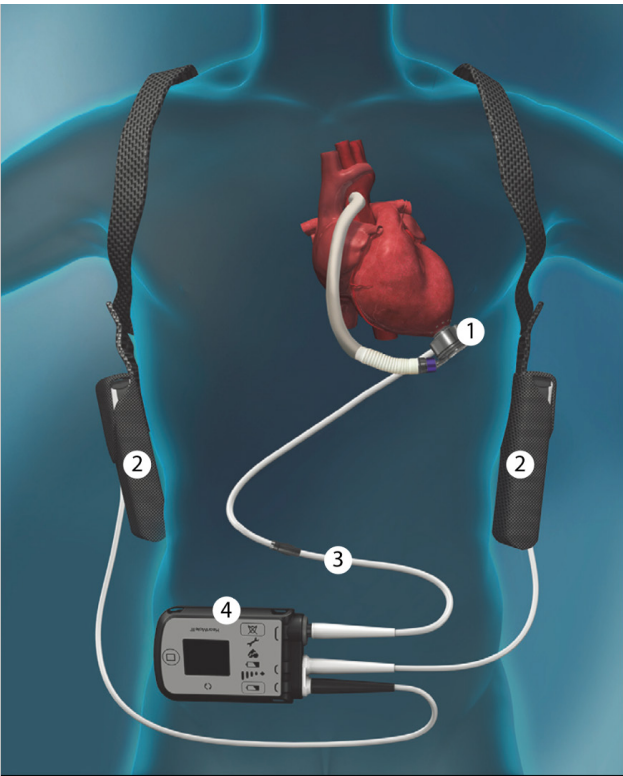


Figure 1: The left ventricular assist device and its components: 1: the pump, consisting of the inflow graft, impeller and outflow graft, 2: batteries in twofold, 3: driveline and 4: the controller. Permission for the use of this figure was granted by Abbott.

CLINICAL OUTCOME AND COMPLICATIONS

Survival outcome of patients on LVAD support has improved drastically, with a five-year survival of 54%.(8) Despite significant advances in clinical outcome, patients often suffer complications and are frequently admitted due to infection, bleeding, thrombosis, arrhythmia or right heart failure.(9)(10) Appendix A lists all complications as defined by INTERMACS.(11) Driveline infections are a frequent problem in patients on LVAD support and are associated with increased mortality.(12,13) The exit site of the driveline at the lower abdomen (figure 1) serves as an entry point for microorganisms. Another difficulty is the thin line between thrombus formation and bleeding, specifically in LVAD patients. The risk of thrombosis is increased after LVAD implantation due to the exposure to foreign materials and in regions of blood stasis. Pump thrombosis (PT) is a scarce, but dreadful complication in patients on LVAD support.(14) Therefore, anticoagulation with a vitamin K-antagonist (e.g. warfarin) and aspirin with an international normalized ratio (INR) target range of 2.0-3.0 is currently recommended for LVAD patients.(15) In addition, patients often suffer from acquired von Willebrand Factor (vWF) disease caused by an increased shear stress of the continuous flow LVAD.(16) Due to the small therapeutic range between thrombus formation and bleeding, optimization of anticoagulation is complex.(17) Reduction or cessation of anti-platelet therapy after a major bleeding may increase the risk for thrombosis. On the other side, intrinsic coagulopathies or over-anticoagulation can increase the risk of a bleeding.(18) In addition, patients are at risk of right heart failure (RHF) failure, which may occur during the initial post-operative phase or later during LVAD support.(19) If the right ventricle (RV) is unable to meet the increased output produced by the LVAD, the septum shifts leftward which negatively affects the RV contraction efficiency, leading to RV failure and may result into a vicious circle.(20)(21) Furthermore, if the pump speed is set too high, suction can occur, where the inflow cannula is occluded by the septal wall. In turn, suction may elicit ventricular arrhythmias (VAs). Atrial and ventricular arrhythmia are common after LVAD implantation. 20-60% of the patients suffer from VAs, with highest incidence in the first post-operative period and an increase in incidence in the long term.(22) In addition to suction, vasopressor and inotropic medication, fibrosis or ischemia can elicit VAs. VAs may arise as a consequence of suction or vice versa.

This broad range of complication types negatively impact the duration and the quality of patients after LVAD implantation. Therefore, research is needed to further improve survival and quality of life of patients on LVAD support, by studying different phases throughout the LVAD support process. For example, the pre-operative phase, timing of the implantation and pre-rehabilitation, and the decision

which LVAD type to use are of interest. Demographical data and clinical variables can be used to predict outcome after LVAD implantation. For example, a risk score for mortality may contribute to a better patient selection.(23) In addition, the timing of LVAD implantation has been of interest.(24) Subsequently, clinicians face the question which LVAD type to use. For such decisions, randomized controlled trials (RCT's) such as the ENDURANCE and MOMENTUM are important.(25)(26) However, the downside of an RCT is that it is time consuming and comes with high costs. Accordingly, retrospective studies on clinical outcome with different device types are useful. Research on LVAD patients is often limited in patient numbers, due to the relatively low number of implantations in each centre. Registries such as EUROMACS and INTERMACS enable the opportunity to study large LVAD patient groups.(27)(28) In turn, registry based studies often need to deal with missing data and are hampered by centre specific differences. Despite extensive efforts in the last decade, it remains difficult to predict outcome after LVAD implantation and to identify patients at risk at the individual level. Hence, patients are monitored extensively on different aspects by a multidisciplinary expert team, predominantly during frequent outpatient clinic visits. In between those visits, monitoring relies solely on patient self-care and an alarm in case of a low LVAD flow. Therefore, research has focused on early detection of pump thrombosis by monitoring pump power using simple or sophisticated algorithms.(29)(30)(31) Moreover, initial experience on remote patient monitoring using mobile phone applications was reported.(32)(33) Despite recognition of its importance, studies on (remote) patient monitoring remain scarce. Additional advancements in (tele-) monitoring after LVAD implantation could play a key role to further improve outcomes. Early identification of deterioration by remote patient monitoring enables early treatment, thereby possibly preventing worsening of symptoms or admission. Therefore, the aim of this thesis was to identify LVAD patients at risk and to explore remote monitoring possibilities after LVAD implantation.

THESIS OUTLINE

LVAD candidacy is tested extensively before primary implantation. Subsequently, the LVAD team needs to decide which LVAD type to implant. Choosing the optimal device is crucial. Therefore, we compare survival and important complications in patients on HeartWare and Heartmate 3 support in a single center retrospective study in **Chapter 2**. As this single center comparison is limited by patient numbers, we perform a multi-center study to confirm our findings in **Chapter 3**, where we also aim to identify which patients on HeartWare support are at highest risk. Data is collected in four different centers that implanted both HeartWare and

HeartMate3. In this chapter, we focus on survival and important complications. As experience in LVAD patient care increases over the years, we present a five-year survival of patients supported with HeartMate3 in **Chapter 4**. Since not only survival, but also quality of life is of importance, we zoom in to a specific complication in **Chapter 5**: late right heart failure (RHF). In contrast to early RHF, late RHF has been studied to a lesser extent. Accordingly, we aim to identify risk factors for late RHF in patients on LVAD support. LVAD therapy requires patients to use several types of medications. In addition, advanced heart failure patients often suffer from other comorbidities that need pharmacological treatment. Likewise, (hyper)polypharmacy is common in LVAD patients. In contrast to the general heart failure population, (hyper)polypharmacy in patients on LVAD support was not studied before. Therefore, in **Chapter 6** we determine the prevalence of (hyper)polypharmacy and its association with adverse outcome after LVAD implantation.

After LVAD implantation, in- and out-of-hospital monitoring is of paramount importance to early detect abnormal situations. A personalized follow-up schedule is preferred, but more scientific basis is needed to stratify patients according to their complication risk. The heart failure field is therefore continuously searching for new biomarkers for prediction purposes. As such, in **Chapter 7**, we study the relationship between soluble suppression of tumorigenicity-2 (sST2) and mortality and late right heart failure in patients after LVAD implantation. Despite the wide range of possibilities and broad recognition of its importance, tele-monitoring in LVAD patients has not yet been fully explored nor integrated into standard care. In **Chapter 8** we discuss the possibilities of tele-monitoring using noninvasive and invasive devices. Challenges and future perspectives in this emerging field are considered. An important aspect to monitor are pump parameters (i.e. power and flow). Currently, the LVAD only alarms in case of a low flow. A personalized monitoring algorithm for pump parameters may help to early detect deterioration. In **Chapter 9** we develop and test a patient tailored algorithm (PRECISION-LVAD) to monitor LVAD parameters. Pump parameters follow a circadian pattern, which restores within several weeks after primary HVAD implantation. Due to a limited data storage, circadian patterns in pump parameters were not previously described in patients on HM3 support. Therefore, in **Chapter 10** we study circadian patterns in pump parameters and its relation to patterns in heartrate by the collection of additional LVAD data and using a biosensor.

Finally, the main results of this thesis will be summarized and discussed in **Chapter 11**. The results will be placed in perspective and possibilities and challenges will be discussed. Finally, I will discuss how future studies should progress.

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APPENDIX A

Hemolysis

Minor Hemolysis: A plasma-free hemoglobin value greater than 20 mg/dl or a serum lactate dehydrogenase (LDH) level greater than two and one-half times (2.5x) the upper limits of the normal range at the implanting center occurring after the first 72 hours post-implant in the absence of clinical symptoms or findings of hemolysis or abnormal pump function.

Major Hemolysis: A plasma-free hemoglobin value greater than 20 mg/dl or a serum lactate dehydrogenase (LDH) level greater than two and one-half times (2.5x) the upper limits of the normal range at the implanting center occurring after the first 72 hours post-implant and associated with clinical symptoms or findings of hemolysis or abnormal pump function. Major Hemolysis requires the presence of one or more of the following conditions:

- o Hemoglobinuria (“tea-colored urine”)
- o Anemia (decrease in hematocrit or hemoglobin level that is out of proportion to levels explainable by chronic illness or usual post-VAD state)
- o Hyperbilirubinemia (total bilirubin above 2 mg/dl, with predominately indirect component)
- o Pump malfunction and/or abnormal pump parameters

Right Heart Failure

Symptoms or findings of persistent right ventricular failure characterized by both of the following:

- Documentation of elevated central venous pressure (CVP) by:
 - o Direct measurement (e.g., right heart catheterization) with evidence of a central venous pressure (CVP) or right atrial pressure (RAP) > 16 mmHg.
 - or
 - o Findings of significantly dilated inferior vena cava with absence of inspiratory variation by echocardiography,
 - or
 - o Clinical findings of elevated jugular venous distension at least half way up the neck in an upright patient.
- Manifestations of elevated central venous pressure characterized by:
 - o Clinical findings of peripheral edema (>2+ either new or unresolved),
 - or

- Presence of ascites or palpable hepatomegaly on physical examination (unmistakable abdominal contour) or by diagnostic imaging,
or
- Laboratory evidence of worsening hepatic (total bilirubin > 2.0 mg/dl) or renal dysfunction (creatinine > 2.0 mg/dl).

Device Malfunction

A Device Malfunction occurs when any component of the MCS system ceases to operate to its designed performance specifications or otherwise fails to perform as intended. Performance specifications include all claims made in the Instructions for Use.

Device malfunctions can be further defined as major or minor:

1. Major device malfunction, otherwise known as failure, occurs when one or more of the components of the MCS system either directly causes or could potentially induce a state of inadequate circulatory support (low cardiac output state) or death. A failure that was iatrogenic or recipient-induced will be classified as an Iatrogenic/Recipient-Induced Failure. A device malfunction or failure is considered major when one of the following conditions occurs:
 - a. Suspected or confirmed pump thrombus (see below)
 - b. Urgent transplantation (immediate 1A listing for transplant)
 - c. Pump replacement
 - d. Pump explant
 - e. Breach of integrity of drive line that required repair
 - f. Death
2. Minor device malfunction includes inadequately functioning external components which require repair or replacement but do not result in 1a-f. Device malfunction does not apply to “routine” maintenance which includes repair/replacement of: external controller, pneumatic drive unit, electric power supplies, batteries and interconnecting cables.

Pump Thrombus represents a special case of major device malfunction and can be delineated as suspected pump thrombus or confirmed pump thrombus. Pump thrombus will be classified as “SUSPECTED” (see definition below) based upon clinical, biochemical, or hemodynamic findings or “CONFIRMED” (see definition below) based upon device inspection or incontrovertible radiologic studies or

absence of appropriate Doppler flow signals that confirms thrombus within the device or its conduits that results in or could potentially induce circulatory failure.

1. Suspected pump thrombus is a pump-related malfunction in which clinical or MCS parameters suggest thrombus on the blood contacting components of the pump, cannulae, or grafts. Signs and symptoms should include at least 2 of the 3 following criteria:
 - a. Presence of hemolysis
 - b. Presence of heart failure not explained by structural heart disease
 - c. Abnormal pump parameters

Suspected pump thrombus should be accompanied by 1 or more of the following events or interventions:

- i. treatment with intravenous anticoagulation (e.g., heparin), intravenous thrombolytics (e.g., tPA), or intravenous antiplatelet therapy (e.g., eptifibatide, tirofiban)
 - ii. pump replacement
 - iii. pump explantation
 - iv. urgent transplantation (UNOS status 1A)
 - v. stroke
 - vi. arterial non-CNS thromboembolism
 - vii. death
2. Confirmed pump thrombus is a major pump-related malfunction in which thrombus is confirmed within the blood contacting surfaces of device inflow cannula or outflow conduit or grafts. This can be reported via direct visual inspection or by incontrovertible contrast radiographic evidence or by the absence of an appropriate Doppler flow signal that results in or could potentially induce circulatory failure or result in thromboembolism.

Major Bleeding

An episode of suspected internal or external bleeding that results in one or more of the following:

- a. Death,
- b. Re-operation,
- c. Hospitalization,
- d. Transfusion of red blood cells as follows:

If transfusion is selected, then apply the following rules:

During first 7 days post implant

- ≥ 50 kg: $\geq 4U$ packed red blood cells (PRBC) within any 24 hour period during first 7 days post implant.
- < 50 kg: ≥ 20 cc/kg packed red blood cells (PRBC) within any 24 hour period during first 7 days post

implant.

After 7 days post implant

- A transfusion of packed red blood cells (PRBC) after 7 days following implant with the investigator recording the number of units given. (record number of units given per 24 hour period).

Note: Hemorrhagic stroke is considered a neurological event and not as a separate bleeding event.

Major Infection

A clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

Localized Non-Device Infection

Infection localized to any organ system or region (e.g. mediastinitis) without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.

Percutaneous Site and/or Pocket Infection

A positive culture from the skin and/or tissue surrounding the drive line or from the tissue surrounding the external housing of a pump implanted within the body, coupled with the need to treat with antimicrobial therapy, when there is clinical evidence of infection such as pain, fever, drainage, or leukocytosis.

Internal Pump Component, Inflow or Outflow Tract Infection

Infection of blood-contacting surfaces of the LVAD documented by positive site culture. (There should be a separate data field for paracorporeal pump that describes infection at the percutaneous cannula site, e.g. Thoratec PVAD).

Sepsis

Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension.

Neurological Dysfunction

Any new, temporary or permanent, focal or global neurologic dysfunction ascertained by a standard neurological history and examination administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note; or an abnormality identified by surveillance neuroimaging. The examining physician will classify the event as a cerebrovascular event as defined below or as a non-vascular acute neurologic event. A neurologic event may be recognized by a clinically evident sign or symptom, or by clinically-silent electrographic seizure activity, or as a clinically silent lesion detected by surveillance neuroimaging. Each neurologic event should be classified by the clinical provider following complete neurologic assessment as one of the following event types:

- a. Transient ischemic attack, defined as an acute transient neurologic deficit conforming anatomically to arterial distribution cerebral ischemia, which resolves in < 24 hours and is associated with no infarction on brain imaging (head CT performed >24 hours after symptom onset; or MRI*).
- b. Ischemic stroke, defined as a new acute neurologic deficit (or acute encephalopathy or seizures in children <6 months**) of any duration associated with acute infarction on imaging corresponding anatomically to the clinical deficit. Ischemic stroke should be sub classified as due to arterial-distribution ischemia or due to venous thrombosis.
- c. Acute symptomatic intracranial hemorrhage, defined as new acute neurologic deficit (or acute encephalopathy or seizures in children < 6 months**) attributable to Intracranial hemorrhage (ICH). ICH subtype should be specified as one or a combination of the following types: subarachnoid, intraventricular, parenchymal, subdural.
- d. Clinically covert ischemic stroke or ICH: infarction or ICH seen by surveillance imaging, without clinical findings of stroke or ICH at the time of event recognition.
- e. Hypoxic-Ischemic Encephalopathy: Acute new encephalopathy*** due to hypoxic-ischemic injury (HIE), manifest as clinically- evident signs or symptoms, or subclinical electrographic seizures found by complete neurological diagnostic evaluation to be attributable to acute global or focal hypoxic or ischemic brain injury not meeting one of ischemic stroke or ICH events as defined above.
- f. Acute new encephalopathy*** due to other causes, manifest as clinically-

evident signs or symptoms or subclinical electrographic seizures found by complete neurological diagnostic evaluation to be attributable causes other than stroke, ICH or HIE, as defined above. This category of “other” acute encephalopathy includes neurologic signs or symptoms or subclinical seizures found to be attributable to other conditions such as meningitis, toxic-metabolic or drug-related processes.

*** Acute encephalopathy is a sign or symptom of some underlying cerebral disorder, and is manifest as depressed consciousness with or without any associated new global or multifocal neurologic deficits in cranial nerve, motor, sensory, reflexes and cerebellar function.

Cardiac Arrhythmias

Any documented arrhythmia that results in clinical compromise (e.g., abnormal VAD function [e.g., diminished VAD flow or suction events], oliguria, pre-syncope or syncope, angina, dyspnea), or requires hospitalization or treatment (drug therapy, defibrillation, cardioversion, ICD therapy (e.g., shock or anti-tachycardia pacing) or arrhythmia ablation procedure). Cardiac arrhythmias are classified as 1 of 2 types:

- 1) Sustained ventricular arrhythmia resulting in clinical compromise, or requiring hospitalization or drug treatment, defibrillation, cardioversion, ICD therapy, or arrhythmia ablation procedure.
- 2) Sustained supraventricular arrhythmia resulting in clinical compromise, or requiring hospitalization or drug treatment, cardioversion, ICD therapy, or arrhythmia ablation procedure.

Pericardial Fluid Collection

Accumulation of fluid or clot in the pericardial space that requires surgical intervention or percutaneous catheter drainage. This event will be subdivided into those with clinical signs of tamponade (e.g. increased central venous pressure and decreased cardiac/VAD output) and those without signs of tamponade.

Myocardial Infarction

Two categories of myocardial infarction will be identified:

Peri-Operative Myocardial Infarction: The clinical suspicion of myocardial infarction together with CK-MB or Troponin > 10 times the local hospital upper limits of normal, found within 7 days following VAD implant together with ECG findings consistent with acute myocardial infarction. (This definition uses the higher suggested limit for serum markers due to apical coring at the time of VAD placement, and does not use wall motion

changes because the apical sewing ring inherently creates new wall motion abnormalities.)

Non-Perioperative Myocardial Infarction: The presence at > 7 days post-implant of two of the following three criteria:

- a) Chest pain which is characteristic of myocardial ischemia,
- b) ECG with a pattern or changes consistent with a myocardial infarction, and
- c) Troponin or CK (measured by standard clinical pathology/laboratory medicine methods) greater than the normal range for the local hospital with positive MB fraction ($\geq 3\%$ total CK). This should be accompanied by a new regional LV or RV wall motion abnormality on a myocardial imaging study.

Psychiatric Episode

Disturbance in thinking, emotion or behavior that causes substantial impairment in functioning or marked subjective distress and requires intervention. Intervention is the addition of new psychiatric medication, hospitalization, or referral to a mental health professional for treatment. Suicide is included in this definition.

Respiratory Failure

Impairment of respiratory function requiring reintubation, tracheostomy or the inability to discontinue ventilatory support within six days (144 hours) post-VAD implant. This excludes intubation for re-operation or temporary intubation for diagnostic or therapeutic procedures.

Venous Thromboembolism

Evidence of venous thromboembolic event (e.g. deep vein thrombosis, pulmonary embolism) by standard clinical and laboratory testing.

Wound Dehiscence

Disruption of the apposed surfaces of a surgical incision, excluding infectious etiology, and requiring surgical repair.

Arterial Non-CNS Thromboembolism

An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:

- 1) standard clinical and laboratory testing
- 2) operative findings
- 3) autopsy findings

This definition excludes neurological events.

Hepatic Dysfunction

An increase in any two of the following hepatic laboratory values (total bilirubin, aspartate aminotransferase/AST and alanine aminotransferase/ALT) to a level greater than three times the upper limit of normal for the hospital, beyond 14 days post-implant (or if hepatic dysfunction is the primary cause of death).

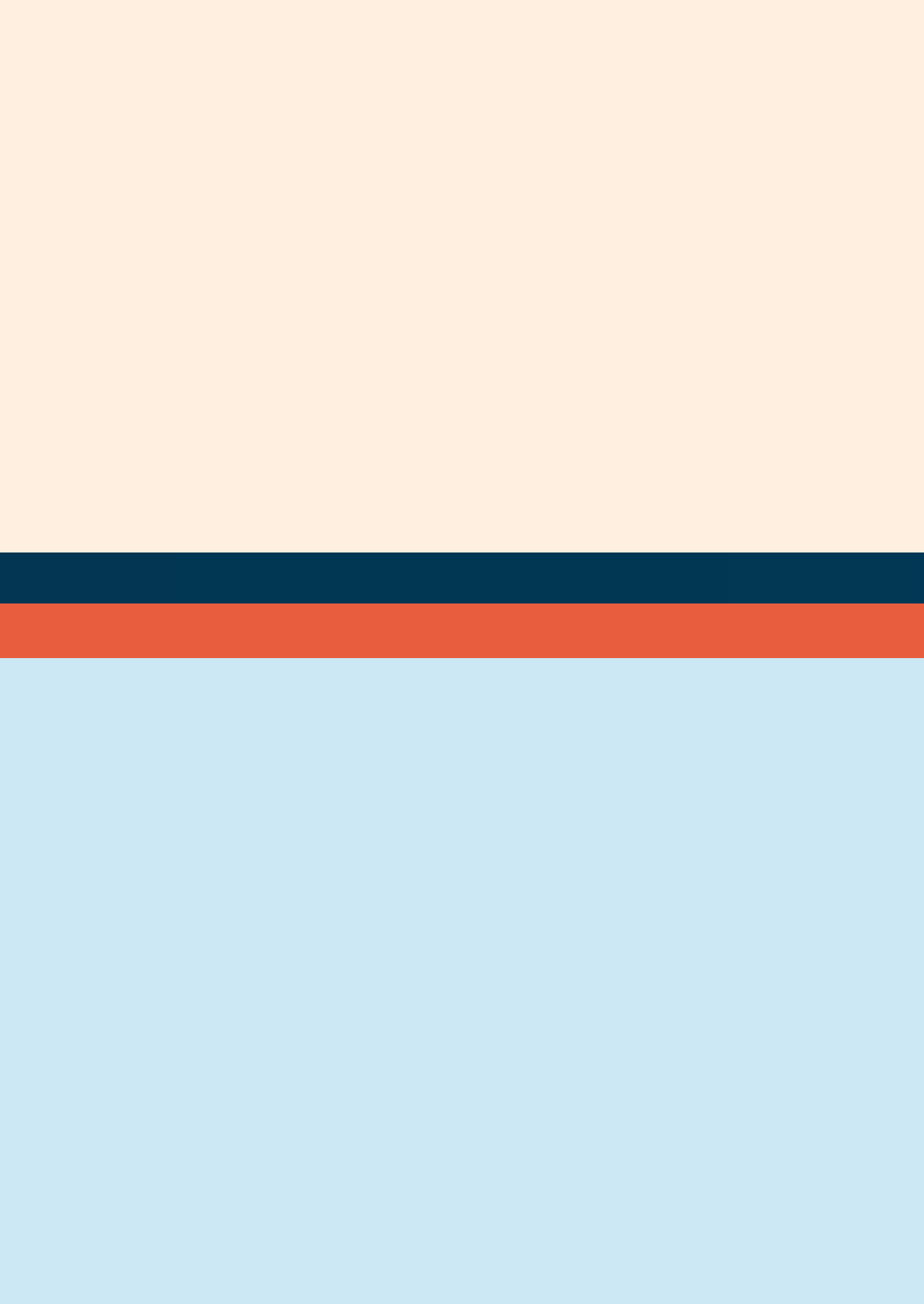
Hypertension

New onset blood pressure elevation greater than or equal to 140 mm Hg systolic or 90 mm Hg diastolic (pulsatile pump) or 110 mm Hg mean pressure (rotary pump).

Renal Dysfunction

Two categories of renal dysfunction will be identified:

1. **Acute Renal Dysfunction:** Abnormal kidney function requiring dialysis (including hemofiltration) in patients who did not require this procedure prior to implant, or a rise in serum creatinine of greater than 3 times baseline or greater than 5 mg/dL (in children, creatinine greater than 3 times upper limit of normal for age) sustained for over 48 hours.
2. **Chronic Renal Dysfunction:** An increase in serum creatinine of 2 mg/dl or greater above baseline, or requirement for hemodialysis sustained for at least 90 days.



CHAPTER 2

Propensity score-based analysis of long-term outcome of patients on HeartWare and HeartMate 3 LVAD support

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ABSTRACT

Objectives

Left ventricular assist device (LVAD) therapy has become the cornerstone in the treatment of end-stage heart failure and is increasingly used as destination therapy next to bridge to transplant or recovery. HeartMate 3 (HM3) and HeartWare (HVAD) are centrifugal continuous flow devices implanted intrapericardially and most commonly used worldwide. No randomised controlled trials have been performed yet. Analysis based on large registries may be considered as the best alternative, but have the disadvantage of different standard-of-care between centres and missing data. Bias is introduced, since the decision which device to use was not random, even more so because many centres use only one type of LVAD. Therefore, we performed a propensity score-based analysis of long-term clinical outcome of patients that received HM3 or HVAD in a single centre.

Methods and Results

Between December 2010 and December 2019, 100 patients received HVAD and 81 patients received HM3 as primary implantation at the University Medical Centre Utrecht. We performed propensity score (PS) matching with an extensive set of covariates, resulting in 112 matched patients with a median follow-up of 28 months. After PS-matching, survival was not significantly different ($p=0.21$), but was better for HM3. The cumulative incidences for haemorrhagic stroke ($p=0.01$) and pump thrombosis ($p=0.02$) were significantly higher for HVAD patients. The cumulative incidences for major bleeding, ischemic stroke, right heart failure and driveline infection were not different between the groups. We found no interaction between the surgeon who performed the implantation and survival ($p=0.59$, $p=0.78$, $p=0.89$). Sensitivity analysis was performed, by PS-matching without patients on pre-operative temporary support resulting in 74 matched patients. This also resulted in a non-significant difference in survival ($p=0.07$). The propensity score adjusted Cox regression showed a worse but non-significant ($p=0.10$) survival for HVAD patients with Hazard Ratio 1.71 (95% confidence interval 0.91-3.24).

Conclusion

Survival was not significantly different between both groups after PS-matching, but was better for HM3, with a significantly lower incidence of haemorrhagic stroke and pump thrombosis for HM3. These results need to be interpreted carefully, since matching may have introduced greater imbalance on unmeasured covariates. A multi-centre approach of carefully selected centres is recommended to enlarge the number of matched patients.

INTRODUCTION

The number of patients with heart failure (HF) continues to increase. Heart transplantation is the gold standard for patients with end-stage heart failure.(1) Due to a shortage of donor hearts, long-term left ventricular assist devices (LVADs) have become an established therapeutic option for these patients, with a one-year survival of approximately 80%.(2)(3) Even though the use of mechanically circulatory support (MCS) results in improved survival rates, patients often suffer from major complications. Only 20% of the patients is not readmitted to the hospital within the first year after primary implantation.(4) The most common causes of death in patients on LVAD support are neurological dysfunction, multi-organ failure, major infection and right heart failure. In addition, pump thrombosis is a dreaded complication and may occur early or late after implantation.(5)

Currently, the most frequently implanted LVADs are the HeartWare (HVAD, Medtronic, Minneapolis, MN, USA) and HeartMate 3 (HM3, Abbott, Chicago, IL, USA). Both intrapericardially implanted third generation pumps are centrifugal continuous flow devices. Three prospective industry-sponsored studies have been performed to evaluate performance of these devices compared to the HeartMate II (HMII), which is an axial flow pump.(6)(7)(8) The ENDURANCE trial compared the survival of patients on HVAD and HMII support. They showed a comparable survival, but higher postoperative incidence of sepsis, ischaemic and haemorrhagic stroke and right heart failure for patients implanted with HVAD.(6) Subsequently, a supplementary trial with strict blood pressure management showed a higher 12-month incidence of transient ischemic attack and stroke with residual deficit for HVAD, but a better survival free from disabling stroke and need for device exchange or urgent transplantation or death.(7) HMII and HM3 were compared in the MOMENTUM 3 trial.(8) This randomised controlled trial showed a significantly lower incidence of pump thrombosis (1.1% vs 15.7%) and ischemic stroke (6.3% vs 13.4%) for HM3 compared to HMII. No differences in haemorrhagic stroke, bleeding, driveline infection or right heart failure were found.(8) In addition, the ELEVATE registry was designed to study two-year outcome with the HM3, with comparable rates for pump thrombosis (1,5%), stroke (10%) and major infection (57%) when compared to the HM3 population within the MOMENTUM trial.(9)

Ideally, survival of patients implanted with HM3 and HVAD is compared with a randomised controlled trial. However, this has not been performed yet and is also not expected to be initiated. Large registries may be considered as the best alternative due to the amount of included patients. However, these have the disadvantage of different standard-of-care between centres, missing data and heterogeneity. Bias is

introduced, since the decision which device to use was not random, even more so because many centres use only one type of LVAD. Therefore, we conducted a single centre retrospective propensity score-based analysis of patients supported with HM3 and HVAD.

METHODS

We conducted an investigator-initiated retrospective single centre analysis of patients on LVAD support. The study was approved by the local ethics committee of the University Medical Centre Utrecht, the Netherlands (METC: 20-195). The need for informed consent was waived and this study was conducted in accordance with Good Clinical Practice and the 2002 Declaration of Helsinki.

All patients who underwent primary implantation of HVAD or HM3 until December 2019 at the UMCU were eligible. HVAD has been implanted since November 2010, whereas the first HM3 implant was in December 2015. The follow-up period was until November 2020. Baseline characteristics and clinical data were retrieved from the electronic health records and our MCS database, which is based on – but not limited to – the definitions of Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). The standard operating technique was a full median sternotomy using cardio pulmonary bypass and was performed by certified surgeons.

Endpoints

The primary endpoint of the study was death or urgent heart transplantation (HTx) during follow-up. Urgent HTx was defined as HTx for which the patient received a priority status on the waiting list (national 1A, national 1B, or international HU). Patients with non-urgent HTx were censored. Secondary endpoints were first occurrence of pump thrombosis, ischemic and haemorrhagic stroke, right heart failure (RHF), extra-cerebral major bleeding and driveline infection as defined according to the INTERMACS definitions.⁽¹⁰⁾

Statistics

Results are presented as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables or as number or percentage for categorical variables. Differences in both groups were tested using the Fisher's exact test for categorical variables and the t-test or Mann-Whitney U-test for continuous variables as appropriate. Because the type of LVAD device was not assigned in a randomized controlled manner, we performed propensity score (PS) matching to obtain two comparable groups. The continuous variables that were used to estimate

the PS were: age, preoperative estimated glomerular filtration rate (eGFR) and bilirubin, body surface area (BSA), body mass index (BMI) and right ventricular (RV) function. Since growing numbers of implantations result in more experience over the years, it is possible that treatment and/or prevention of complications has improved in recent years. Therefore, we also accounted for the moment of implantation, by using the number of months after the start of the study period as a covariate for PS-matching. In addition, sex, diabetes mellitus (DM), concomitant surgery, ischemic cardiomyopathy as underlying disease, pre-operative temporary support, INTERMACS=1 and stroke in medical history were used as binary variables. RV function was classified as 1 (poor), 2 (intermediate) or 3 (good) by two independent cardiologist who were blinded for the type of LVAD. They individually classified the RV of each patient and subsequently discussed the discrepancies to reach agreement on the right ventricular function. The inter-rater reliability was assessed by the intraclass correlation coefficient. Classification was based on the available information of the echocardiography report and right heart catheterization: tricuspid annular plane systolic excursion (TAPSE), degree of tricuspid valve insufficiency (TI), peak systolic velocity of the right ventricle measured with tissue Doppler imaging (TDI), right atrial pressure, pulmonary artery pressure, and the right ventricular stroke work index (RVSWI). Concomitant surgery was defined as any other intervention that was conducted during the primary LVAD implantation; heart valve repair or replacement, atrial septal defect closure, coronary artery bypass surgery or left ventricle aneurysm repair. Pre-operative temporary support was defined as being supported with extra corporeal life support (ECLS), Centrimag or an intra-aortic balloon pump (IABP).

The PS, defined as the probability of being implanted with either HM3 or HVAD, was estimated by multivariable logistic regression with device type as dependent variable. Subsequently, nearest neighbour PS-matching was performed using a calliper width of 0.1. Baseline differences between both groups were tested using the Wilcoxon signed-rank test or McNemar test. The balance of covariates were considered satisfactory for a standardized mean difference (SMD) of less than 10%. The effect of the surgeon who performed the LVAD implantation on survival was tested. Cox regression was performed within the PS-matched group with survival as dependent variable and device type and the interaction between each of the three main surgeons and device type as independent variables.

For both unmatched and matched patient groups, the primary endpoint was evaluated by Kaplan-Meier analysis censoring for non-urgent transplantation and ongoing support at the end of the follow-up. Difference in survival was assessed by log-rank testing. Competing risk analysis was performed for the PS-matched patients to compare the cumulative incidence of the secondary endpoints, with HTx, death

and ongoing support at follow-up as competing risks. The primary and secondary end-points were evaluated up to 36 months after implantation. Sensitivity analysis for survival was performed using two methods. First, PS-matching was conducted with all patients without pre-operative temporary support. Secondly, we used propensity score adjusted Cox regression analysis. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using R Version 3.6.3.

RESULTS

Between November 2010 and December 2019, 100 patients received HVAD and 81 patients received HM3 as their first long-term device. All preoperative characteristics of these unmatched patients were complete and are shown in Table 1. Patients who received an HVAD were slightly older and had a lower BSA. In addition, more patients with HVAD had a stroke in their medical history and the number of patients with pre-operative temporary support was higher, whereas the number of patients with INTERMACS 2-7 was relatively smaller. Additionally, more HVAD patients had ischemic cardiomyopathy. The intraclass correlation coefficient of the initial assessment of the right ventricular function assessed by two independent cardiologists was 0.78.

Table 1: Baseline characteristics of all patients and PS-matched patients.

Covariate	All patients (n=181)			PS-matched patients (n=112)		
	HM3 (n=81)	HVAD (n=100)	p-value	HM3 (n=56)	HVAD (n=56)	p-value
Age (years)	56.0 (14.0)	58.5 (13.0)	0.21	56.0 (13.3)	57.0 (19.5)	0.74
Sex (% male)	65.4	68.0	0.75	66.1	64.3	1.00
BSA (m ²)	1.98 (0.23)	1.94 (0.21)	0.22	1.95 (0.21)	1.93 (0.20)	0.63
BMI (kg/m ²)	24.7 (6.1)	24.1 (5.6)	0.53	23.9 (6.6)	23.8 (6.2)	0.89
eGFR (ml/min/1.73m ²)	61.0 (41.0)	60.0 (42.3)	0.56	64.5 (38.3)	59.0 (36.8)	0.78
Bilirubin (μmol/l)	19.0 (26.0)	19.0 (18.0)	0.63	20.0 (24.5)	21.0 (19.3)	0.75
RV function (1=bad,2=moderate,3=good)	2.19 (0.69)	2.15 (0.64)	0.73	2.18 (0.66)	2.21 (0.65)	0.77
Diabetes mellitus (%)	14.8	13.0	0.83	16.1	14.3	1.00
Stroke in medical history (%)	3.7	8.0	0.35	5.4	7.1	1.00
Concomitant surgery (%)	23.5	26.0	0.73	26.8	30.4	0.86
Temporary support (%)	13.6	29.0	0.02	17.9	16.1	1.00
INTERMACS 1 (%)	6.2	5.0	0.75	7.1	5.4	1.00
INTERMACS 2-7 (%)	80.2	66.0	0.04	75.0	78.6	0.91
Aetiology - dilated CMP (%)	70.4	55.0	0.05	62.5	58.9	0.90
Aetiology - ischemic CMP (%)	23.5	37.0	0.05	30.4	33.9	0.87
Months after start of study period (nr.)	89.0 (24.0)	71.0 (48.3)	0.00	83.0 (24.3)	85.0 (27.8)	0.79

Continuous data are shown as mean ± standard deviation or median and interquartile range. Categorical data are shown as the percentage (%). BMI; Body Mass Index; BSA, Body Surface Area; CMP, cardiomyopathy; eGFR, Estimated Glomerular Filtration Rate; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; RV, right ventricle; PS, propensity score

PS matching resulted in 112 matched patients, with SMD of less than 10% for all covariates (Table 1), indicating a substantial reduction of bias (Figure 1). The median follow-up period was 28 months (IQR: 26 months). None of the PS matched patients were weaned during follow-up. Three surgeons implanted 97% of the devices, who individually performed at least 25% of the implantations. Interaction testing was performed for surgeon and device type and was not found to be significant for any of the surgeons ($p=0.59$, $p=0.78$, $p=0.89$) for the primary outcome.

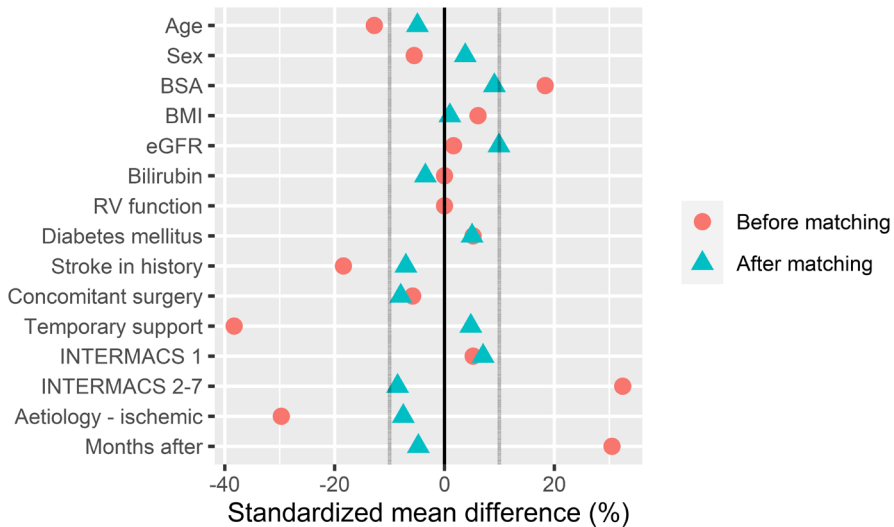


Figure 1: Love plot for standardized mean difference before and after propensity score matching comparing covariate values for patients on HeartMate 3 and HeartWare support.

Survival of unmatched patients (Figure 2A) was significantly better for patients on HM3 support ($p=0.0049$). After PS-matching a difference in survival was still present (Figure 2B), although non-significant ($p=0.21$). Figure 3 illustrates the cumulative incidence for different complication types of the PS-matched patients. Haemorrhagic stroke occurred more frequently in patients on HVAD support ($p=0.01$), as well as pump thrombosis ($p=0.02$). The incidences for extra-cerebral major bleeding ($p=0.96$), ischemic stroke ($p=0.38$), right heart failure ($p=0.63$) and driveline infection ($p=0.90$) were comparable in both groups.

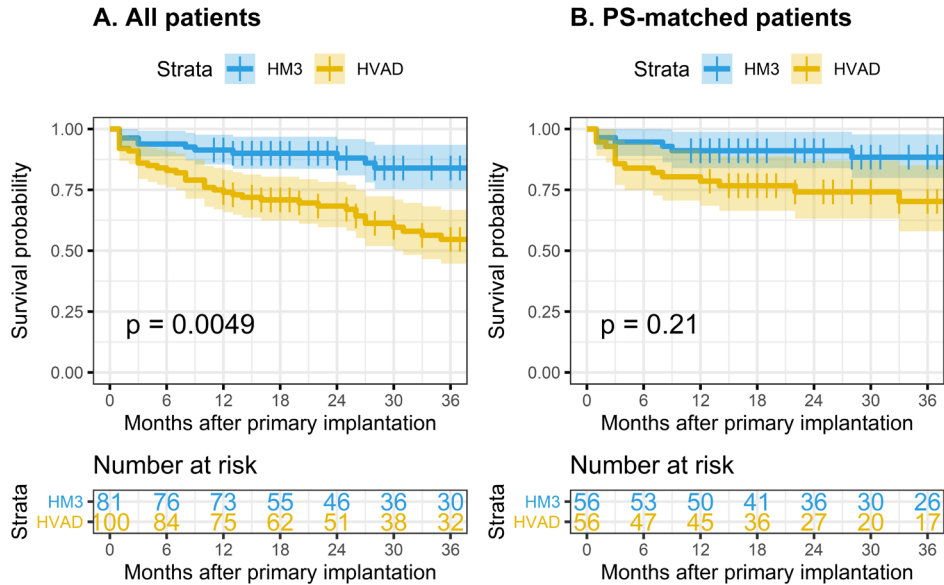


Figure 2: Kaplan Meier survival of all patients (A) and PS-matched patients (B) with 95 % Confidence Interval, with censoring for non-urgent heart transplantation and ongoing support at follow-up.

Table 2 provides an overview of the number of PS-matched patients that underwent HTx and the number and causes of deaths. One patient on HVAD support needed urgent transplantation because of severe RV failure. In addition, three HVAD patients received non-urgent HTx, whereas five HM3 patients received non-urgent HTx. One patient on HM3 support died due ischemic stroke and six HVAD patients died due to a haemorrhagic stroke. The patient on HM3 support had an ischemic stroke one day after the surgery and died three days afterwards. Six HVAD patients had a haemorrhagic stroke at a median of 3 (IQR: 5) months after surgery and died after a median of one day afterwards.

A PS-matched sensitivity analysis was performed in patients without temporary support resulting in 74 matched patients (Supporting Information, *table S1*). All covariates were balanced, except for bilirubin, which was higher for HVAD patients and one HM3 patient had a stroke in medical history, whereas none of the HVAD patients had a prior stroke. Survival of these PS-matched patients was not significantly different ($p=0.07$), but was better for patients on HM3 support (Supporting information, *Figure S1*). Secondly, the propensity score adjusted Cox regression showed a worse but non-significant ($p=0.10$) survival for HVAD when compared to HM3, with Hazard Ratio 1.71 (95% confidence interval 0.91-3.24).

Table 2: Number and causes of death and number of heart transplantations

		PS-matched patients (n=112)	
Endpoint		HeartMate 3 (n=56)n (%)	HeartWare (n=56)n (%)
Cause of death	Device malfunction	0 (0 %)	0 (0 %)
	Infection	3 (5 %)	2 (4 %)
	Multi-organ failure	5 (9 %)	2 (4 %)
	Ischemic Stroke	1 (2 %)	0 (0 %)
	Haemorrhagic stroke	0 (0 %)	6 (11 %)
	RV failure	0 (0 %)	3 (5 %)
	Other	3 (5 %)	3 (5 %)
HTx (urgent)		0 (0 %)	1 (2 %)
HTx (non-urgent)		5 (9 %)	3 (5 %)

HTx, heart transplantation

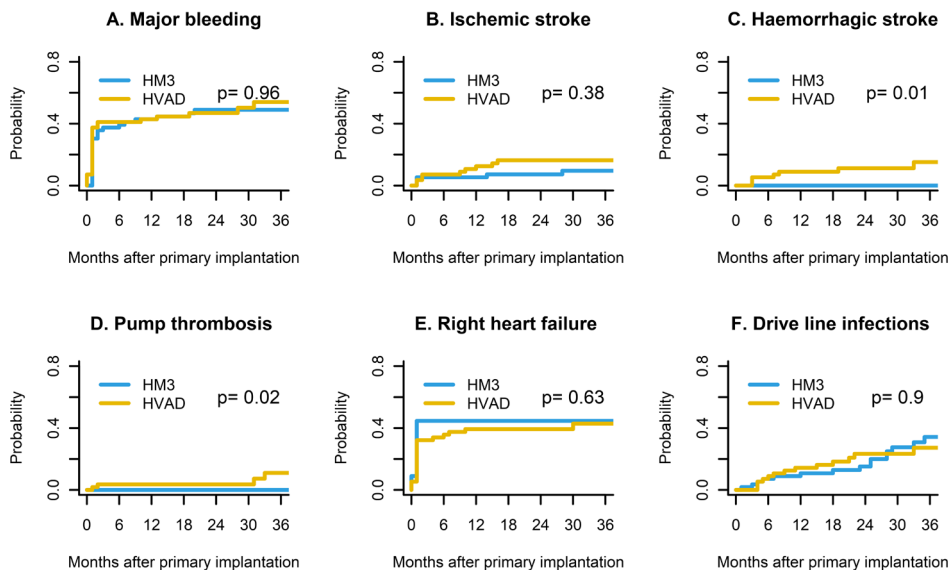


Figure 3: Cumulative risk of PS-matched patients with death, heart transplantation and ongoing support as competing risk.

DISCUSSION

In this single centre retrospective study we compared long-term survival and cumulative incidence of major complications in patients on HM3 and HVAD support. All patients implanted with HM3 or HVAD between December 2010 and December 2019 within the UMCU were included for a propensity score-matched analysis. This resulted in a complete and non-heterogeneous dataset of patients with the same

standard of care with reduced bias for the measured covariates. Although non-significant, survival was better for patients on HM3 support for the PS-matched patients. This was confirmed by sensitivity analysis with PS-matching without patients on temporary support and PS-adjusted Cox regression. The cumulative incidence of haemorrhagic stroke and pump thrombosis was significantly higher for HVAD patients, whereas incidence of major bleeding, ischemic stroke, right heart failure and driveline infection were comparable in both groups.

The baseline characteristics were unbalanced for HM3 and HVAD within the unmatched patient groups, which may partly account for the significant difference in survival. HVAD patients were slightly older than patients on HM3 support. LVAD patients above 70 years old have a higher incidence of GI-bleeding and the absolute risk of death is 11% higher when compared to younger patients.(11) More HVAD patients had pre-operative temporary support when compared to HM3 patients, which is associated with a worse prognosis.(2) In addition, patients on HVAD had a lower pre-operative INTERMACS, which is also associated with a worse survival. Further, more HVAD patients had ischemic cardiomyopathy when compared to HM3 patients. Akin et al. found that ischemic cardiomyopathy was more common in patients who died within 90 days after LVAD implantation when compared to other cardiomyopathies.(12) This suggested a possible worse prognosis for patients with ischemic cardiomyopathy. However, one year survival of patients with ischemic and dilated cardiomyopathy was not significantly different in a retrospective study.(13) HVAD patients had a lower BSA. Smaller patients more often receive an HVAD, due to its smaller size. A retrospective study showed that a small BSA is an independent predictor for mortality after LVAD implantation.(14) Within the UMCU HM3 is implanted since December 2015, whereas the first HVAD was implanted in November 2010. Because of the growing experience over the years, it is likely that treatment of complications continuously improves over the years. The number of months after the start of the study period was therefore higher in HM3 patients and was used as covariate for PS-matching, to have a fair comparison between both groups.

No randomised controlled trials have been performed to compare long-term outcome of HM3 and HVAD. Instead, several retrospective studies were conducted comparing survival and complications of both LVAD types.(15)(16)(17) Mueller et al. compared short term outcome of HM3 and HVAD and showed similar 1-year survival (66 vs 62 % for HM3 vs HVAD, $p=0.372$), but found differences in complication rate. Although non-significant, more pump thrombotic events were observed after HVAD implantation.(15) The fully magnetically levitated internal rotor and relatively wide rotor housing of the HM3 or the artificial pulse might explain the lower number of patients with pump thrombosis. In addition, the

incidence of cerebral bleedings was significantly higher for HVAD patients. No differences were found for gastro-intestinal bleeding, driveline infection and ischemic stroke.(15) These results were confirmed by the findings of our study which had a longer follow-up. Moreover, Schramm et al. compared short term outcome after HVAD and HM3 implantation and reported no difference in survival (median follow-up of 15 months) and freedom from strokes between both groups. Within 30 months after implantations 24% HM3 and 29% HVAD patients died ($p=0.568$). Even though not significant, an increased number of strokes for patients on HVAD support was found.(16) In contrast to our results, patients implanted with HM3 developed driveline infections less frequently when compared to HVAD patients. These differences in driveline infections remain unexplained and need further investigation. Finally, Ben Zadok et al. compared clinical outcome of HMII, HM3 and HVAD and showed better survival for HM3, accompanied with lower rates of haemorrhagic and ischemic stroke, pump thrombosis and non-gastro intestinal (GI) bleeding events.(17) In contrast to their approach of uncorrected comparison of all-comers (51 patients on either HVAD or HM3 support), our cohort was larger with a longer follow-up. In addition, we used a propensity score-based analysis to reduce bias.

Even though the majority of the findings of the previously mentioned studies are in line with the current study, some differences were found.(15)(16)(17) These differences could be explained by centre specific performance, but also the used methods and covariates may account for these differences. Schramm et al. performed PS matching based on age, sex, serum creatinine levels, INTERMACS, perioperative right ventricular failure, and the implantation strategy (bridge to transplant or destination therapy).(16) Instead, we used pre-operative right ventricular function as a covariate instead of perioperative right failure, since we consider the latter an intermediate effect modifier. Mueller et al. corrected for age, gender, INTERMACS and preoperative use of extracorporeal life support.(15) Within our MCS database, patients on temporary support were not assigned to any of the INTERMACS classes. Therefore, in contrast to Schramm et al, who used a continuous INTERMACS score, we used a categorical variable for INTERMACS and temporary support, since patients on temporary support clinically differ from patients assigned with INTERMACS 1.(16) Interestingly, within the patient groups of Mueller et al. and Schramm et al. patients on HVAD support had a worse INTERMACS score at implantation than HM3 patients.(15)(16) This is in line with the current study. Apparently, patients assigned with INTERMACS 1 or patients on temporary support more often receive an HVAD. More years of experience with implanting HVAD and technical considerations could possibly explain the preference to implant HVAD in patients that urgently need MCS. In addition, there

was a preference to implant HVAD in patients that were on Centrimag temporary support. Lastly, our follow-up time was longer than the studies mentioned above giving a more reliable indication of long-term results between the two LVAD types.

The current study has some limitations. The most important limitations are the number of patients and the retrospective study design. Our current study and previously conducted retrospective studies all showed no significant difference in survival, but all in favour of HM3.(16)(15)(17) To confirm or disprove a significant difference in survival or specific complications between both devices, it is necessary to increase the number of PS-matched patients. A multi-centre approach including all centres that implant both HM3 and HVAD is recommended. Secondly, since the decision which device to use is not always completely random, we performed PS-matching, which entails some disadvantages. For a balanced comparison of survival and complication rates these unmatched patients were excluded from analysis, resulting in a smaller group of patients with a loss of precision and generalisability. (18) Additionally, after PS-matching, we assumed having two comparable groups. Nevertheless, not all covariates were unequivocally balanced. Even though the SMD was less than 10 % for all measured covariates, these small imbalances may sum up and may together cause a worse survival for patients on HVAD support. Therefore, we performed two sensitivity analyses, which both showed similar results to our primary analysis. Lastly, it is possible to create a greater imbalance for unknown or unmeasured covariates after PS-matching.(18) Even though we matched on an extensive set of possible confounders, we cannot rule out any imbalance on unknown or unmeasured covariates. A randomised controlled trial could solve this. In conclusion, we demonstrated that in a propensity matched cohort of patients with end-stage heart failure, although non-significant, survival was better for HM3 when compared to HVAD. A significantly higher incidence for haemorrhagic stroke and pump thrombosis was found for HVAD patients after PS-matching. To confirm or disprove a difference in survival, a multi-centre analysis including all centres that implant both HM3 and HVAD is recommended. Finally, a randomised controlled trial is needed to rule out any effect of unknown or unmeasured covariates.

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SUPPLEMENTARY MATERIAL

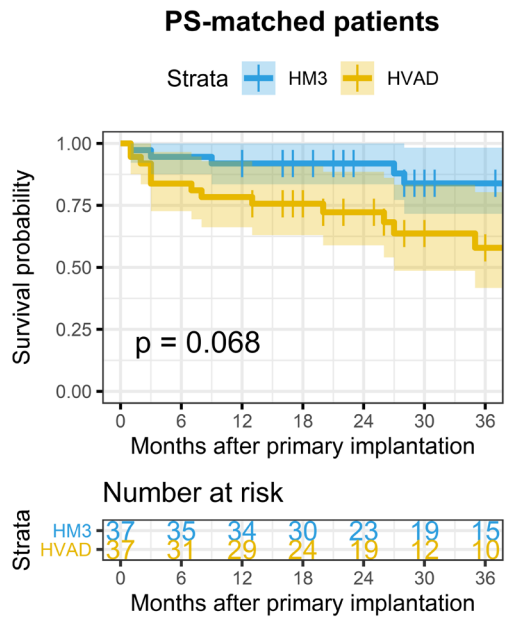
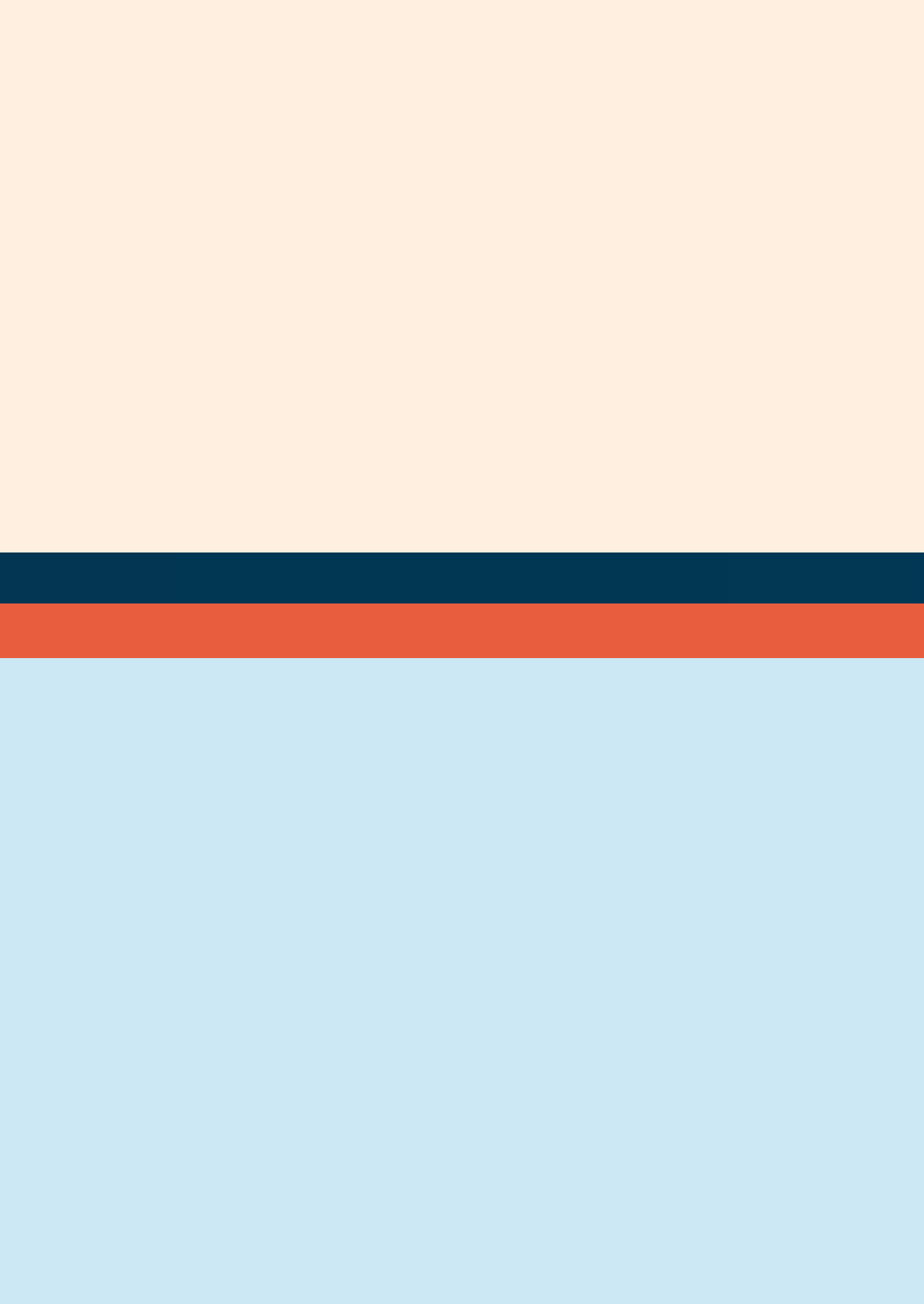


Figure S1: Kaplan Meier survival of all PS-matched patients without pre-operative support for sensitivity analysis. Censored for non-urgent heart transplantation and ongoing support at follow-up, with 95 % Confidence Interval.

Table S1: Baseline characteristics of PS-matched patients of the sensitivity analysis, using all patients without pre-operative temporary support.

Covariate	PS-matched patients (n=74)			
	HM3 (n=37)	HVAD (n=37)	p-value	SMD (%)
Age (years)	56.0 (13.0)	55.0 (19.0)	0.69	3.6
Sex (% male)	62.2	59.5	1.0	5.5
BSA (m ²)	1.90 (0.19)	1.91 (0.22)	0.74	-7.8
BMI (kg/m ²)	23.6 (3.8)	23.3 (4.6)	0.81	4.2
eGFR (ml/min/1.73m ²)	63.0 (39.0)	62.0 (31.0)	0.75	2.5
Bilirubin (μmol/L)	18.0 (29.0)	24.0 (18.0)	0.98	-17.6
RV function (1=bad,2=moderate,3=good)	2.27 (0.77)	2.30 (0.62)	0.87	-3.9
Diabetes Mellitus (%)	13.5	16.2	1.0	-7.6
Stroke in medical history (%)	2.7	0.0	1.0	23.6
Concomitant surgery (%)	24.3	21.6	1.0	6.4
Temporary support (%)	0.0	0.0	1.0	0.0
INTERMACS 1 (%)	10.8	8.1	1.0	9.2
INTERMACS 2-7 (%)	89.2	91.9	1.0	-9.2
Aetiology - dilated CMP (%)	64.9	64.9	1.0	0.0
Aetiology - ischemic CMP (%)	24.3	24.3	1.0	0.0
Months after start of study period (nr.)	89.0 (18.0)	85.0 (30.0)	0.52	8.0

BMI; Body Mass Index; BSA, Body Surface Area; CMP, cardiomyopathy; eGFR, Estimated Glomerular Filtration Rate; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support ;RV, right ventricle; SMD, standardized mean difference; PS, propensity score



CHAPTER 3

Towards identifying patients at risk: Multicentre comparison of Heartmate3 and HeartWare left ventricular assist devices

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ABSTRACT

Aims

Since the withdrawal of HeartWare (HVAD) from the global market, there is an ongoing discussion if and which patients require prophylactically exchange for a HeartMate3 (HM3). Therefore, it is important to study outcome differences between HVAD and HM3 patients. Since centres differ in patient selection and standard of care, we performed a propensity score (PS)-based study including centres that implanted both devices and aimed to identify which HVAD patients are at highest risk.

Methods

We performed an international multi-centre study (n=1021) including centres that implanted HVAD and HM3. PS-matching was performed using clinical variables and the implanting centre. Survival and complications were compared. As a sensitivity analysis, PS-adjusted cox-regression was performed. Landmark analysis with conditional survival >2 years was conducted to evaluate long-term survival differences. To identify which HVAD patients may benefit from a HM3 upgrade, cox-regression using pre-operative variables and their interaction with device type was performed.

Results

Survival was significantly better for HM3 patients ($p<0.01$) in 458 matched patients, with a median follow-up of 23 months. Within the matched cohort, HM3 patients had a median age of 58 and 83% were male, 80% of the HVAD patients were male, with a median age of 59. PS-adjusted cox regression confirmed a significantly better survival for HM3 patients when compared to HVAD, with a HR of 1.46 (95% CI 1.14-1.85, $p<0.01$). Pump thrombosis ($p<0.01$) and ischemic stroke ($p<0.01$) occurred less in HM3 patients. No difference was found for haemorrhagic stroke, right heart failure, driveline infection and major bleeding. Landmark-analysis confirmed a significant difference in conditional survival >2 years after implantation ($p=0.03$). None of the pre-operative variable interactions in the cox-regression were significant.

Conclusion

HM3 patients have a significantly better survival and a lower incidence of ischemic strokes and pump thrombosis than HVAD patients. This survival difference persisted after 2 years of implantation. Additional research using post-operative variables is warranted to identify which HVAD patients need an upgrade to HM3 or expedited transplantation.

INTRODUCTION

Since Medtronic's announcement in June 2021 on withdrawing HeartWare (HVAD, Medtronic, Minneapolis, MN, USA) from the global market, HVADs are not implanted anymore.⁽¹⁾ Approximately 4000 patients worldwide are still on HVAD support, of which many patients are on destination therapy or on a long waiting list for heart transplantation. It remains unclear which HVAD patients are at highest risk and elective device exchange is considered by some. It is therefore important to study differences in outcome between patients on HM3 and HVAD support. No randomized controlled trial has been performed comparing long-term outcomes of HM3 and HVAD. Both third generation devices were only compared with its predecessor the axial flow pump HMII.⁽²⁾⁽³⁾ Instead, retrospective comparisons were conducted. Several single centre studies were performed comparing HM3 and HVAD.⁽⁵⁾⁽⁶⁾⁽⁷⁾⁽⁸⁾⁽⁹⁾ Different outcomes were considered, but all studies showed a worse complication profile for HVAD. None of those studies showed a significant difference in survival for HM3 and HVAD. This could be caused by the low number of patients included, for which registry based studies with larger patient numbers could be the solution. Three registry-based studies were performed which showed a higher incidence of pump thrombosis and device malfunction in HVAD patients⁽¹⁰⁾, and fewer neurological events for patients on HM3 support.⁽¹⁰⁾⁽¹¹⁾ Potapov et al. found a non-significant difference in survival, whereas Pagani et al. showed a significant better one-year survival for patients on HM3 support.⁽¹⁰⁾⁽¹²⁾ Those general registry-based studies included a higher number of patients, but were limited by several factors such as missing data. More importantly, registry based studies usually include all centres, including centres that only implant one of the two devices. These centres may have a different standard-of-care and patient selection. Therefore, we propose a multi-centre propensity score based approach to compare survival in patients on HVAD and HM3 support. Moreover, we aimed to identify which HVAD patients are at greatest device-specific risk and HM3 upgrade or priority status on the waiting list for heart transplantation may be desired.

METHODS

This investigator-initiated study was designed as a multicentre retrospective study to compare outcome of patients on HVAD and HM3 support. The study was approved by the local ethics committee of the University Medical Centre Utrecht (UMCU), the Netherlands (METC: 20-195). The study was conducted in accordance with Good Clinical Practice and the 2002 Declarations of Helsinki and in compliance with the

ISHLT Ethics Statement. The need for informed consent was waived.

Inclusion criteria

All adult patients (n=1021) that were primarily implanted with a (sintered) HVAD or HM3 LVAD in one of the participating centres up until December 2019 were included for analysis. Participating centres: Heart and Diabetes Centre North Rhine-Westphalia (HDZ NRW, Bad Oeynhausen, Germany), Medical University of Vienna (MedUni Vienna, Vienna, Austria), University Medical Centre Utrecht (UMCU, Utrecht, The Netherlands) and Rabin Medical centre (RMC, Petah Tikva, Israel). Only centres that implanted both devices were asked to participate in the current multi-centre study, to eliminate the effect of the performance of the centre on the outcome. Patients that received an HVAD with non-sintered inflow cannula were excluded from analysis, as this was an important design change preventing tissue ingrowth encircling the external surface of the inflow cannula, which might result in emboli.⁽¹³⁾ Baseline characteristics and outcome data were collected by each centre using the electronic health record and their databases.

Endpoints

The follow-up of the study was until January 2020. The primary endpoint was death or urgent heart transplantation (HTx) during follow-up. Urgent HTx was defined as a transplantation that was done after a patient received a priority status on the waiting list. Patients were censored if receiving HTx after normal listing or for ongoing support at follow-up. Secondary endpoints were complications that were registered locally according to the definitions of Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS): major bleeding, ischemic stroke, haemorrhagic stroke, pump thrombosis, right heart failure or driveline infections.

Statistical analysis

Baseline characteristics of all unmatched patients were presented as median and interquartile range (IQR) for continuous variables, and categorical variables were presented as number or percentage. The Mann-Whitney U test was used for continuous variables and the Fisher's exact test was used for categorical variables. The percentage of missing data was displayed for all variables per centre. The Across method was used to create two comparable groups, combining multiple imputation and Propensity Score (PS) matching. At first, missing data of all variables necessary for PS-matching were imputed using multiple imputation (R-package: mice), resulting in five imputed datasets.⁽¹⁴⁾ The PS was calculated for every patient within each dataset. Subsequently, the average PS was calculated for each patient, which was then used to perform 1:1 matching using the nearest

neighbour method, with a calliper of 0.1 without replacement. The covariates that were used for PS-matching are reported in Table 1. Patients with pre-operative temporary support were considered as being a separate group from INTERMACS 1, and were classified as “pre-operative temporary support”. In addition to those clinical covariates, the implanting centre was used for PS-matching as well. Since HVADs were available prior to the introduction of HM3, the number of months after the start of the first implantation (February 2012) in the study cohort was considered for PS-matching, to ensure comparing survival of patients implanted within the same time period. Within the PS-matched groups, differences between both groups were tested using the Wilcoxon signed-rank test or McNemar test. The standardized mean difference (SMD) was calculated to assess the balance after matching. We assumed having two comparable groups if the SMD was < 10 % for all covariates.

The primary endpoint in both unmatched and matched patient groups was assessed using Kaplan-Meier analysis with 95% confidence intervals (CI), censoring for ongoing support at the end of the follow-up, LVAD explantation and non-urgent heart transplantation. Log-rank testing was performed to assess difference in survival between HVAD and HM3 patients. In addition, competing risk analysis was conducted to evaluate differences in the cumulative incidences of all secondary outcomes: major bleeding, ischemic and haemorrhagic stroke, pump thrombosis, right heart failure and driveline infection.

In addition to the primary analysis, two sensitivity analyses were performed. PS-adjusted cox regression was performed using the average PS in all imputed data-sets. The second sensitivity analysis that was performed was similar to the primary analysis. However, now patients were also censored for urgent heart transplantation, since this was usually done in previous literature.

To identify in which HVAD patients a HM3 upgrade should be considered, we first performed a landmark analysis, to check if the survival difference remains after two years after implantation. We included only patients that survived for more than two years for PS-matching (with a similar approach as the primary analysis). Lastly, to assess which HVAD patients are more at risk for the primary outcome (death and urgent HTx) when compared to HM3 patients, we performed a cox regression (complete case analysis) with the pre-operative variables age at primary implantation, sex, BSA, BMI, diabetes and stroke, in addition to device type and the interaction with the variables and device type. Since the proportional hazard assumption for sex was not met, we used a step function for the regression coefficient of sex, i.e. a time dependent coefficient, using three segments (<1 year, >1

& <2 years, >2 years after primary implantation). A p-value <0.05 was considered statistically significant. All statistical analyses were done using R software version 4.0.3.

RESULTS

Between 2011 and December 2019, 1021 adult patients were primarily implanted with HM3 (n=433) or sintered inflow cannula HVAD (n=588) in all four participating centres. Baseline characteristics of all patients are presented in Table 1, categorized per centre and device type. Within all centres, fewer females were implanted with HM3 and patients on HVAD support had a lower body surface area (BSA) and body mass index (BMI). In addition, age at implantation, the number of patients with ischemic cardiomyopathy, concomitant surgery, bilirubin, diabetes and the number of months after the first implantation differed significantly within each centre. The percentage of patients on temporary support before LVAD implantation differed across centres, but overall temporal support was more common in HVAD patients. Furthermore, patients on HVAD support more often had a stroke in their medical history. Table S2 shows the percentage of missing data for each covariate per centre. A minimum of 14 out of 16 covariates per patient were available.

Matching substantially reduced imbalance, as the SMD was smaller than 10% for all covariates (Figure 1). After PS-matching, 458 matched patients were included for analysis (Table 2). Patients were followed-up for a median of 23 months (IQR: 30 months). Both before and after PS-matching, survival was significantly better for HM3, with $p<0.01$ (Figure 2). The cumulative incidences of important complications were compared in PS-matched patients (Figure 3). Ischemic stroke ($p<0.01$) and pump thrombosis ($p<0.01$) more frequently occurred in patients on HVAD support. The incidences for major bleeding ($p=0.49$), haemorrhagic stroke ($p=0.11$), right heart failure ($p=0.92$) and driveline infections ($p=0.96$) did not differ significantly between HM3 and HVAD.

In total, in 2 patients the LVAD was explanted after a median of 6 months and 69 patients received a heart transplantation after a median of 18 months (IQR: 18 months). Table 3 shows the number of patients with urgent and non-urgent HTx, the number of deaths and the number of LVAD explants. Patients on HVAD support more often received an urgent HTx and a higher percentage of HVAD patients died during follow-up.

Table 1: Baseline characteristics of all patients (before PS-matching) categorized by device type and centre.

Covariate	HDZ NRW (n=560)		MedUni Vienna (n=218)		UMCU (n=165)		RMC (n=78)		p-value
	HM3 (n=194)	HVAD (n=366)	HM3 (n=103)	HVAD (n=115)	HM3 (n=80)	HVAD (n=85)	HM3 (n=56)	HVAD (n=22)	
Sex (% male)	88.1	82.2	89.3	81.7	65.0	64.7	85.7	81.8	<0.01
Age (years)	60 [53-66]	58 [50-63]	64 [56-68]	60 [52-66]	56 [47-61]	58.0 [49-62]	61.0 [55-66]	63 [58-69]	<0.01
Ischemic CMP (%)	50.5	48.8	66.0	60.0	23.8	38.8	64.3	63.6	<0.01
BMI (kg/m ²)	25.7 [24-30]	25.3 [23-28]	27.2 [24-31]	25.4 [23-29]	24.7 [22-28]	24.0 [22-27]	26.1 [23-29]	23.5 [21-26]	<0.01
BSA (m ²)	2.0 [1.9-2.2]	2.0 [1.8-2.1]	2.0 [1.9-2.2]	1.9 [1.8-2.1]	2.0 [1.8-2.1]	1.9 [1.8-2.1]	1.9 [1.8-2.0]	1.8 [1.6-1.9]	<0.01
eGFR (ml/min/1.73m ²)	53 [36-78]	56 [35-84]	51 [35-90]	57 [38-90]	61 [43-83]	63 [47-90]	65 [46-86]	59 [39-90]	0.07
Bilirubin (μmol/L)	22 [13-33]	24 [15-38]	13 [9-21]	22 [12-39]	19 [12-37]	19 [12-30]	15 [10-20]	23 [12-30]	<0.01
RV-function (1=poor, 2=moderate, 3=reasonable, 4=good)	3 [2-4]	3 [2-4]	4 [2-4]	4 [2-4]	3 [2-3]	2 [2-3]	3 [3-4]	3 [2-3]	<0.01
Diabetes (%)	35.0	30.1	33.0	26.1	15.0	11.8	55.4	50.0	<0.01
Stroke (%)	11.7	14.4	7.8	9.6	3.8	8.2	8.9	13.6	0.14
Concomitant surgery (%)	34.0	30.6	23.3	16.5	23.8	29.4	5.4	9.1	<0.01
Pre-operative support (%)	18.0	36.9	9.7	31.3	12.5	27.1	5.4	9.1	<0.01
INTERMACS 1 (%)	4.6	9.3	10.7	7.8	6.2	4.7	3.6	0.0	0.24
INTERMACS 2 (%)	36.6	27.6	21.4	15.7	32.5	30.6	10.1	22.7	<0.01
INTERMACS 3-7 (%)	40.7	26.2	58.3	45.2	48.8	37.6	80.4	68.2	<0.01
Number of months	75 [63-78]	42 [29-58]	69 [51-83]	38 [18-61]	75 [61-85]	62 [43-79]	73 [61-82]	32 [21-46]	<0.01

HDZ NRW; Heart and Diabetes Centre North Rhine-Westphalia, MedUni Vienna; Medical University of Vienna, UMCU; University Medical Centre Utrecht, RMC; Rabin Medical centre, CMP; cardiomyopathy, BMI; body mass index, BSA; body surface area, eGFR; estimated glomerular filtration rate, RV; right ventricle, INTERMACS; Interagency Registry for Mechanically Assisted Circulatory Support



Figure 1: Love plot showing the standardized mean difference (SMD) before and after PS-matching. RMC, Rabin Medical Centre; UMCU, University Medical Centre Utrecht; MedUni Vienna, Medical University of Vienna; HDZ NRW, Heart and Diabetes Centre North Rhine-Westphalia; BMI, body mass index; BSA, body surface area; eGFR, estimated glomerular filtration rate; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; RV, right ventricular

The PS-adjusted cox regression also showed a significantly better survival for HM3 when compared to HVAD, with a HR of 1.46 (95% confidence interval 1.14-1.85) with $p < 0.01$. The sensitivity analysis where patients were censored for urgent heart transplantation confirmed a significant worse survival for patients on HVAD support, with $p < 0.01$.

The landmark analysis confirmed a significant better conditional survival in patients that were on HM3 support for more than two years ($p = 0.03$). Lastly, we analysed which variables are predictive for a worse survival for HVAD patients compared to patients on HM3 support for a subset of variables. Table S2 reports the hazard ratio's and p-values of all used variables and interactions. None of the interactions were significant.

Table 2: Baseline characteristics before and after PS-matching.

Covariate	Unmatched patients		p-value	PS-matched patients		p-value
	HM3 (n=433)	HVAD (n=588)		HM3 (n=229)	HVAD (n=229)	
Centre (%)						
HDZ NRW	44.8	62.2	<0.01	51.1	47.6	0.90
MedUni Vienna	23.8	19.6		22.3	24.0	
UMCU	18.5	14.5		21.8	23.1	
RMC	12.9	3.7		22.3	24.0	
Sex (% male)	83.8	79.9	0.10	82.5	79.9	0.55
Age (years)	60 [53-66]	58 [50-64]	<0.01	58 [51-65]	59 [52-64]	0.28
Ischemic CMP (%)	51.0	49.8	0.75	51.5	50.7	0.93
BMI (kg/m²)	25.7 [23-29]	25.0 [23-28]	<0.01	25.5 [23-29]	25.6 [23-29]	0.91
BSA (m²)	2.00 [1.8-2.2]	2.0 [1.8-2.1]	<0.01	2.0 [1.8-2.1]	2.0 [1.8-2.1]	0.36
eGFR (ml/min/1.73m²)	55.6 [39-83]	57 [37-90]	0.71	59 [39-88]	58 [39-87]	0.66
Bilirubin (μmol/L)	18 [11-30]	23 [14-37]	<0.01	20 [12-34]	21 [12-32]	0.74
RV function (1=poor, 2=moderate, 3=reasonable, 4=good)	3 [2-4]	3 [2-4]	0.03	3 [2-4]	3 [2-4]	0.32
Diabetes (%)	33.4	27.4	0.05	29.6	28.9	0.95
Stroke (%)	8.8	12.5	0.08	11.6	10.2	0.73
Concomitant surgery (%)	25.9	26.9	0.77	26.2	28.8	0.60
Pre-operative support (%)	13.4	33.3	<0.01	20.1	17.9	0.63
INTERMACS 1 (%)	6.2	8.2	0.30	7.9	7.9	1.0
INTERMACS 2 (%)	28.9	25.5	0.26	27.9	31.4	0.47
INTERMACS 3-7 (%)	51.5	33.2	<0.01	44.1	42.8	0.85
Number of months (nr.)	74 [60-85]	43 [29-62]	<0.01	64 [53-79]	67 [51-80]	0.73

HDZ NRW; Heart and Diabetes Centre North Rhine-Westphalia, MedUni Vienna; Medical University of Vienna, UMCU; University Medical Centre Utrecht, RMC; Rabin Medical centre, CMP; cardiomyopathy. BMI; body mass index, BSA; body surface area, eGFR; estimated glomerular filtration rate, RV; right ventricle, INTERMACS; Interagency Registry for Mechanically Assisted Circulatory Support

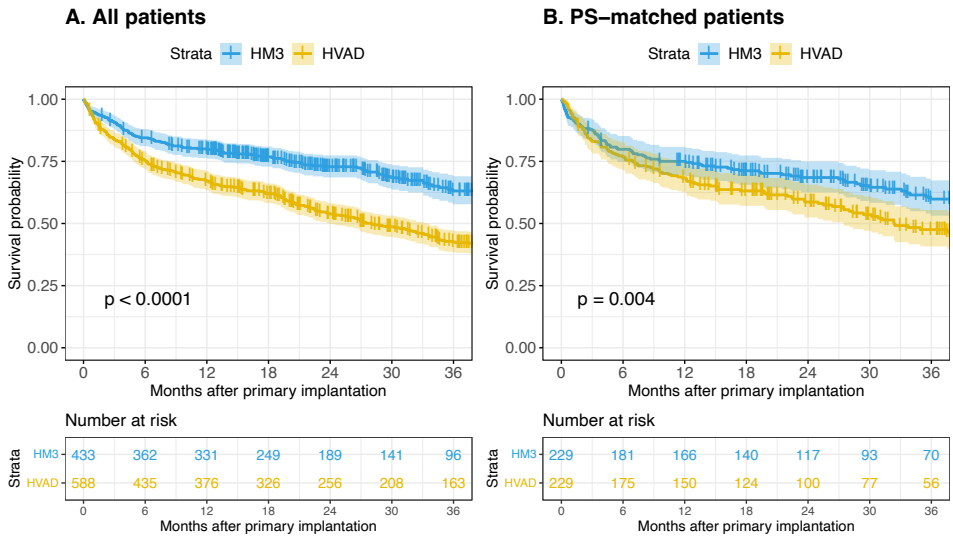


Figure 2: Kaplan-Meier survival of (A) All patients and (B) propensity score matched patients, censoring for non-urgent transplantation and ongoing support at follow-up.

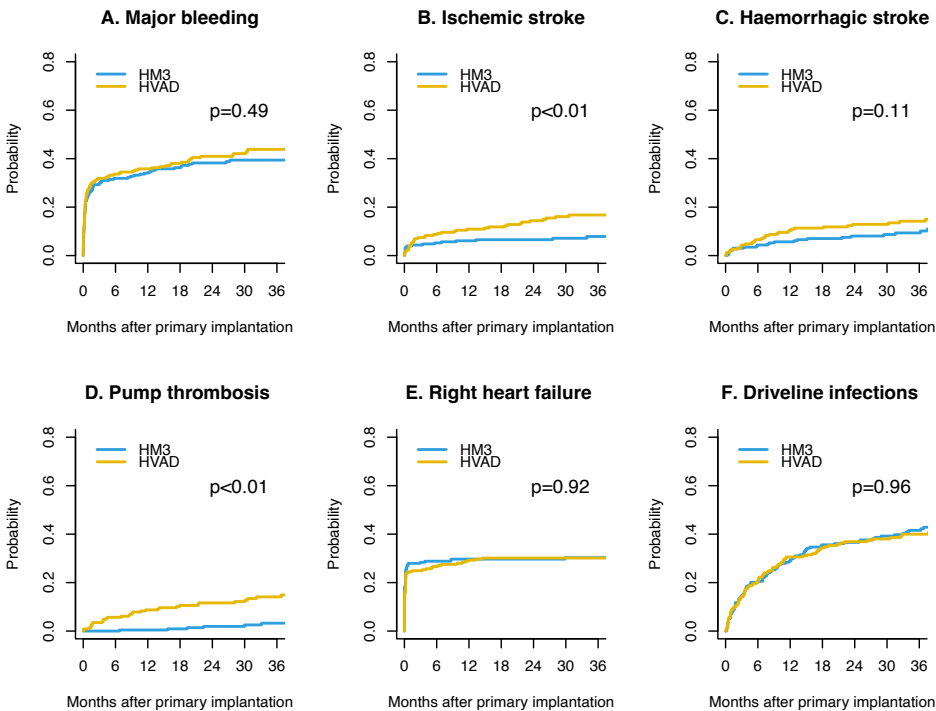


Figure 3: Cumulative incidence of propensity-score matched patients of complications: (A) Major Bleeding. (B) Ischemic stroke. (C) Haemorrhagic stroke. (D) Pump thrombosis. (E) Right heart failure. (F) Driveline infections. Death, heart transplantation and ongoing support were considered as a competing risk.

Table 3: Number of patients that were explanted, (non-urgent) HTx and causes of death in PS-matched groups.

		PS-matched patients (n=458)	
		HVAD (n=229)	HM3 (n=229)
Explant n(%)		1 (0.4)	1 (0.4)
HTx n(%)	Non-urgent	18 (7.9)	20 (8.7)
	Urgent	18 (7.9)	13 (5.7)
Death n(%)		111 (48.5)	82 (35.8)
Cause of death n(%)	Device malfunction	0 (0.0)	1 (0.4)
	Infection	9 (3.9)	6 (2.6)
	Stroke	21 (9.2)	13 (5.7)
	Multi-organ failure	49 (19.3)	43 (18.8)
	RV failure	2 (1.7)	1 (0.9)
	Other	17 (7.4)	14 (6.1)
	Unknown	10 (4.3)	3 (1.3)

HTx; heart transplantation, RV; right ventricle, PS; propensity score

DISCUSSION

In this multi-centre retrospective study, we compared survival and incidence of major complications in patients on HM3 and HVAD support (graphical abstract). After PS-matching, patients on HM3 support showed a significantly better survival, with a lower incidence of ischemic strokes and pump thrombosis, whereas major bleeding, haemorrhagic stroke, right heart failure and driveline infections did not differ significantly. Also, in patients who survived for more than two years, survival was significantly better in HM3 patients. We were not able to identify which HVAD patients are more at risk compared to HM3 patients using a subset of pre-operative variables.

So far, four single centre retrospective studies and three registry-based studies compared the outcome of patients on HM3 and HVAD support (5)(6)(7)(8)(10)(11). Different methods were used, with PS-matching being the most used method. In addition to survival, different complication types were compared in HM3 and HVAD patients. Potapov et al. studied the combined incidence of pump thrombosis and outflow graft twisting, which did not differ significantly between both groups(10). In line with the current study, two studies found a significantly higher incidence of pump thrombosis for patients on HVAD support, whereas Schramm et al. showed no significant difference between both groups.(5)(7)(8) Two out of five studies reported a significant higher incidence of stroke for patients on HVAD support.(5)(6)(8)(10)(11) Two single centre studies and a registry-based study observed a significantly higher incidence of haemorrhagic stroke in HVAD patients(6)(7)(10),

but not of ischemic stroke in contrast to our study. Furthermore, we found fewer thrombotic events in HM3 patients, potentially due to the different pump designs. Both devices are third generation devices with a continuous and centrifugal blood flow pattern, but the HM3 has a fully magnetically levitated rotor, a relatively wide rotor housing and an artificial pulse.(15)

We demonstrated no difference in right heart failure and major bleeding incidences, which is in line with previous research.(7)(10) Driveline infections were diagnosed significantly more often in patients on HVAD support in the study of Schramm et al., whereas Potapov et al. found a trend towards a higher incidence of infections for HM3 patients.(5)(6) These variations across single centres emphasize the importance of considering the implanting centre as covariate when combining patient outcomes, since these differences may be caused by centre specific effects in addition to a dissimilar patient population. Although differences in complications existed, all retrospective studies confirmed a less favourable complication profile for patients on HVAD support compared to HM3.(5)(6)(7)(8)(10)(11)

Itzhaki Ben Zadok et al., observed a better survival free from stroke or device change in HM3 supported patients.(8) In addition, Pagani et al. observed a significant better 1-year survival in patients on HM3 support when compared to patients on HVAD support.(12) Although in several studies insignificant, the Kaplan-Meier survival curves were less favourable for HVAD patients in all studies. An important difference in the current and previous studies, is that next to death we also considered urgent heart transplantation as the primary endpoint. Without the urgent heart transplantation, the patient would probably not have survived and we therefore consider this as adverse outcome in addition to death. Since in literature patients that receive a heart transplantation, including patients that were listed as high urgent, are usually censored, we performed a sensitivity analysis. This confirmed our primary results.

In comparison to previous studies, this study is unique in also considering the implanting centre as a covariate for PS-matching. We showed that patients on HM3 and HVAD support differed significantly on several covariates across the four included centres. Besides different patient characteristics, probably due to a different patient selection, it is likely that there are centre specific effects that affect the results, as all centres have a different standard-of-care. For example, anti-thrombotic and anti-coagulation protocols may differ among centres. Moreover, the hospital and surgeon volume may differ. Cowger et al. demonstrated that higher volume LVAD centres have better survival rates.(16) In addition, the number of implantations per surgeon was correlated with reduced mortality.(17) In addition

to measurable and known differences between centres, it is likely that there are other unknown covariates related to the implanting centre. To reduce this centre bias as much as possible, we used centre as a covariate to match on.

Clinicians now face the question if HVAD patients may benefit from a HM3 exchange. Cogswell et al. studied patients undergoing HVAD to HM3 exchange and HVAD to HVAD exchange.(18) The results need to be interpreted carefully, as the subgroup undergoing HVAD to HM3 exchange for a specific cause were generally sicker than patients who would be undergoing an elective device exchange. Even though device exchange may lead to better clinical outcomes on a population level, the replacement surgery entails peri-operative risks such as bleeding, right heart failure or stroke. (19) The benefit of the device exchange should outweigh those initial post-operative risks. Both the current study and previous research showed a worse patient profile for patients before HVAD implantation. To determine which HVAD patients are more at risk, we performed a cox regression with a subset of pre-operative variables and its interaction with device type. None of the interaction terms were significant. Therefore, we conclude that the selection of patients who will benefit from a HM3 upgrade, cannot be made based on solely pre-operative variables. Post-operative information should be included to identify HVAD patients at high but reducible risk.

Our study has several limitations. First, we have some missing data, but a minimum of 14 out of 16 covariates were complete. Multiple imputation was used to be able to include all patients for matching. Moreover, almost half of the patients were implanted in one of the four centres, which may affect generalizability. However, we do not expect this to heavily impact generalizability of the study results, as the difference in primary outcome between HM3 and HVAD was consistent across the four centres and the centre effect was minimized by PS-matching. Another limitation of the study is the observational nature of the study. Even though imbalance was drastically reduced due to PS-matching, the risk of unknown or unmeasured covariates that are more imbalanced after matching cannot be excluded.(20) We minimized centre specific effects by including the centre as a covariate for PS-matching. Sensitivity analysis was performed using PS-adjusted cox regression, which showed a significant better survival for HM3, confirming our primary analysis. The current study was not designed to advise about which patients on HVAD support need elective device exchange, but can inform HVAD patients and their treating physicians in their shared-decision making. Ongoing research is still warranted to identify those at highest risk for complications or death within the HVAD group. Although randomized controlled trials are needed to confirm retrospective studies, registries have shown to be valuable resources for outcome research. With further enriched registries, a continuous learning healthcare

system can be developed, allowing early detection of a possible difference in device performance. The current proposed method provides guidance for the design of future registries and research (graphical abstract), to enable comparison of outcome in short cycles or even real time.

We demonstrated that in a multi-centre PS-matched cohort, patients on HM3 support have a significantly better survival than patients on HVAD support. In addition, a significantly higher incidence of ischemic strokes and pump thrombosis was found in patients on HVAD support. Future research is warranted to pinpoint which HVAD patients are at highest risk. The current proposed method provides guidance for the design of future registries and research, to enable comparison of outcome in short cycles or even real time.

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SUPPLEMENTARY MATERIAL

Table S1: Percentage of missing data categorized by device type

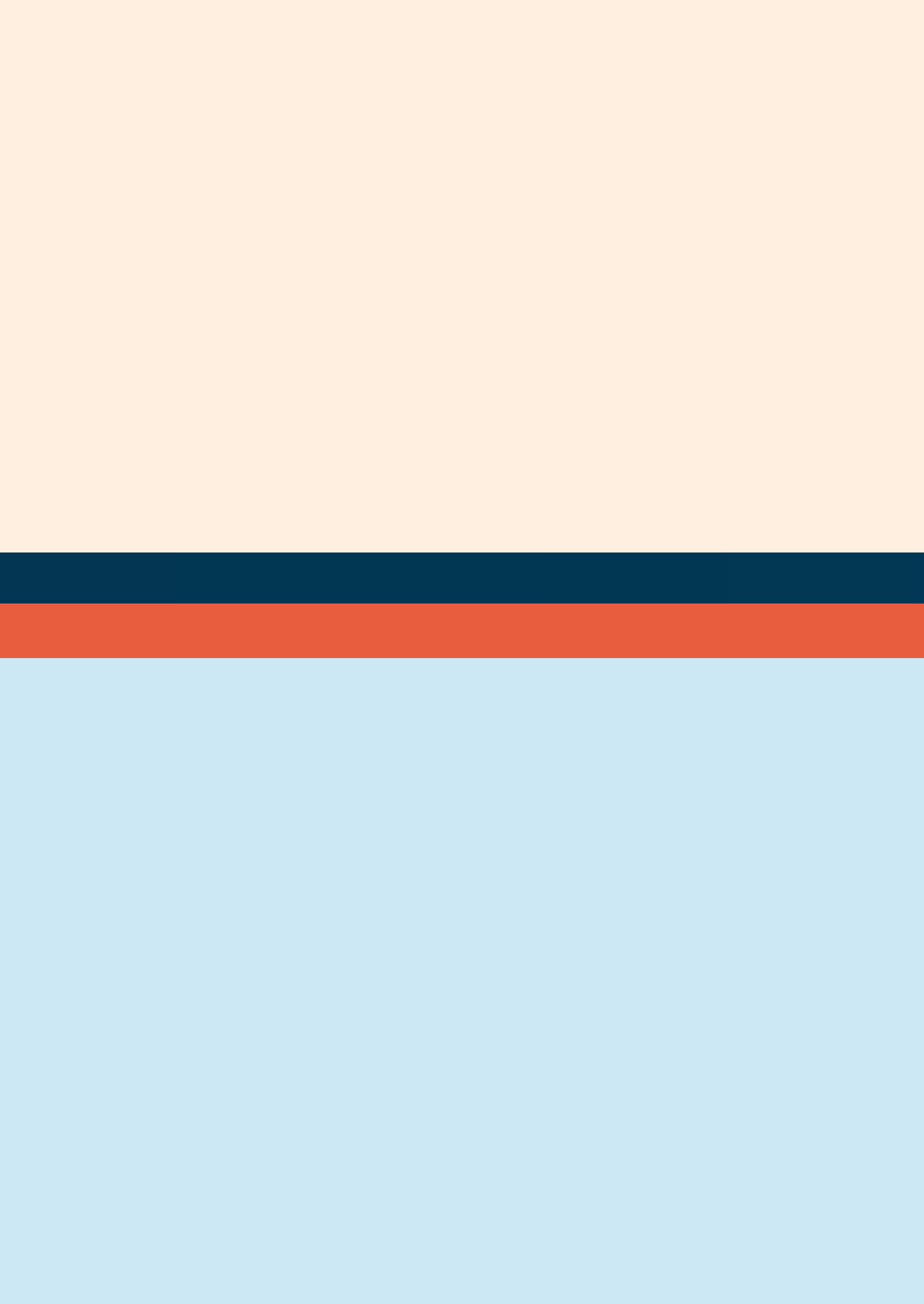
Covariate	HeartMate 3 (n=433)	HeartWare (n=588)
Sex	0	0
Age	0	0
Ischemic CMP	0	0
BMI	0	0
BSA	0	0
eGFR	0.2	0
Bilirubin	0.5	0.3
RV function	3.0	15.1
Diabetes	3.2	1.9
Stroke	3.2	0.9
Concomitant surgery	0	0
Pre-operative support	0	0
INTERMACS	0	0
Number of months	0	0

CMP; cardiomyopathy, BMI; body mass index, BSA; body surface area, eGFR; estimated glomerular filtration rate, RV; right ventricle, INTERMACS; Interagency Registry for Mechanically Assisted Circulatory Support

Table S2: Hazard ratio's of the static pre-operative variables and its interaction with device type, with a time dependent coefficient for sex to fulfill the PH-assumption.

Variable	Hazard Ratio [95% confidence interfals]	p-value
Device type (1=HVAD, 0=HM3)	0.92 [0.08-10.29]	0.94
Age (years)	1.02 [0.98-1.04]	0.05
Ischemic cardiomyopathy	1.03 [0.72-1.48]	0.86
BSA (m ²)	0.56 [0.15-2.08]	0.39
BMI (kg/m ²)	1.03 [0.97-1.09]	0.35
Diabetes	1.08 [0.74-1.58]	0.70
Stroke	1.48 [0.68-0.86]	0.16
Male sex (<1 year after implantation)	1.29 [0.71-2.37]	0.40
Male sex (>1 and <2 years after implantation)	2.24 [0.91-5.48]	0.08
Male sex (>2 years after implantation)	1.31 [0.59-2.90]	0.50
Interaction with Device type (1=HVAD, 0=HM3)		
Age (years)	1.00 [0.98-1.02]	0.92
Ischemic cardiomyopathy	0.91 [0.60-1.37]	0.64
BSA (m ²)	2.53 [0.53-11.98]	0.24
BMI (kg/m ²)	0.97 [1.03-0.91]	0.39
Diabetes	0.96 [0.62-1.51]	0.87
Stroke	0.64 [0.34-1.22]	0.18
Male sex (<1 year after implantation)	0.68 [0.35-1.35]	0.27
Male sex (>1 and <2 years after implantation)	0.82 [0.38-1.78]	0.61
Male sex (>2 years after implantation)	0.99 [0.46-2.14]	0.97

HVAD; HeartWare, HM3; HeartMate3,CMP; cardiomyopathy, BMI; body mass index, BSA; body surface area



CHAPTER 4

Survival after HeartMate 3 left ventricular assist device implantation: real-world data from Europe

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ABSTRACT

Aims

Survival of patients on left ventricular assist device (LVAD) support has improved over the last decades. Among available LVADs, HeartMate3 (HM3) is the most commonly used device. The aim of this study is to present the real world long term survival (5-years) of patients on HM3 implanted in three high volume LVAD centres in Europe.

Methods

All patients primarily implanted with HM3 between December 2015 and December 2019 in three high volume European LVAD centres were included, with a follow-up until September 2022. The primary endpoint was survival and the secondary endpoint was survival free from stroke and pump replacement. Both endpoints were analyzed using Kaplan-Meier analysis, where patients were censored for explantation and heart transplantation.

Results

377 patients on HM3 support were included for analysis, with a median follow-up time of 4.4 years (IQR: 2.2 years). 83.6% were male and patients had a median age of 60 at the time of implantation. 144 patients died during follow-up, 7 LVADs were explanted and 75 patients were transplanted. The 5-year survival was 54%. 62 patients suffered from a stroke and 8 patients needed pump replacement surgery. Survival free from stroke and pump replacement was 48% at 5 years.

Conclusions

Real-world data from patients on HeartMate 3 support implanted in Europe confirm the promising findings of the MOMENTUM 3 trial, demonstrating the vital role of LVAD therapy in contemporary treatment of advanced heart failure.

BACKGROUND

Survival of end-stage heart failure patients on left ventricular assist device (LVAD) support continuously increases.(1) Nowadays, the HeartMate 3 (HM3, Abbott, Chicago, IL, USA) LVAD is most commonly implanted. Mehra et al. showed a 5-years survival of 58.4 % in HM3 patients included in the extended-phase analysis of the MOMENTUM 3 trial. Patients included in this trial were treated in the United States (US).(2) LVAD patient selection and donor heart availability differ between US and Europe.(3) In addition, outcomes in clinical trials may differ from those in common practice due to patient selection criteria and intensity of follow-up.

AIM

The aim of this study was to present the real world long term survival data of HM3 patients implanted in three large centers in Europe.

METHODS

A cohort study was performed that was approved by the local ethics committee of the University Medical Centre Utrecht (UMCU), the Netherlands (METC: 20-195). The need for informed consent was waived. The study was conducted in accordance with Good Clinical Practice and the 2002 Declarations of Helsinki. Patients primarily implanted with HM3 between December 2015 and December 2019 in three European participating centers were included for analysis. Participating centers were: University Medical Centre Utrecht (UMCU, the Netherlands), Heart and Diabetes Centre North Rhine-Westphalia (HDZ NRW, Bad Oeynhausen, Germany) and the Medical University of Vienna (MedUni Vienna, Austria).(4) Baseline characteristics and survival data were retrieved from the electronic health record and local databases. Patients were followed-up until September 2022. The primary and secondary endpoints were survival and survival free from stroke and pump replacement, respectively. Kaplan-Meier analysis was used to evaluate the endpoints, censoring for LVAD explantation, heart transplantation or ongoing support at the end of the follow-up. Stroke (including both haemorrhagic and ischemic stroke) was defined using the definition of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS).(5) Baseline characteristics were presented as mean and standard deviation (SD) or median and interquartile range (IQR). All statistical analyses were done using R software version 4.0.3.

RESULTS

In total, 377 patients were included for analysis. The median time from primary implantation to the end of the follow-up was 4.4 years (IQR 2.2 years). Patients had a median age of 60 at implantation and 83.6% were male (table 1). Baseline characteristics were complete for all patients except for diabetes, stroke in medical history (i.e. before LVAD) and eGFR, with 3.7%, 3.7% and 8.2% missing data, respectively. 144 patients (38%) died, 7 patients (2%) were explanted and 75 patients (20%) were transplanted during follow-up. 8 patients underwent replacement surgery after a median of 419 days (IQR: 892 days). 62 patients suffered from a stroke after a median of 159 days (IQR: 436 days). Figure 1 shows survival of all HM3 patients, with a 5-year survival of 54%. Survival free from stroke and pump replacement was 48% at 5 years.

Table 1: Baseline demographics of all primary HeartMate3 implantations in all three included centers compared to MOMENTUM characteristics.

Variable	Total (n=377)	UMCU (n=80)	HDZ NRW (n=194)	MedUni Vienna (n=103)	MOMENTUM 3 (n=515)
Age, median (IQR), y	60 (52-66)	56 (47-61)	60 (53-66)	64 (56-68)	62 (52-68)
Sex (% male)	315 (83.6)	52 (65.0)	171 (88.1)	92 (89.3)	410 (79.6)
BSA, mean (SD), m ²	2.03 (0.21)	1.98 (0.23)	2.05 (0.20)	2.03 (0.20)	2.07 (0.27)
BMI, median (IQR), kg/m ²	25.7 (23.1-29.4)	24.7 (21.6-27.8)	25.7 (23.6-29.6)	27.2 (24.2-31.2)	28.4 (24.6-33.0)
Ischemic CMP (%)	185 (49.1)	19 (23.8)	98 (50.5)	68 (66.0)	216 (41.9)
Diabetes (%)	109 (30.0)	12 (15.0)	63 (35.0)	34 (33.0)	233 (45.2)
Stroke (%)	32 (8.8)	3 (3.8)	21 (11.7)	8 (7.8)	50 (9.7)
eGFR (ml/min/1.73m ²)	51 (36-70)	61 (43-83)	53 (36-78)	41 (32-53)	58 (43-75)
INTERMACS (%)	1-2	198 (52.5)	41 (51.2)	114 (58.8)	43 (41.7)
	3	98 (26.0)	21 (26.2)	56 (28.9)	21 (20.4)
	4-7	81 (21.5)	18 (22.5)	24 (12.4)	39 (37.9)
IABP (%)	8 (2.1)	1 (1.2)	6 (3.1)	1 (1.0)	64 (12.4)

UMCU; University Medical Centre Utrecht, HDZ NRW; Heart and Diabetes Centre North Rhine-Westphalia, MedUni Vienna; Medical University of Vienna, BSA; body surface area, BMI; body mass index, CMP; cardiomyopathy, eGFR; estimated glomerular filtration rate, INTERMACS; Interagency Registry for Mechanically Assisted Circulatory Support

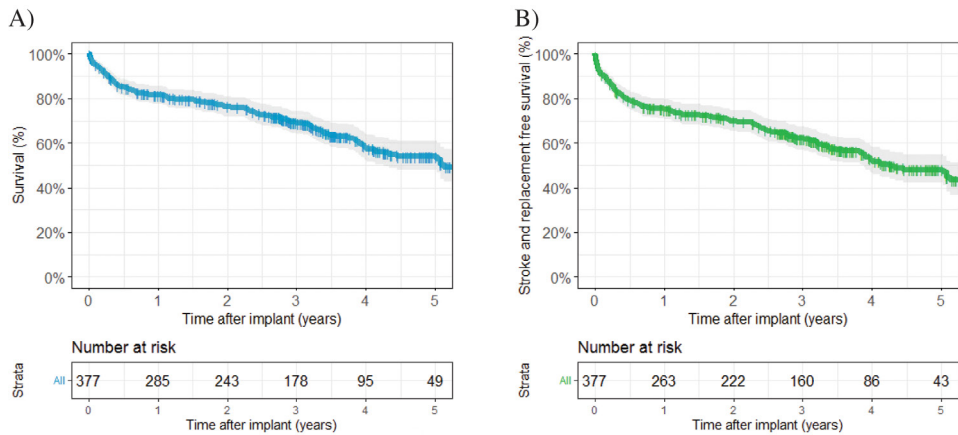


Figure 1: A: Long-term survival of patients on HeartMate3 left ventricular assist device support. B: Survival free from stroke and pump replacement.

CONCLUSIONS

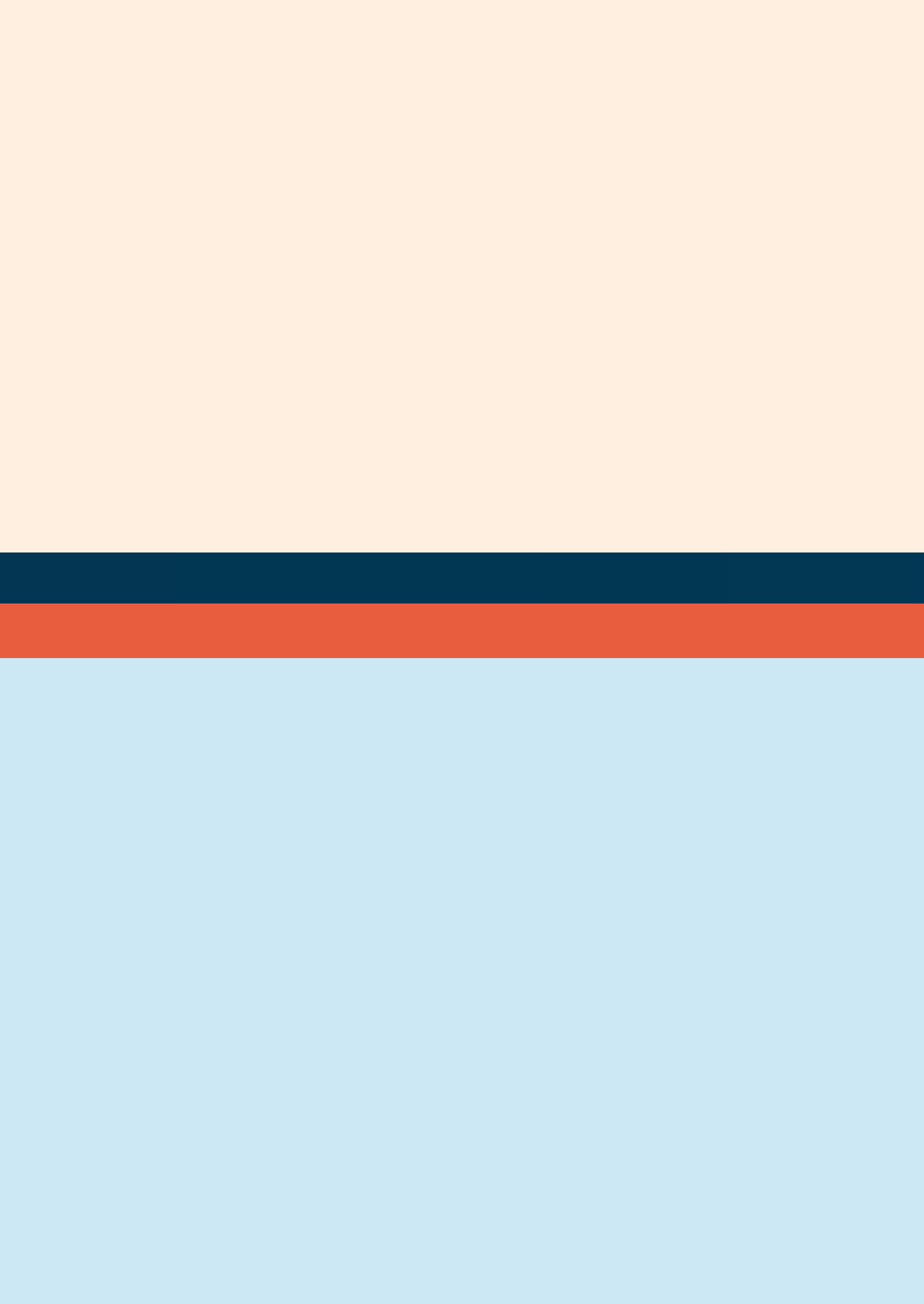
HM3 is increasingly used in end-stage HF patients with a 5-year survival of 54.0% in three large centers across Europe. To put this in perspective, patients included in the extended phase of the MOMENTUM 3 trial had a survival of 58.4% at 5 years.(6) Moreover, they showed a survival free of debilitating stroke or pump replacement of 54.0% at 5 years, which is in line with our results. Although we used a slightly stricter definition in our database(s) and included all hemorrhagic stroke and ischemic stroke, whereas the extended Momentum 3 study used “disabling stroke”. Nevertheless the results are similar, compatible with the very low rate of disabling stroke seen in both studies. Patients in the MOMENTUM cohort and our cohort differ in baseline characteristics, due to a different patient selection in the US and Europe. Our cohort included patients with a lower BMI and lower prevalence of diabetes, a higher number of patients with ischemic cardiomyopathy, and more kidney dysfunction. In addition, patients more often were classified as INTERMACS 1 or 2 classification before implantation compared to patients included in the MOMENTUM 3 trial. LVAD patients awaiting a donor heart in the US have a shorter median duration of LVAD support and a higher frequency of comorbid conditions when compared to patients in Europe.(3) Despite differences in patient selection and donor heart availability, long-term survival after HM3 implantation is comparable. In addition, the ELEVATE registry showed similarly beneficial outcomes in a cohort of 463 patients from 26 centres in Europe and the Middle East, although the cohort was slightly different in some baseline characteristics.

(7)(8) For example, they included more male patients, less patients classified as INTERMACS 1 or 2 and patients were slightly younger when compared to our cohort, including 377 implanted in three large volume centres.

In conclusion, real-world data from patients on HeartMate 3 support implanted in Europe confirm the promising findings of the MOMENTUM 3 trial, demonstrating the vital role of LVAD therapy in contemporary treatment of advanced heart failure.

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CHAPTER 5

Incidence and risk factors of late right heart failure in chronic mechanical circulatory support

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ABSTRACT

Background

Late right heart failure (LRHF) is a common complication during long-term left ventricular assist device (LVAD) support. We aimed to identify risk factors for LRHF after LVAD implantation.

Methods

Patients undergoing primary LVAD implantation between 2006-2019 and surviving the perioperative period were included for this study (n=261). Univariate Cox proportional hazards analysis was used to assess the association of clinical covariates and LRHF, stratified for device type. Variables with $p < 0.10$ entered the multivariable model. In a subset of patients with complete echocardiography or right catheterization data this multivariable model was extended. Post-operative cardiopulmonary exercise test data were compared in patients with and without LRHF.

Results

19% patients suffered from LRHF after a median of 12 months, of which 67% required hospitalization. A history of atrial fibrillation (AF) (HR: 2.06 [1.08-3.93], $p = 0.029$), a higher pre-operative body mass index (BMI) (HR: 1.07 [1.01-1.13], $p = 0.023$) and intensive care unit (ICU) duration (HR: 1.03 [1.00-1.06], $p = 0.025$) were independent predictors of LRHF in the multivariable model. A significant relation between the severity of tricuspid regurgitation (TR) and LRHF (HR: 1.91 [1.13-3.21], $p = 0.016$) was found in patients with echocardiographic data. Patients with LRHF demonstrated a lower maximal workload and peak VO_2 at 6 months postoperatively.

Conclusion

A history of AF, BMI and longer ICU stay may help identify patients at high risk for LRHF. Severity of TR was significantly related to LRHF in a subset of patients.

INTRODUCTION

Mechanical circulatory support (MCS) has been established as a valuable treatment option for patients with advanced heart failure.(1) Left ventricular assist device (LVAD) therapy is characterized by a good survival (58% at 5 years)(2)(3)(4), improved quality of life and exercise capacity.(5) Despite this favourable outcome, adverse events in patients on LVAD support, including infection, bleeding, thrombosis, arrhythmias and right heart failure (RHF), each may occur in up to 40% of patients. (6)(7) As a result of the increased use of MCS and the longer duration of support per patient, more information on adverse events and long term management is obtained. Right heart failure after LVAD implantation is a major clinical problem, that may occur early after implantation, but also later in the course. Early perioperative RHF is encountered in approximately 10% of the patients and is associated with impaired survival and major adverse events.(6)(7)(8) Several risk scores were developed for the prediction of early RHF, including the EUROMACS-RHF score, which is based on data derived from the European Registry for Patients with Mechanical Circulatory Support (EUROMACS) database.(9)(10)(11) Despite these risk scores, early RHF remains difficult to predict in daily clinical practice.(6)(9)(11) Late RHF after MCS however, was studied to a lesser extent. Apart from the need for hospitalization, late RHF has been associated with a decreased functional capacity (6-minute walk distance) and a reduced quality of life.(12) In addition, the occurrence of late RHF might increase the need for urgent heart transplantation. Furthermore, the definition of late RHF used in current literature is not uniform. (11)(13)(14) Recently, the MCS academic research consortium updated the definition of all adverse events related to MCS.(15) Late RHF was defined as the need for implantation of an RVAD > 30 days following LVAD implantation or the need for hospitalization > 30days post-implant with the requirement of intravenous diuretics or inotropes for at least 72 hours in association with clinical signs of right sided congestion or hemodynamic compromise (e.g. renal failure, elevated lactate). (15) Two studies on this subject defined late RHF as the need for hospitalization after indexed LVAD implant hospitalization and either the need for inotropes or the need for intensified diuretic therapy, inotropic support and right ventricular assist device (RVAD) implantation. (12)(14)(16)

The above mentioned definitions of RHF are heavily based on hospitalization of the patient, while an important argument for LVAD therapy actually is to keep the patient with severe HF out of hospital. Furthermore, the initial treatment of late RHF consists mainly of increasing oral dosages of diuretics. So relying only on hospitalization for the definition of late RHF negates those patients which do show signs of RHF but can be treated by higher doses of diuretics. Therefore, we

aimed to identify risk factors for the development of late RHF in all patients on MCS, including patients without the need for hospitalization.

MATERIALS AND METHODS

Study sample and data collection

Between 2006 and 2019, 262 out of 296 patients were successfully discharged after LVAD implantation using the HeartMate II (HM-II, Abbott, St. Paul, MN, USA), the HeartMate 3 (HM3, Abbott, St. Paul, MN, USA) or the HeartWare (HVAD, Medtronic, Framingham, MA, USA) at the University Medical Centre of Utrecht, all initially implanted as a bridge to transplantation or bridge to decision (BTT or BTD). The standard surgery technique was a full median sternotomy using cardiopulmonary bypass. Cardiopulmonary exercise test (CPET) was prospectively planned at 6 months postoperatively together with laboratory test including haemoglobin and B-type natriuretic peptide (BNP). CPET was performed on a bicycle ergometer using previously published methods.⁽⁵⁾

Baseline data, including pre-implant demographics, medical history and clinical status were collected in a central database, and is further addressed as “baseline dataset”. This dataset was enriched with the data obtained from the post-operative CPET results and adverse events defined according to the Inter-agency Registry for Mechanically Assisted Circulatory Support (INTERMACS) criteria (except for late RHF, which is defined below).⁽¹⁵⁾ Pre-operative right ventricular function was evaluated using echocardiogram and hemodynamic measurements, maximally 90 days before LVAD implantation. Echocardiographic parameters included the tricuspid annular plane systolic excursion (TAPSE, in mm), peak systolic velocity on tissue Doppler imaging (TDI-RV, in cm/s), and severity of tricuspid regurgitation (TR, categorized as no/mild or moderate/severe TR). Invasively measured hemodynamic parameters included central venous pressure (CVP, in mmHg), mean pulmonary artery pressure (mPAP, in mmHg), cardiac index (CI, in l/min/m²) and RVSWI (in mL x mmHg/m²). An overall assessment of right ventricular function (categorized as poor, intermediate or good) was made by two independent cardiologists using previously published methods.⁽¹⁷⁾

Retrospectively, the occurrence of late RHF during MCS, in both outpatients and hospitalized patients was extracted from the electronic health records. Follow-up was completed for all patients until death, heart transplantation, explantation or the end of the study (March 2019). This study was approved by our institutional ethical board and the need for informed consent was waived.

Definitions of RHF and end points

Early (perioperative) RHF was defined as right ventricular dysfunction, requiring right ventricular assist device (RVAD)-implantation, inhaled nitric oxide or inotropic therapy for more than 1 week during the index hospitalization for LVAD implantation < 30 days post implantation.

Late RHF was defined as the occurrence of right ventricular dysfunction associated with symptoms of right heart failure (i.e. jugular venous distension, hepatic congestion and peripheral edema), if diagnosed by a cardiologist after the index hospitalization for LVAD implantation > 30 days post implantation. The primary end point of this study was the diagnosis of late RHF in combination with the need for intensification of diuretics (either with or without hospitalization) and/or the need for inotropes and/or RVAD. Secondary outcomes include the requirement for hospitalization due to late RHF and functional capacity, examined by CPET at 6 months postoperatively.

Statistical analysis

Categorical variables are reported in percentages. Comparison of dichotomous variables between patients with and without late RHF were performed with Fisher's exact test. Continuous variables are reported as median (interquartile range). Differences in continuous variables between patients with and without late RHF were analyzed with the Mann-Whitney U test. Kaplan-Meier analysis was used to evaluate the LRHF free survival, censoring for explantation and heart transplantation. The relationship between the occurrence of early and late RHF was tested using a chi-squared test.

Univariate stratified cause-specific Cox proportional hazards models were used to assess the association between each of the demographic, pre- and peri-operative covariates and the occurrence of late RHF. Patients were censored for heart transplantation, death, explantation or ongoing support at the end of the follow-up. Univariate variables with $p < 0.10$ entered the multivariable Cox model. In addition, we separately assessed an extension of this multivariate Cox model in a subset of patients who had a complete assessment of right ventricular function by echocardiography or right catheterization prior to the LVAD implantation. We stratified by device type, since the hazards were not proportional for the different devices. All covariates with $p < 0.05$ were defined significant in the multivariable analysis.

RESULTS

Between 2006 and 2019, 296 LVAD implants were performed at our center. Thirty-four (11%) patients died during the index hospitalization, leaving 262 for inclusion of this study with complete baseline data in 261 (99.6%) (66% male, median age 53 (interquartile range (IQR): 17) years at implantation). The median duration of MCS was 779 (IQR: 881) days, resulting in 647 patient-years MCS experience. During follow-up, 49 (19%) patients developed late RHF. Figure 1 depicts LRHF free survival after LVAD implantation. In all patients medical therapy was intensified, 2/3 (n=33, 67%) required hospitalization, of which one patient underwent RVAD implantation. This patient suffered from recurrence of giant cell myocarditis. Late RHF occurred after a median of 363 (IQR: 837) days after LVAD implantation. Nineteen patients (7%) who suffered from late RHF died after a median of 120 (IQR: 292) days after diagnosis and twelve were transplanted after a median of 200 (176) days after the first diagnosis of late RHF.

In comparison to patients without late RHF (n=212), patients with late RHF had a significantly higher pre-operative body mass index (BMI), more often received pre-operative temporary support and were less frequently classified as INTERMACS 3-7 at the time of LVAD implantation. In addition, the duration of index hospitalization (including stay on the intensive care unit (ICU)) was longer, as shown in Table 1. Baseline laboratory results representing renal and liver function did not differ between patients with or without late RHF. In the postoperative course, significantly more patients with late RHF suffered from atrial fibrillation (AF: paroxysmal, persistent or permanent).

Table 1: Baseline data in patients with and without late right heart failure (LRHF)

Patient characteristics	No LRHF (n=212) n (%) or median [IQR]	LRHF (n=49) n (%) or median [IQR]	p-value
Gender – male	70 (33.0)	18 (36.7)	0.743
Age at implant	53.1 [44-60]	53.2 [44-61]	0.744
Body mass index (kg/m ²)	23.4 [22-26]	25.3 [23-28]	0.006
Etiology – dilated cardiomyopathy	135 (63.7)	27 (55.1)	0.341
INTERMACS 0 (Pre-operative temporary support)	31 (14.6)	17 (34.7)	0.002
Pre-operative support: ECMO	20 (9.4)	15 (30.6)	<0.001
Pre-operative support: IABP	8 (3.8)	0 (0)	0.357
Pre-operative support: Impella	1 (0.5)	0 (0)	1.000
Pre-operative support: Other	2 (0.9)	2 (4.1)	0.334
INTERMACS 1	10 (4.7)	2 (4.1)	1.000
INTERMACS 2	86 (40.6)	18 (38.8)	0.945
INTERMACS 3-7	90 (42.5)	11 (22.4)	0.016

Table 1: CONTINUED.

Patient characteristics	No LRHF (n=212) n (%) or median [IQR]	LRHF (n=49) n (%) or median [IQR]	p-value
<u>Details primary LVAD implantation</u>			
TV concomitant	32 (15.1)	8 (16.3)	1.000
Previous (CABG)	14 (6.6)	4 (8.2)	0.940
Previous major cardiac surgery	34 (16.0)	13 (26.5)	0.129
CPB time (min)	112 [92-135]	115 [103-132]	0.201
Device type			
HeartMate II	119 (56.1)	22 (44.9)	0.005
HeartWare	48 (22.6)	22 (44.9)	
HeartMate 3	45 (21.2)	5 (10.2)	
Total duration hospitalization (days)	42 [31-54]	47 [36-70]	0.036
ICU stay (days)	6.0 [4-9]	7.0 [5-19]	0.005
<u>Medical history</u>			
History of hypertension	22 (10.4)	3 (6.1)	0.520
Diabetes mellitus	23 (10.8)	9 (18.4)	0.228
COPD	10 (4.7)	3 (6.1)	0.965
TIA/CVA	18 (8.5)	2 (4.1)	0.455
Atrial fibrillation	47 (22.2)	17 (34.7)	0.098
<u>Pre-operative laboratory results</u>			
Blood urea nitrogen (mg/dL)	29.0 [22-38]	32.0 [24-41]	0.354
Kreatinin (mg/dL)	1.27 [1.0-1.6]	1.22 [1.0-1.6]	0.784
eGFR < 60ml/min/m2	89 (42)	25 (51)	0.322
Bilirubin total (mg/dL)	1.29 [0.9-2.1]	1.17 [0.9-1.8]	0.730
AST (U/L)	41.5 [26-68]	41.0 [33-64]	0.562
ALT (U/L)	55.0 [27-132]	44.0 [24-95]	0.383
<u>Right heart function – echo (n=159)</u>			
TAPSE (mm)	14.0 [12-17]	14.0 [12-17]	0.984
TDI-RV (cm/s)	8.1 [7-10]	8.4 [7-10]	0.641
No/mild tricuspid regurgitation	96 (49.5)	18 (43.9)	0.633
Moderate tricuspid regurgitation	58 (29.9)	7 (17.1)	0.140
Severe tricuspid regurgitation	40 (20.6)	16 (39.0)	0.021
Poor RV function	31 (14.9)	8 (17.0)	0.889
Intermediate RV function	151 (72.2)	36 (76.6)	0.706
Good RV function	26 (12.5)	3 (6.4)	0.348
<u>Right heart catheterization (n= 165)</u>			
Central venous pressure (mmHg)	9.0 [5-13]	11.0 [8-15]	0.016
Mean pulmonary artery pressure (mmHg)	32.0 [25-37]	30.0 [24-42]	0.793
Cardiac index (l/min/m ²)	1.77 [1.4-2.1]	1.75 [1.5-2.0]	0.954
Right ventricular stroke work index (mL x mmHg/ m ²)	411 [278-582]	288 [241-486]	0.079
<u>Post-operative adverse events</u>			
Early right heart failure	49 (23.1)	16 (32.7)	0.227
Dialysis	21 (9.9)	7 (14.3)	0.524
Hypertension	11 (5.2)	1 (2.0)	0.569
Atrial fibrillation	64 (30.2)	27 (55.1)	0.002

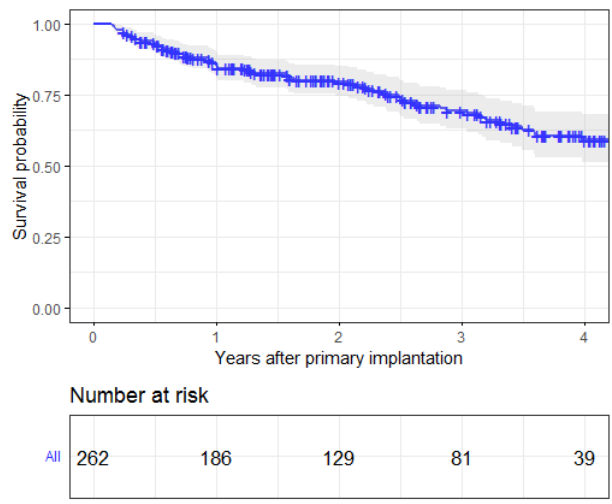


Figure 1: Late right heart failure free survival after primary left ventricular assist device implantation, censoring for explantation and heart transplantation.

Using the chi-squared test, no relation was found between the occurrence of early RHF and late RHF ($p=0.220$), although one third of the patients who developed late RHF, also suffered from early RHF and a quarter of patients showing early RHF later-on developed late RHF.

Cox proportional hazard analysis

Univariate factors significantly associated with late RHF were: a higher BMI (hazard ratio (HR) 1.06 [95% confidence interval (CI) 1.01 to 1.11], $p=0.018$), pre-operative temporary support (HR: 2.41 [95% CI: 1.34-4.35], $p=0.003$), a history of AF prior to implantation (1.79 [95% CI: 0.99-3.23], $p=0.054$). In addition, a longer duration on the intensive care unit (ICU) (1.03 [95% CI: 1.01-1.04], $p=0.003$) and duration of hospitalization (1.01 [95%CI: 1.00-1.02], $p=0.042$) after primary implantation were significant univariate factors. Renal and liver function before MCS implantation were not associated with the occurrence of late RHF. Table 2 shows the results of all univariate regression results.

Table 2: Univariate and significant multivariable demographic and perioperative risk factors for late RHF (n= 261)

Parameters	Univariate risk factors		Multivariable risk factors	
	HR [95% CI]	p-value	HR [95% CI]	p-value
Gender - male	1.05 [0.59-1.88]	0.865		
Age at implantation (years)	1.01 [0.98-1.03]	0.556		
Body mass index (kg/m ²)	1.06 [1.01-1.11]	0.018	1.07 [1.01-1.13]	0.023
Etiology – dilated cardiomyopathy	0.72 [0.41-1.27]	0.261		
Pre-operative temporary support	2.38 [1.32-4.29]	0.004	1.45 [0.71-2.96]	0.305
INTERMACS 1	1.21 [0.29-4.98]	0.796		
INTERMACS 2	0.92 [0.52-1.64]	0.775		
<u>Details primary LVAD implantation</u>				
TV concomitant	1.12 [0.53-2.40]	0.761		
Previous CABG	1.10 [0.39-3.07]	0.861		
Previous major cardiac surgery	1.64 [0.87-3.10]	0.126		
Cardiopulmonary bypass time	1.00 [1.00-1.01]	0.429		
Duration on ICU (days)	1.03 [1.01-1.04]	0.003	1.03 [1.00-1.06]	0.025
Duration of hospitalization (days)	1.01 [1.00-1.02]	0.042	0.99 [0.98-1.01]	0.402
<u>Medical history</u>				
History of hypertension	0.84 [0.26-2.71]	0.771		
Diabetes mellitus	1.55 [0.75-3.20]	0.235		
History of COPD	1.80 [0.56-5.82]	0.326		
History of TIA/CVA	0.59 [0.14-2.42]	0.462		
History of atrial fibrillation	1.79 [0.99-3.23]	0.054	2.06 [1.08-3.93]	0.029
<u>Pre-operative laboratory results</u>				
Blood urea nitrogen (mg/dL)	1.01 [0.99-1.02]	0.307		
Kreatinin (mg/dL)	1.07 [0.64-1.81]	0.781		
eGFR < 60 ml/min/m ²	1.36 [0.77-2.38]	0.288		
Bilirubin (mg/dL)	0.91 [0.66-1.27]	0.597		
Aspartate aminotransferase (U/L)	1.00 [1.00-1.00]	0.290		
Alanine transaminase (U/L)	1.00 [1.00-1.00]	0.111		

Multivariable stratified Cox proportional hazard analysis showed a history of AF (HR 2.06; 95% CI 1.08-3.93, p=0.029), a higher pre-operative BMI (in kg/m², HR 1.07; 95% CI 1.01-1.13, p=0.023) and longer duration on the ICU after primary implantation (in days, HR 1.03; 95% CI 1.00-1.06, p=0.025) to be independent predictors of late RHF.

Additional pre-operative diagnostic results to predict late right heart failure

Complete echocardiographic data, including TAPSE, TDI-RV, severity of tricuspid regurgitation and overall right ventricular function, were available in 145 (55%) patients. Right heart catheterization (RHC) before LVAD implantation was available in 155 (59%) patients. The incidence of late RHF in this subgroup with complete echocardiographic data (18%) and hemodynamic data (19%) was similar to the

incidence in the whole group in the “baseline dataset” (19%). Noteworthy, patients in the group with complete ECHO differed from patients without complete ECHO data, especially in INTERMACS score. Patients with complete RHC data differed from patients without RHC data, especially in age, etiology, INTERMACS score and cardio pulmonary bypass (CPB) time. Baseline difference for both groups are displayed in supplementary table 2 and 3.

Out of all echocardiographic variables, pre-operative TR severity was a significant univariate predictor (HR 1.95 [95% CI 1.23-3.08, $p=0.004$]). For the RHC variables, RVSWI (HR 0.99 [95% CI 1.00-1.00, $p=0.05$]), CVP (HR 1.11 [95% CI 1.05-1.17, $p<0.001$]) and PAPI (HR 0.68 [95% CI 0.53-0.89, $p=0.005$]) were selected for the multivariate model.

To analyze the contribution of echocardiography and/or right heart catheterization at baseline to the prediction of late RHF, these parameters were included in the multivariable Cox regression model in subsets of patients with complete echocardiographic and/or invasive hemodynamic assessment of right ventricular function (Supplementary table 4 and 5). TR-severity remained significant in the multivariable Cox regression analysis in the ECHO dataset, with HR 1.91 [95% CI 1.13-3.21, $p=0.016$]. For the hemodynamic parameters, none of the selected covariates remained significant in the multivariable model.

Functional capacity

Since it is known that patients with late RHF have an impaired exercise tolerance, we analyzed the results of routinely planned CPET at 6 months after implantation. Results of the CPET were compared between patients who developed late RHF (after a median of approximately 1 year after implantation) and patients who did not develop late RHF. CPET data at 6 months after LVAD implantation were available in 146 patients. Those patients who developed late RHF ($n=23$) demonstrated already a significant lower maximal work load and peak VO_2 (both $p<0.001$) 6 months after LVAD implantation in comparison to patients without late RHF ($n=123$), while respiratory quotient did not differ significantly ($p=0.185$) (Table 3). In addition, patients with late RHF had a significantly lower peak heart rate during the test ($p=0.011$).

Table 3: Results of cardiopulmonary exercise test at 6 months postoperatively in patients with and without late RHF (n=146)

Parameter	No late RHF (n=123)	Late RHF (n=23)	p-value
Gender - male (no, %)	89 (72%)	13 (57%)	0.129
Age (years, mean \pm SD)	49.4 \pm 12.8	50.6 \pm 11.4	0.910
Body mass index (kg/m ²)	24.4 \pm 3.4	23.7 \pm 3.6	0.277
Max load (Watt, mean \pm SD)	106 \pm 33	76 \pm 18	< 0.001
VO2 (L/min, mean \pm SD)	1.28 \pm 0.40	0.96 \pm 0.24	< 0.001
VO2 % predicted (mean \pm SD)	53 \pm 12	42 \pm 9	< 0.001
VO2/kg (mean \pm SD)	16.7 \pm 4.8	13.2 \pm 3.5	< 0.001
VO2/kg % predicted (mean \pm SD)	52 \pm 12	43 \pm 12	0.001
Anaerobic threshold (mean \pm SD)	11.1 \pm 3.0	9.1 \pm 2.6	0.004
Respiratory exchange ratio (mean \pm SD)	1.21 \pm 0.11	1.21 \pm 0.12	0.737
EqCO2 (mean \pm SD)	36.4 \pm 6.5	38.2 \pm 5.5	0.185
Max heart rate (bpm, mean \pm SD)	140 \pm 28	122 \pm 30	0.011
Hemoglobin (g/dL, mean \pm SD)	12.9 \pm 1.5	12.6 \pm 1.4	0.474
B-type natriuretic peptide (pg/ml, mean \pm SD)	180 \pm 146	312 \pm 330	0.060

DISCUSSION

We presented the prevalence and risk factors for late right heart failure after LVAD implantation including patients presented at the outpatient clinic in addition to patients in need of hospitalization (graphical abstract). In a cohort of 261 patients, successfully discharged after LVAD implantation, 19% of patients suffered from late RHF, indicated by the need for intensification of diuretics with/without inotropes, of which two third required hospitalization. The incidence of late RHF is higher in comparison to previous studies (12)(16), since patients treated at the outpatient clinic were included as well. Using the stricter criteria, 1/3 of the cases in our study (16 patients) would have been missed. We prefer to include those cases as early recognition and treatment of late RHF might even prevent re-hospitalization. Readmission for late RHF was necessary in 33 patients (13% of the total population), which is in line with current literature (8-17%).(12)(16)

In contrast to Alkhunaizi et al., we found no association between early RHF and LRHF.(14) One third of the patients who suffered from late RHF also had early RHF, though only a quarter of the patients with early RHF developed late RHF. Probably late RHF is caused by other mechanisms than RHF in the early postoperative phase. Wagner et al. demonstrated that pre-operative right heart failure increases the risk of early RHF and persistent RHF, but not for new onset LRHF.(18) Early RHF can be caused by acute volume overload and septal shift of the RV at the start of left ventricular unloading by the pump (LVAD) in combination with a rise in pulmonary vascular resistance due to excessive blood loss.(19)(20)

Late RHF in our study was significantly associated with a post-operative duration on the ICU, likely related to the severity of disease in the perioperative phase. This could be explained by different mechanisms. First, in the severely hemodynamically compromised patients, volume overload of the right ventricle might result in increased cardiomyocyte apoptosis, compromising the remaining cardiomyocytes in the RV with dire consequences in the long run.(21) On univariate analysis, INTERMACS 0 was significantly related to late RHF. However, it was not significant in the multivariable model. Patients with a worse INTERMACS classification are probably reflected by patients with a longer hospitalization and ICU-duration, which was a significant predictor in the multivariable model. Cotts et al. demonstrated a significant relation between INTERMACS classification and the hospital duration after primary LVAD implantation.(22) Furthermore, progression of the underlying disease, such as dilating cardiomyopathy, might enhance further deterioration of right ventricular function.(23)(24)(25)(26) In addition, pump speed of the LVAD is important to the pre- and afterload of the right ventricle, also affecting the position of the interventricular septum. Too much unloading of the LVAD, will shift the interventricular septum leftward together with an increased preload of the right ventricle resulting in RV overload.(27) Initially this volume overload is well tolerated by the RV but in the end it will result in RV failure.(20) This could well explain the timing of clinical appearance of right heart failure in MCS patients. Therefore, echocardiographic follow-up is very important to identify alterations in right ventricular dimensions, function and the position of the interventricular septum.(28)

We showed for the first time that a history of AF increases the risk of developing late RHF. Alkunaizi et al. found a trend towards increased post-operative (6 months) AF in LRHF patients, but no significant association between pre-operative AF and LRHF.(14) In general, atrial fibrillation is known to affect prognosis in heart failure patients in a negative way, both in heart failure with a reduced ejection fraction and heart failure with a preserved ejection fraction.(29)(30) A recent study identified an association between atrial fibrillation and the development of right ventricular dysfunction in patients with a preserved left ventricular systolic function during 4 year follow-up.(31) This is an interesting observation and seems analogous to the situation in long-term MCS. In addition we showed that a higher BMI, probably a surrogate for other risk factors, is associated with late RHF. This relationship was previously published in a meta-analysis.(32) In contrast to previous studies, we did not find an association between pre-operative renal function and late RHF. Significantly higher pre- and post-operative BUN levels were correlated with LRHF. (12)(14)(16) Generally, BUN levels in these studies were higher in comparison to our study, probably reflecting an older population with a higher prevalence of

ischemic heart disease.

As expected, we showed that a pre-operative TR severity was an independent predictor for late RHF, as it is a surrogate marker for RV dysfunction. Consistent with our study, Schlöglhofer et al. found no significant relation between pre-operative CVP and right heart failure. However, they showed that early post-operative CVP is an independent predictor of right heart failure.(13) Wagner et al. demonstrated no predictive value of echocardiographic of hemodynamic parameters for new onset LRHF.(18)

An important finding in our study is that physical impairment in patients developing late RHF is already apparent at an exercise test 6 months postoperatively, long before the RHF is clinically discernable in most patients. This reduced exercise may result from subclinical right heart failure, as the right ventricular ejection fraction is related to peak VO₂ in patients with advanced heart failure.(33) Thus, setting standards for expected peak VO₂ after LVAD implantation will help identify patients with a reduced exercise capacity during follow-up, in whom closer monitoring and early treatment is indicated to prevent LRHF. In addition to our between group comparison of VO₂, it is of interest whether VO₂ is predictive at the individual level.

Limitations

There are some inherent limitations to this study. First, this study was conducted in patients initially implanted as a BTT or BTD. Although many patients were supported for a longer time as a result of the shortage of donor hearts, results might not be extrapolated directly to patients with MCS as destination therapy which generally is an older population with more comorbidities. Additionally, analysis were done including patients on HMII, HVAD or HM3 support. This is a limitation, since HMII and HVAD are withdrawn from the market. Hence, larger studies including HM3 patients only are warranted to confirm current findings. Since the data were not complete for all patients, we performed the multivariate stratified Cox model with the addition of echocardiography and right heart catheterization parameters in a subpopulation with available data, which may not account for the whole population as these patients differed in baseline characteristics.

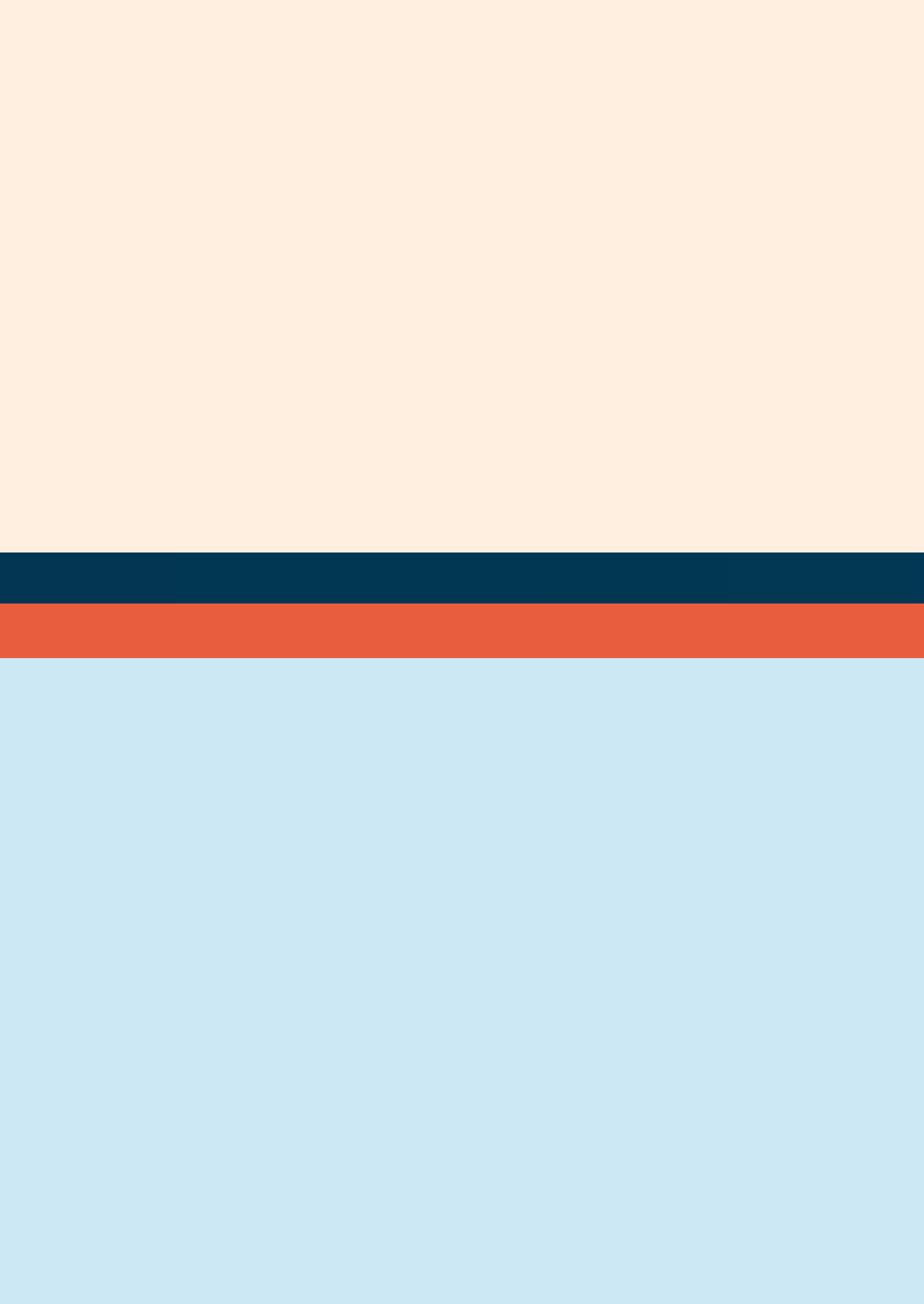
Late RHF warranting increased medical therapy with or without admission to the hospital is a dreaded complication of chronic MCS and affects 19% of the patients, after a median post-operative duration of one year. We demonstrated that a history of atrial fibrillation, a higher pre-operative BMI, and a longer duration of stay on the ICU after implantation were significantly related to late RHF. In a sub analysis,

we showed that a TR-severity pre-operatively is an independent predictor for late RHF. Furthermore, patients with late RHF demonstrated a reduced exercise capacity already at 6 months after implantation in comparison to patients without late RHF. Patients at higher risk of development of late RHF should be followed-up more closely and treated more intensively to prevent hospitalization

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CHAPTER 6

Hyperpolypharmacy is a predictor of mortality after Left Ventricular Assist Device implantation

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ABSTRACT

Background

The prevalence of (hyper)polypharmacy in patients on left ventricular assist device (LVAD) support and its effect on clinical outcome is unknown. Therefore, we aimed to determine the prevalence of (hyper)polypharmacy in LVAD patients and evaluate its association with mortality and complications.

Materials and methods

210 patients aged ≥ 40 years who received a primary LVAD implantation between 2011 and 2019 were included for analysis. Polypharmacy and hyperpolypharmacy were defined as the concomitant use of 5–9 and ≥ 10 medications at discharge after LVAD implantation, respectively. Cause specific cox regression was used to assess the association of ≥ 10 medications with mortality, cardiac arrhythmia, driveline infection and major bleeding.

Results

The median age of the patients was 57.5 years, and 35.7% were female. The average number of discharge medications was 8.8 ± 2.3 per patient. The prevalence of patients with 5–9 medications and ≥ 10 medications was 62.9% and 34.8%, respectively. The median follow-up duration was 948 days (interquartile range 874 days). The prescription of ≥ 10 medications was significantly associated with a higher risk of mortality (HR 2.03; 95% CI 1.15–3.6, p-value 0.02) adjusted for sex, age, comorbidity and stratified for device type. The prescription of ≥ 10 medications was not associated with a higher risk of major bleeding, cardiac arrhythmia or driveline infection.

Conclusions

(Hyper)polypharmacy is highly prevalent in LVAD patients and is independently associated with a higher risk of mortality. Future research is needed to assess the efficacy of individual risk-benefit profiling of (cardiovascular) medication to ensure appropriate polypharmacy and to decrease negative health outcomes.

INTRODUCTION

Heart failure (HF) is a chronic and progressive clinical syndrome affecting at least 26 million people worldwide and its prevalence continues to increase.(1) Treatment options include lifestyle changes, pharmacological treatment, device therapy, coronary revascularisation and cardiac rehabilitation according to HF severity. In case of therapy-resistant symptomatic end-stage HF, there may be an indication for heart transplantation or mechanical support with a Left Ventricular Assist Device (LVAD).(2) Due to the progressive nature of HF and current donor heart scarcity, patients on the heart transplant waiting list often need LVAD implantation to maintain adequate cardiac output (bridge to transplantation). LVAD implantation is also a permanent therapy for those who do not qualify or opt for heart transplantation (destination therapy). The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial has shown that LVAD destination therapy leads to a higher survival rate and quality of life in patients ineligible for transplantation.(3) Current survival at one, two and three years after LVAD implantation in the Netherlands is 83%, 76% and 70%, respectively.(4) Despite these promising results, major adverse events are common after LVAD implantation: one year after LVAD implantation 41% of the patients have suffered from a major infection (a clinical infection treated by antimicrobial agents), 21% from gastro-intestinal bleeding and 13% from stroke.(5)

HF patients have a higher prevalence of co-morbidities when compared to patients of similar age without HF.(6) This is especially the case of patients for LVAD destination therapy, not eligible for heart transplantation due to advanced age, non-cardiac comorbidities or frailty.(7) The pharmacological treatment of these cardiac and non-cardiac comorbidities in patients with end stage HF generates a high prevalence of polypharmacy (17 to 99%), (8) usually defined as the concomitant use of ≥ 5 regularly prescribed medications, and even of hyperpolypharmacy (26% to 74%), (9)(10) which is defined as the use of at least 10 different medications. Although sometimes unavoidable in order to comply with guidelines, (hyper)polypharmacy should not be considered harmless. In patients with HF, polypharmacy is associated with a higher risk of overtreatment, undertreatment, medication errors, poor adherence, adverse drug-reactions and drug-drug interactions.(11)(12)(13) Kennel et al. showed that hyperpolypharmacy in patients with HF is independently associated with an increased rate of ambulatory contacts and hospital admissions.(9) No studies are available on the prevalence of polypharmacy and hyperpolypharmacy in patients on LVAD support and the association with adverse outcomes after LVAD implantation. The aim of our study was to determine the prevalence of polypharmacy (5-9 medications) and hyperpolypharmacy (≥ 10 medications) in patients after

primary LVAD implantation and to evaluate the association of hyperpolypharmacy with overall mortality and complications while on LVAD support.

METHODS

Study design, setting and population

We conducted a retrospective cohort study at the University Medical Centre Utrecht, a tertiary hospital in the Netherlands. All consecutive patients who underwent primary LVAD implantation between 01-01-2011 and 31-12-2019 were included if they were 40 years or older at implantation and survived the index admission. Data on mortality and complications were collected until 1-1-2021, so each patient was followed for at least one year. We included patients 40 years of age or older, because a medication review is part of a comprehensive geriatric assessment (CGA) and we assume that a CGA in patients younger than 40 years will provide relatively few clinically relevant findings, since a CGA focuses on problems that occur particularly in older age (including impaired cognition, decreased functionality, limited social network). Patients who died during the index admission, i.e. the admission in which the LVAD was implanted, were not included in this study as no discharge medication was available for these patients. For these patients, it was not possible to use the medication list that was in use at the time of death to determine whether they were taking ≥ 10 medications because it often involved intercurrent medications (antibiotics, strong analgesics, inotropics), and this biased the presence of the prescription of ≥ 10 medications. The local medical ethics committee gave approval for a waiver to obtain informed consent (reference number WAG/mb/20/013298) given the anonymity of data collection and the non-interventional nature of the study.

Data collection

Data were collected on patient characteristics (age at implantation, sex, body mass index), aetiology of cardiomyopathy, device type and Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile before primary implantation. The INTERMACS classification comprises 7 severity profiles corresponding to New York Heart Association class III and IV, with INTERMACS 7 corresponding to advanced New York Heart Association class III heart failure and INTERMACS 1 representing the situation of critical cardiogenic shock.⁽¹⁴⁾ Data were also collected on mortality and the occurrence of complications.⁽¹⁵⁾

The medical history, both cardiac and non-cardiac, was obtained from the discharge letter of the index admission. Chronic conditions and acute somatic problems from

which a patient had not yet recovered during admission were documented using the 2016 version of the tenth edition of the International Classification of Diseases.(15) This data was then used to determine the Charlson Comorbidity Index (CCI) score. (16) The CCI scores the presence of certain comorbidities, with a maximum score of 33, and predicts the 10-year survival in patients with multiple comorbidities. Originally, age is included in the calculation of 10-year survival using the CCI. However, because we already included age as a variable in the cox proportional hazards models, we calculated the CCI for each patient without assigning points to age.

Discharge medication was also collected from the discharge letter of the index admission. Medications were grouped to present medication use in a convenient way and to perform analyses of associations between specific medication groups and outcomes. The internationally widely and long-used Anatomical Therapeutic Chemical (ATC) classification system was used for this purpose.(17) In the ATC classification system, the active substances are classified at five levels. We chose to use discharge medication to determine medication use because it better reflects the overall medical situation after LVAD implantation than admission medication, where some of the patients are not yet on cardiac medication or medication for other co-morbidities. The following medication was excluded from data collection: medication prescribed as needed, medication administered by cutaneous (skin cream) or ophthalmic routes (eye drops), medication without an existing ATC code and over-the-counter vitamins. Medication use was divided into 0-4 medications (no polypharmacy), 5-9 medications (polypharmacy) and ≥ 10 medications (hyperpolypharmacy).

Primary and secondary endpoints

The primary endpoint of the study was death or urgent heart transplantation (HTx). We chose to combine these two outcomes under the assumption that without receiving the heart transplantation (urgent recipient) the patient would die in the very short term. Urgent heart transplantation was defined as heart transplantation for which the patient received a priority status on the waiting list (national 1A, national 1B, or international HU). The secondary outcomes were defined using the adverse event definitions formulated by INTERMACS that occurred in at least 50 patients after discharge: cardiac arrhythmia, driveline infection and major bleeding.(18)

Statistical analysis

Baseline variables are expressed as numbers and percentages for categorical variables, and mean and standard deviations (SD) or median and inter quartile

ranges (IQR) for continuous variables. Differences in baseline variables and prevalence of mortality and complications between patients with 0-9 medications and ≥ 10 medications were determined by the Fisher's exact test for categorical variables, and independent T-tests or Mann-Whitney U test for continuous variables. Kaplan-Meier analysis was performed, categorized in patients with 0-9 medications and ≥ 10 medications. Cox proportional hazards models were applied, to assess the association of the prescription ≥ 10 medications with our primary outcome. Patients on ongoing support at the end of follow-up and patients that received a non-urgent heart transplantation were censored. Hazard Ratios (HR) and 95% Confidence Intervals (95% CI) were calculated. In addition, the HRs were stratified for device type and adjusted for age at implantation, sex, comorbidities (by means of the CCI score), to examine whether the prescription ≥ 10 medications merely reflects the presence of comorbidities or an independent factor. As a sensitivity analysis, an additional cox model was used with the number of medications as a continuous variable. In addition, in another cox model tertiles of the number of medications were used as a variable to study the association with the primary outcome. Because most of the decesses had a neurologic (stroke) or cardiac cause, an additional cox analysis was performed to examine the association of medications to prevent stroke and cardiac medication, with the primary outcome. Medications to prevent stroke concerned the medication groups antihypertensives (ATC groups C07-C09), antithrombotics (B01) and lipid-lowering agents (C10). Cardiac medications involved the ATC groups B01, C01, C03, C07, C08, C09, C10. Another sensitivity analysis was performed, similar to the primary multivariate cox regression analysis. However, now patients were also censored for urgent heart transplantation, as this was usually done in literature. The proportional hazard assumption was met in all cox models. The predictor variables age, sex, CCI, device type and the prescription ≥ 10 medications were tested for multicollinearity by inspection of correlation coefficients and variance inflation factor (VIF) values, and there was no indication of multicollinearity. To determine whether the effect of ≥ 10 medications on mortality was modified by age, a cox model with the interaction between age and the prescription ≥ 10 medications was performed.

To evaluate the association between the prescription ≥ 10 medications and the secondary outcomes, cause-specific cox models were used, censoring for competing outcomes (death, heart transplantation, explantation). In case of recurrent adverse events, the first event was used for analysis. HR's were stratified for device type and adjusted for age, sex and CCI. For all tests, a p-value ≤ 0.05 was considered statistically significant. All analyses were performed using R version 3.6.3.

RESULTS

Patient inclusion and baseline characteristics

A total of 232 consecutive patients aged 40 years and older underwent primary LVAD implantation between January 2011 and January 2020. For 22 patients (9%) discharge medication was not available due to postoperative in-hospital mortality. These patients were excluded from the study. In total, 210 patients were included in the study. Baseline characteristics are presented in Table 1.

The median age was 57.5 years at the time of LVAD implantation and 35.7% were female. The number of comorbidities and the CCI score was significantly higher in the group of patients with ≥ 10 medications than in the group of patients with 0-9 medications (number of comorbidities 6.3 ± 2.4 versus 5.0 ± 1.8 , CCI score 2.0 ± 0.9 versus 1.7 ± 0.8).

Table 1. Baseline characteristics of patients with 0-9 medications and ≥ 10 medications

Demographics		All patients (n = 210)	0-9 medications (n = 137)	≥ 10 medications (n = 73)	P-value
Sex number (%)		75 (35.7)	51 (37.2)	24 (32.9)	0.64
-Female					
Age at implantation (years) median [IQR]		57.5 [11]	57.0 [13]	58 [10]	0.44
Body mass index (kg/m ²) median [IQR]		24.2 [6]	23.7 [6]	25.2 [5]	0.04
Comorbidities mean \pm SD					
- Total number		5.5 \pm 2.1	5.0 \pm 1.8	6.3 \pm 2.4	<0.001
- Charlson Comorbidity Index*		1.8 \pm 0.8	1.7 \pm 0.8	2.0 \pm 0.9	0.002
Number of discharge medications mean \pm SD		8.8 \pm 2.3	7.4 \pm 1.4	11.3 \pm 1.6	<0.001
Ischemic cardiomyopathy number (%)		66 (31.4)	43 (31.4)	23 (31.5)	1.00
Dilated cardiomyopathy number (%)		129 (61.4)	87 (63.5)	42 (57.5)	0.49
Device type number (%)	HeartMate II	70 (33.3)	48 (35.0)	22 (30.1)	0.57
	HeartWare	75 (35.7)	49 (35.8)	26 (35.6)	1.00
	HeartMate 3	65 (31.0)	40 (29.2)	25 (34.2)	0.55
INTERMACS profile number (%)	Temporary support	37 (17.6)	28 (20.4)	9 (12.3)	0.20
	1	7 (3.3)	2 (1.5)	5 (6.8)	0.10
	2	61 (29.0)	38 (27.7)	23 (31.5)	0.68
	3	71 (33.8)	46 (33.6)	25 (34.2)	1.00
	4	32 (15.2)	22 (16.1)	10 (13.7)	0.80
	5	2 (1.0)	1 (0.7)	1 (1.4)	1.00
	6	0 (0)	0 (0)	0 (0)	1.00
	7	0 (0)	0 (0)	0 (0)	1.00

IQR: interquartile range, SD: standard deviation.

* Points for age not included

Prevalence of polypharmacy and hyperpolypharmacy

The average number of discharge medications was 8.8 ± 2.3 . Five patients (2.4%) used 0-4 medications (no polypharmacy), with a mean number of 3.6 medications per patient. The majority (132 patients, 62.9%) used 5-9 medications (polypharmacy), with a mean of 7.6 prescriptions per patient. A total of 73 patients (34.8%) used ≥ 10 medications (hyperpolypharmacy), with on average 11.3 medications per patient. Figure 1 shows the distribution of the number of medications per patient, ranging from 3 to 15. Since only 5 patients met the criterion for no polypharmacy (0-4 medications), this group was combined with patients with 5-9 medications and compared to patients with ≥ 10 medications.

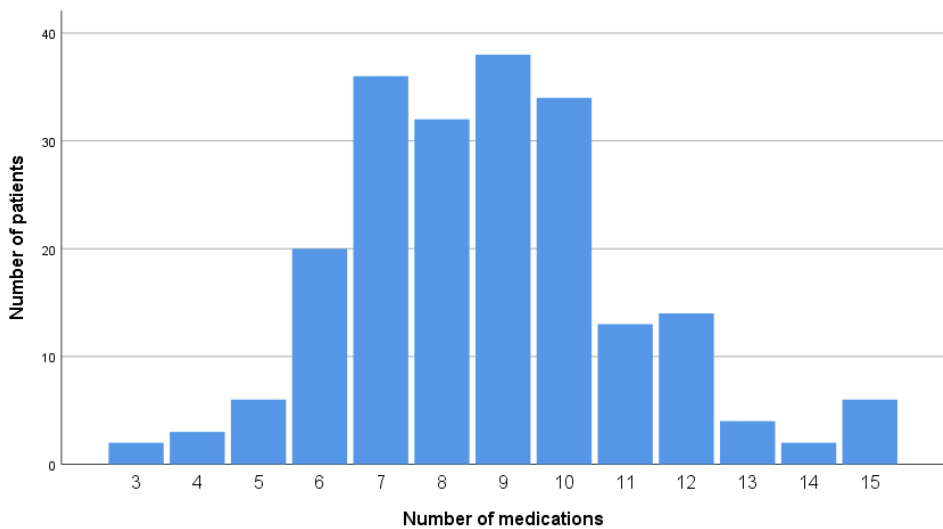


Figure 1: Distribution of the numbers of discharge medication of the LVAD patients.

Of the total of 1839 prescribed medications, 1001 (54.4%) were cardiovascular medications. Most frequently prescribed were antithrombotics (vitamin K antagonists and acetylsalicylic acid are routine medications for patients with an LVAD), diuretics, agents acting on the renin-angiotensin system and antiarrhythmic medications (predominantly amiodarone). (Supplementary Table S1) Most commonly used non-cardiovascular medications were medications for acid related disorders (in particular proton pump inhibitors), analgesics (predominantly paracetamol), and mineral supplements (mainly potassium chloride). Finally, sildenafil was commonly used. Sildenafil falls under urological agents according to the ATC classification system, but the patients in this study used it to lower pulmonary pressure (right ventricle afterload reduction).

Supplementary Figure S1 presents the difference in medication use between patients who survived during the follow-up period and those who died or underwent urgent HTx. Antithrombotics, medication for acid related disorders and diuretics were the most commonly used medication groups. There were no differences between both patient groups.

Mortality and complications

The median follow-up duration was 948 days (interquartile range 874 days). Figure 2 shows the survival (time to death or urgent HTx, as a proxy of mortality) of patients with 0-9 medications and ≥ 10 medications. Patients with ≥ 10 medications had a significantly lower survival compared to patients 0-9 medications (crude HR 1.76; 95% CI 1.03-2.98, p-value 0.04) (Table 2). This association remained significant after adjusting for age, sex, CCI and stratified for device type (adjusted HR 2.03; 95% CI 1.15-3.6, p-value 0.02). A total of 56 patients (27%) died after a median of 828 days following LVAD implantation. Table 3 lists the causes of death. A total of 56 patients received a heart transplant after a median of 1029 days, of which 32% (n=18) were urgent transplants. The adjusted hazard ratio was 1.23 (95% CI 1.09-1.38, p-value 0.001) for the number of medications as a continuous variable in the multivariate cox proportional hazards model of the primary outcome (mortality or urgent HTx).

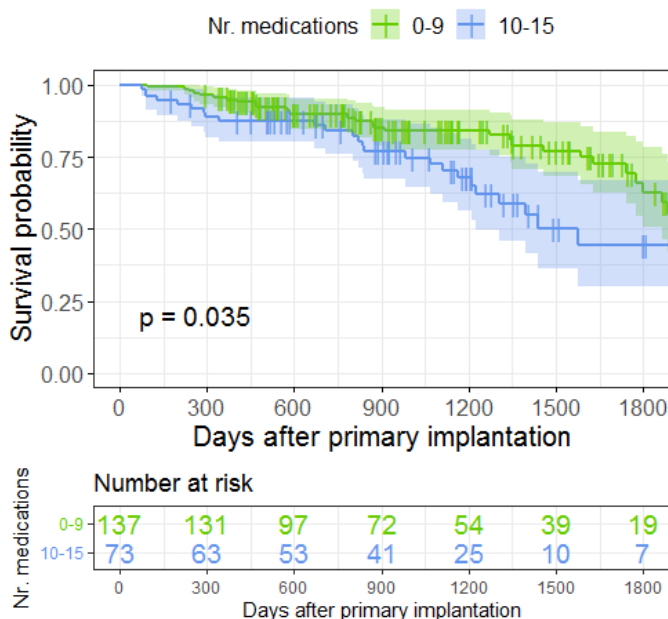


Figure 2: Survival (time to death or urgent heart transplantation) of patients with 0-9 medications and ≥ 10 medications.

Table 2. The association between the prescription of ≥ 10 medications and survival (mortality and urgent heart transplantation)

Variables added to the cox proportional hazards models	Univariate model			Multivariate model*		
	HR	95% CI	P-value	HR	95% CI	P-value
≥ 10 medications	1.76	1.03-2.98	0.04	2.03	1.15-3.62	0.02
Age				1.04	0.99-1.08	0.04
Sex				0.92	0.53-1.62	0.78
Charlson Comorbidity Index				0.96	0.69-1.35	0.83

CI: confidence interval, HR: hazard ratio.

* Stratified for device type

The tertiles for the number of medications were determined. The first tertile concerned 3-8 medications, the second tertile 8-10 medications and the third tertile 10-15 medications. Compared with the first tertile, the use of 8-10 medications did not significantly increase the risk of the combined outcome of mortality and urgent HTx (HR adjusted for age, sex, CCI and stratified for device type 1.79; 95% CI 0.84-3.81, p-value 0.13), but the use of 10-15 medications did (adjusted HR 2.96; 95% CI 1.40-6.26, p-value <0.01). Figure 3 displays the survival for the three different tertiles. Supplementary Tables S2 and S3 show the association of the use of medications to prevent stroke and cardiac medications, respectively, with survival. The sensitivity analysis with additional censoring for urgent heart transplantation also showed a significantly higher mortality (urgent HTx not included) for patients with ≥ 10 medications (adjusted HR 1.77; 95% CI 1.07-2.95, p-value 0.03). An additional analysis was performed to assess whether the effect of ≥ 10 medications was modified by age at the time of implantation. The interaction term for age - ≥ 10 medications was not statistically significant when entered into the multivariate model (p-value 0.43), i.e. the association between ≥ 10 medications and mortality was not different for persons younger and older than 60 years. The prescription of ≥ 10 medications was not associated with any of the adverse events as listed in Table 4.

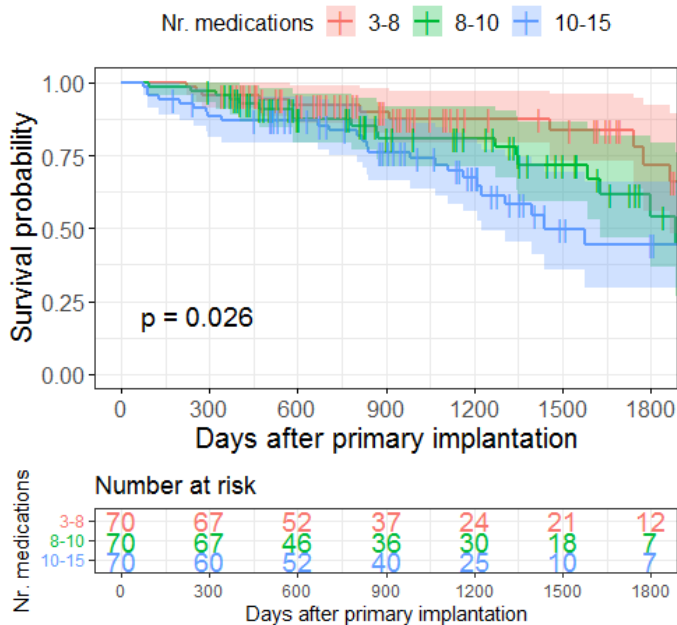
Table 3

Cause of death	All = 56 n (%)
Device malfunction	3 (5.4)
Infection	7 (12.5)
Multi-organ failure	7 (12.5)
Neurological	18 (32.1)
Right ventricle failure	7 (12.5)
Other	14 (25)

Table 4. Cause specific cox regression: association of the prescription of ≥ 10 medications with complications.

Complication type	Number of patients (after index discharge) n (%)	Crude			Adjusted for age, sex, CCI, stratified for device type		
		HR	95% CI	P-value	HR	95% CI	P-value
Cardiac arrhythmia	98 (47)	0.80	0.53-1.25	0.35	0.76	0.48-1.20	0.24
Driveline infection	65 (31)	0.82	0.49-1.40	0.47	0.99	0.57-1.71	0.96
Major bleeding	74 (35)	1.26	0.78-2.02	0.34	1.29	0.78-2.15	0.31

CI: confidence interval, CCI: Charlson Comorbidity Index (without points for age), HR: hazard ratio.

**Figure 3:** Survival (time to death or urgent heart transplantation) of patients with 3-8 medications, 8-10 medications and 10-15 medications (tertiles)

DISCUSSION

This study showed that the prescription of 5-9 medications (polypharmacy) is highly prevalent (62.9%) in patients after LVAD implantation. The prescription of ≥ 10 medications (hyperpolypharmacy) was also common (34.8%) with on average 11.3 medications per patient. Hyperpolypharmacy was independently associated with the risk of mortality, but not with the risk of complications (major bleeding, cardiac arrhythmia or driveline infection). Supplementary Figure S1 and Supplementary Table S3 and S4 indicate that not the type but the number of medications are associated with survival.

The prevalence and the association of (hyper)polypharmacy with outcomes in patients with an LVAD has not been investigated before. However, several previous studies addressed polypharmacy in patients with HF. A recent systematic review on the identification of a standard definition and the prevalence of polypharmacy in patients with HF, concluded that there is no standard definition of polypharmacy in HF literature and the prevalence ranged from 17.2% to 99%.⁽⁸⁾ In four studies where a definition of ≥ 10 medications was used, the prevalence of hyperpolypharmacy varied from 26-74%.⁽⁹⁾⁽¹⁰⁾⁽¹⁹⁾⁽²⁰⁾ Extrapolating these findings to our study, however, is of limited value due to heterogeneity of the study populations, particularly concerning the severity of HF. Where LVAD patients have severe, end-stage HF during admission for an LVAD implantation, the overall HF population has a broad case-mix ranging from mild HF to end-stage HF. A number of medications are used routinely in every patient who receives an LVAD. In our tertiary centre, patients are prescribed at least a vitamin K antagonist, an antiplatelet drug and a proton pump inhibitor after LVAD. Blood pressure is also strictly regulated (mean arterial pressure < 80 mmHg) to reduce the risk of stroke and other complications. The evidence on the association of polypharmacy with mortality in the general HF population is conflicting. Again, comparison with the results of the current study is hampered by the heterogeneity of the study populations. Sunaga et al. evaluated the relationship between various clinical factors and mortality in patients with HF.⁽²⁰⁾ They found that patients who were taking < 6 medications on admission experienced a significantly lower all-cause 2 year-mortality than patients taking ≥ 6 medications (10.0% vs. 25.0%, $P = 0.045$). However, the study by Sunaga et al concerned the number of medications before admission and this study determined the number of medications on discharge from hospital, with the study of Sunaga et al not taking into account medication changes during admission. Wu et al. examined the association between the use of 10-14 medications and several adverse outcomes in patients with HF with preserved ejection fraction (HFpEF). Contrary to the finding in this study and the study of Senaga et al, Wu et al. found that the prescription of 10-14 medications was associated with a reduced risk of all-cause mortality (HR 0.61; 95% CI 0.39-0.96, $P=0.031$), and an increased risk of HF hospitalisation (HR 2.83; 95% CI 1.37-5.86, $P=0.01$) and all-cause hospitalisation (HR 1.81; 95% CI 1.29-2.53, $P=0.001$).⁽¹⁹⁾ However, Wu et al. included relatively stable patients with HF, whereas the study of Sunaga and our study included patients with unstable or advanced/end stage HF.

Strengths and limitations

This study was the first to examine the prevalence of the prescription of 5-9 medications (polypharmacy) and ≥ 10 medications (hyperpolypharmacy) and its association with adverse outcomes in a large sample of patients after

primary LVAD implantation. The risk of selection bias is very small, because an existing prospective database was used for patient selection, in which data of all consecutive LVAD patients was registered. Data on the occurrence of a selection of complications were collected, using the definition of the international INTERMACS registry, making the results internationally interpretable.

This study has some limitations. The medical history and discharge medication were extracted from the discharge letter. There is a chance that these letters contained incomplete or incorrect information due to human error. Second, due to the retrospective collection of medication data, we could not take into account medication adherence, correct use or changes in medication after hospital discharge. Third, the incidence of many adverse events was very low, and therefore were not included for analysis in the current study, as there was not enough power here to demonstrate a significant association. Finally, although this study showed that there is a significant association between the prescription of ≥ 10 medications and mortality, it cannot be determined whether there is a causal relationship. Despite adjustment for age, sex, device type and comorbidities, it is still possible that hyperpolypharmacy reflects the presence of frailty. Several observational studies demonstrated a significant association between an increased number of medications and frailty (possibly bidirectional) and frailty is a known risk factor for mortality in patients with HF.(21)(22) Because there is no agreement on the definition of frailty and the way it should be assessed in (end stage) heart failure, hyperpolypharmacy as a proxy of frailty would in that case simplify prognostication of patients post LVAD.

Clinical implications and future research

Over the last few years, awareness of polypharmacy in patients with HF has been growing. The fact that this study showed that the prescription of ≥ 10 medications was associated with mortality, independent of the presence of comorbidities, demonstrates the importance of adequately addressing hyperpolypharmacy. However there is a lack of clarity on how best to manage polypharmacy.(23)(24)(25) Thereby, it is important to realise that polypharmacy in a number of patients with heart failure cannot be prevented and is indicated if current guidelines are followed. The common ground for addressing (hyper)polypharmacy seems to be a multidisciplinary individual approach, where a risk-benefit profile of (cardiovascular) medication should be determined and inappropriate polypharmacy should be identified and prevented. In our study, more non-cardiovascular medications were used in the hyperpolypharmacy group (reflecting the presence of more comorbidities) than in the group with 0-9 medications, which are possible targets for a medication review. A medication review leads

to improved medication appropriateness, reduced polypharmacy and reduced adverse drug reactions(26), however, there is little evidence for an effect on clinical outcomes.(27)(28) Future research should confirm the association between hyperpolypharmacy and mortality, adjust for the presence of frailty, assess the appropriateness of the hyperpolypharmacy and study the effect of optimising polypharmacy in a randomised controlled trial. It is recommended to collect the medication data prospectively. The completeness of the medication list, medication adherence and the correct use of medication should be verified. For longer follow-up periods, information on changes in medication use should also be collected.

CONCLUSION

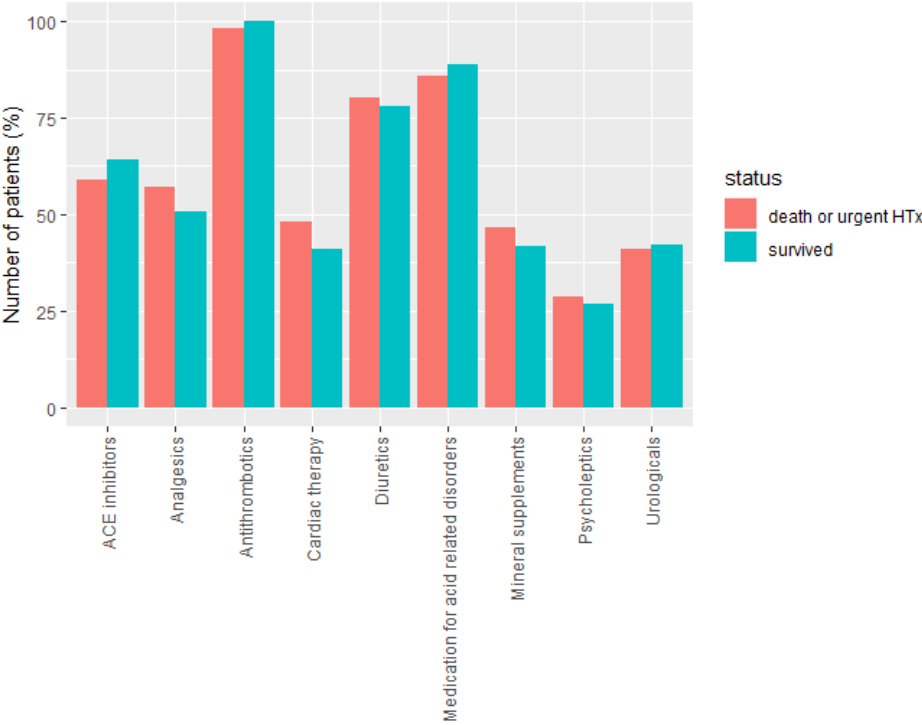
This study showed that polypharmacy is highly prevalent in patients with primary LVAD implantation. Hyperpolypharmacy also occurred frequently, and was independently associated with mortality. Future research is warranted to confirm this association and to assess the efficacy of individual risk-benefit profiling of (cardiovascular) medication to ensure appropriate polypharmacy and to decrease negative health outcomes.

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SUPPLEMENTARY MATERIAL



Supplementary Figure S1. The percentage of patients using a particular medication (i.e. the 10 most commonly used medications in the entire study population), stratified by survival

Supplementary Table S1. Use of cardiovascular medication and non-cardiovascular medication in patients with LVAD categorised according to the Anatomical Therapeutic Chemical (ATC) classification (second level) and stratified by the level of polypharmacy

ATC code (second level)	all patients (n=210)	0-9 medications (n=137)	≥10 medications (n=73)
Cardiovascular medications¹			
B01 Antithrombotic agents	209 (99.5%)	137 (100%)	72 (98.6%)
C01 Cardiac therapy (cardiac glycosides (i.a. digitalis), antiarrhythmics, cardiac vasodilators (i.a. nitrates))	90 (42.9%)	49 (35.8%)	41 (56.2%)
C03 Diuretics	165 (78.6%)	99 (72.3%)	66 (90.4%)
C07 B-blockers	15 (7.1%)	8 (5.8%)	7 (9.6%)
C08 Calcium channel blockers	20 (9.5%)	13 (9.5%)	7 (9.6%)
C09 ACE inhibitors, angiotensin II receptor blockers	132 (62.9%)	79 (57.7%)	53 (72.6%)
C10 Lipid modifying agents	79 (37.6%)	39 (28.5%)	40 (54.8%)
Non-cardiovascular medications¹			
A02 Medications for acid related disorders	185 (88.01%)	117 (85.4%)	68 (93.2%)
A03 Medications for functional gastrointestinal disorder	1 (0.5%)	1 (0.7%)	0
A06 Medications for constipation	26 (12.4%)	13 (9.5%)	13 (17.8%)
A07 Antidiarrheals, intestinal antiinflammatory/antiinfective agents	3 (1.4%)	0	3 (4.1%)
A10 Medications used in diabetes	25 (11.9%)	7 (5.1%)	18 (24.7%)
A11 Vitamins	10 (4.8%)	6 (4.4%)	4 (5.5%)
A12 Mineral supplements	90 (42.9%)	55 (40.1%)	35 (47.9%)
B03 Antianemic preparations	33 (15.7%)	12 (8.8%)	21 (28.8%)
B05 Blood substitutes and perfusion solutions	4 (1.9%)	1 (0.7%)	3 (4.1%)
G03 Sex hormones and modulators of the genital system	5 (2.4%)	1 (0.7%)	4 (5.5%)
G04 Urologicals (I.a. medications used in prostatic hypertrophy)	88 (41.9%)	50 (36.5%)	38 (52.1%)
H01 Pituitary and hypothalamic hormones and analogues	2 (1.0%)	0	2 (2.7%)
H02 Corticosteroids for systemic use	9 (4.3%)	2 (1.5%)	7 (9.6%)
H03 Thyroid therapy	20 (9.5%)	9 (6.6%)	11 (15.1%)
H05 Calcium homeostasis	1 (0.5%)	1 (0.7%)	0
J01 Antibacterials for systemic use	23 (11.0%)	10 (7.3%)	13 (17.8%)
J02 Antimycotics for systemic use	2 (1.0%)	1 (0.7%)	1 (1.4%)
J05 Antivirals for systemic use	1 (0.5%)	0	1 (1.4%)
J06 Immune sera and immunoglobulins	1 (0.5%)	0	1 (1.4%)
L01 Antineoplastic agents	1 (0.5%)	0	1 (1.4%)
L02 Endocrine therapy	3 (1.4%)	2 (1.5%)	1 (1.4%)
L04 Immunosuppressants	4 (1.9%)	0	4 (5.5%)
M04 Antigout preparations	23 (11.0%)	5 (3.6%)	18 (24.7%)
M05 Medications for treatment of bone disease	2 (1.0%)	0	2 (2.7%)
N02 Analgesics	110 (52.4%)	64 (46.7%)	46 (63.0%)
N03 Antiepileptics	8 (3.8%)	3 (2.2%)	5 (6.8%)
N04 Anti-parkinson medications	1 (0.5%)	1 (0.7%)	0
N05 Psycholeptics	57 (27.1%)	24 (17.5%)	33 (45.2%)
N06 Psychoanaleptics	15 (7.1%)	7 (5.1%)	8 (11.0%)
N07 Other nervous system medications (parasympathomimetics, medications used in addictive disorders, antvertigo preparations)	1 (0.5%)	0	1 (1.4%)

Supplementary Table S1. CONTINUED.

ATC code (second level)	all patients (n=210)	0-9 medications (n=137)	≥10 medications (n=73)
P01 Antiprotozoals	2 (1.0%)	1 (0.7%)	1 (1.4%)
R01 Nasal preparations	3 (1.4%)	3 (2.2%)	0
R03 Medications for obstructive airway diseases	11 (5.2%)	4 (2.9%)	7 (9.6%)
R05 Cough and cold preparations	4 (1.9%)	2 (1.5%)	2 (2.7%)
R06 Antihistamines for systemic use	2 (1.0%)	0	2 (2.7%)
S01 Ophthalmologicals	1 (0.5%)	0	1 (1.4%)

¹ ATC categories of medications used by at least one patient are presented.

ACE, angiotensin-converting enzyme; ATC, Anatomical Therapeutic Chemical; LVAD, left ventricular assist device; NOAC, non-vitamin K antagonists;

Supplementary Table S2. The association between the prescription of medications preventing stroke (antihypertensives, antithrombotics and lipid-lowering agents) and survival (mortality and urgent heart transplantation)

Variables added to the Cox proportional hazards model	Univariate model			Multivariate model*		
	HR	95% CI	P-value	HR	95% CI	P-value
Medications to prevent stroke±	0.88	0.67-1.74	0.40	0.83	0.61-1.12	0.22
Age				1.04	1.00-1.07	0.06
Sex				1.05	0.60-1.82	0.88
Charlson Comorbidity Index				1.14	0.81-1.60	0.45

* Stratified for device type

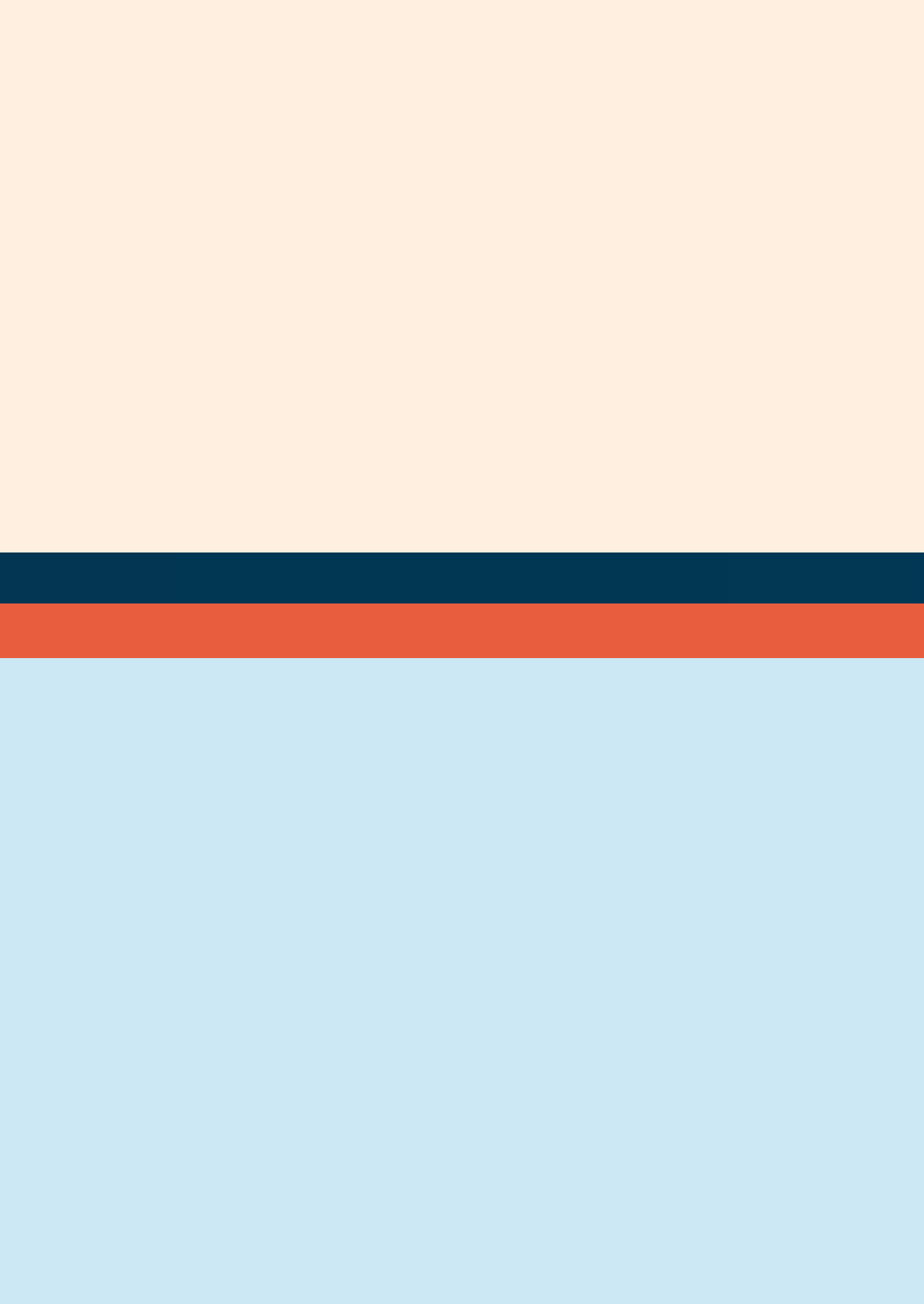
± ATC groups C07-C09, B01, C10

Supplementary Table S3. The association between the prescription of cardiac medications and survival (mortality and urgent heart transplantation)

Variables added to the Cox proportional hazards model	Univariate model			Multivariate model*		
	HR	95% CI	P-value	HR	95% CI	P-value
Cardiac medications±	1.16	0.93-1.44	0.20	1.17	0.93-1.49	0.19
Age				1.03	1.00-1.07	0.06
Sex				0.99	0.57-1.73	0.97
Charlson Comorbidity Index				1.03	0.74-1.44	0.86

* Stratified for device type

± ATC groups B01, C01, C03, C07, C08, C09, C10.



CHAPTER 7

Soluble suppression of tumorigenicity-2 (sST2) predicts mortality and right heart failure in LVAD patients

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ABSTRACT

Background

Soluble suppression of tumorigenicity-2 (sST2) predicts mortality in heart failure patients. The predictive value of sST2 in left ventricular assist device (LVAD) patients remains unknown. Therefore, we studied the relationship between sST2 and outcome after LVAD implantation.

Methods

Patients implanted between January 2015 and December 2022 were included. Survival of patients with normal and elevated pre-operative sST2 levels was compared using Kaplan-Meier analysis. The relationship between post-operative sST2, survival and right heart failure (RHF) was evaluated using a Joint Model (JM). Multivariate JM analysis adjusted for serially measured NT-proBNP was performed.

Results

The median follow-up was 25 months, during which 1573 post-operative sST2 levels were measured in 199 patients, with a median of 29 ng/ml. Survival in patients with normal or elevated pre-operative sST2 levels (n=86) did not differ significantly (p=0.22). Time-dependent post-operative sST2 levels were significantly associated with mortality, with a hazard ratio (HR) of 1.20 (95% CI: 1.10-1.30, p<0.01) and a HR of 1.22 (95% CI: 1.07-1.39, p=0.01) for RHF, both per 10 unit sST2 increase. The sST2 instantaneous change was not predictive for survival or RHF (p=0.99, p=0.94 respectively). Multivariate JM analysis showed a significant relationship between sST2 with mortality adjusted for NT-proBNP with HR 1.19 (95% CI: 1.00-1.42, p=0.05), while the HR of RHF was not significant (1.22, 95% CI: 0.94-1.59, p=0.14), both per 10 unit sST2 increase.

Conclusion

Time-dependent post-operative sST2 predicts all-cause mortality after LVAD implantation independently of NT-proBNP. Future research is warranted into possible target interventions and the optimal monitoring frequency.

INTRODUCTION

Soluble suppression of tumorigenicity-2 (sST2) is a prognostic indicator for mortality in heart failure (HF) patients and may help in risk stratification in HF patients.(1) Although the mechanism has not been elucidated completely, it is known that sST2 is part of the ST2/interleukin-33 (IL33)-pathway, which is activated by increased cardiac wall stress.(2) Cardiac myocytes and lung epithelial cells are amongst the sources of sST2 production, enhanced by pro-inflammatory cytokines.(3)(4) Normally, IL-33 binds to the membrane bound transmembrane isoform of ST2 (ST2L) and thereby prevents apoptosis and fibrosis. Soluble ST2 acts as a decoy receptor for IL-33, so the cardioprotective effect of IL-33 is lost when IL-33 binds to soluble ST2.(5)

In contrast to the general HF population, only a few studies examined the role of sST2 in patients with end-stage heart failure. Left ventricular assist device (LVAD) implantation results in unloading of the left ventricle and promotes reverse modeling(6). Despite improving survival and complication rates, patients on LVAD support have a relatively high mortality rate and frequently suffer from adverse events such as right heart failure.(7)(8) Hence, there is a continuous search for new biomarkers as a potential tool for early prediction and treatment. sST2 could contribute to stratification and early recognition of deterioration in patients on LVAD support. Tseng et al. demonstrated very high sST2 levels in patients with end-stage HF before LVAD implantation, especially in patients in cardiogenic shock at implantation. After LVAD implantation, sST2 levels dropped significantly, with normalized values after three months, suggesting that LVAD implantation leads to a reduction of fibrosis and inflammation(9). Opfermann et al. showed a significant increase in sST2 during the initial post-operative period after LVAD implantation and normalization to pre-operative levels after one week and normal levels after three weeks.(10)

Although repeated sST2 measurements appeared to be a strong predictor of outcome in patients with acute HF(11), the predictive value of serially measured sST2 levels in LVAD patients on long term outcomes has not been elucidated yet. Therefore, we aimed to assess the relationship of serially measured sST2 and long-term outcome in patients on LVAD support. We hypothesized that elevated or increasing sST2 levels predict adverse outcome such as right heart failure or death.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study design

In this single Center retrospective cohort study patients receiving a HeartWare (HVAD) or HeartMate3 (HM3) between January 2015 until December 2021 in the University Medical Center Utrecht (UMCU) were included. The follow-up was until May 2022. The study was approved by the local ethics committee of the UMCU (no: 20-195) and was handled in accordance with the Declarations of Helsinki and Good Clinical Practice. The need for informed consent for the use of retrospective data was waived. Data were retrieved from the electronic health records.

Endpoints

The primary endpoints of the study were all-cause mortality and right heart failure. All-cause mortality was defined as: death or urgent heart transplantation (HTx) during follow-up. Transplantation was labelled as urgent HTx if a patient had received priority status on the waiting list (National 1A, national 1B, or international HU). Without the urgent heart transplantation, the patient would probably not have survived and we therefore considered this as adverse outcome in addition to death. Patients were censored for ongoing support at the end of follow-up, explantation and non-urgent HTx. Right heart failure was defined using the definitions of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) as: requiring right ventricular assist device support or nitric oxide inhalation and/or inotropic therapy for more than 1 week at any time after LVAD implantation. For the current study we included the first right heart failure event > 30 days post-implantation for analysis, since sST2 was mostly measured after the initial post-operative period.

sST2 measurement

Both pre- and post-operative sST2 levels were analyzed. sST2 was measured during regular outpatient visits (every 3-4 months) and from biobanked samples if available. Written informed consent was provided by patients that were included in the biobank. sST2 was measured in heparin plasma using the ASPECT-PLUS ST2 assay on an ASPECT Reader (Critical Diagnostics, San Diego, CA, USA). Biobanked samples were centrifuged within 6 hours after withdrawal, and plasma was stored at -80°C. Levels of sST2 using biobanked samples after a maximum of one freeze/thaws cycle were analyzed by using the Presage ST2 ELISA assay according to manufacturer's instructions (Critical diagnostics, San Diego, CA, USA).(9) The

ASPECT Reader and Presage ST2 ELISA techniques are comparable ($R^2=0.92$).⁽¹²⁾

Statistics

Pre-operative sST2

We assessed survival (all-cause mortality) in patients within normal and elevated pre-operative sST2 levels (cut-off: 35 ng/ml, which is used in heart failure patients) using Kaplan-Meier analysis. As a sensitivity analysis, we used a cut-off of 27 ng/ml, which was demonstrated to be the best cut-off in chronic HF patients for all-cause and cardiovascular death and HF hospitalization.⁽¹³⁾ The last sST2 measurement within 30 days before the primary implantation was included.

Post-operative sST2

The intracluster correlation coefficient was calculated to express the variation of post-operative sST2 within patients and between patients. To visualize the trajectory of post-operative sST2, a heatmap was created, which is a visualization technique (not for quantification) that shows the height of the average sST2 levels for all patients in one figure. Time bins of 90 days were used, and the heatmap was sorted on patients with the highest sST2 measurement in the entire dataset. Primary and secondary endpoints were indicated in the heatmap.

In addition, to study the association between longitudinal sST2 measurements and our primary and secondary endpoints using a joint model (JM) approach⁽¹⁴⁾. A JM approach was chosen, since it deals with irregular measurement intervals and missing data and was used in comparable settings in previous studies.⁽¹⁵⁾⁽¹⁶⁾ Within this two-step method, the trajectory of sST2 over time is combined with a time-to-event model. The longitudinal pattern of sST2 is estimated using linear mixed effects (LME) modeling). The LME included a random effect for both the intercept and time, with patient ID as the clustering level. A natural spline was used to allow for non-linearity in the association between time and sST2, with a knot at 90 days. Four random cases were displayed, to visualize the estimated trajectory and the sST2 measurements. The accuracy of the predicted levels of sST2 was evaluated using the median square error of the LME. Time to-event analysis in the JM was done using two cause-specific multivariable Cox regression for the primary and secondary outcome, stratified for device type (HVAD or HM3) adjusting for clinically relevant variables: age at primary implantation, body mass index (BMI), sex, temporary mechanical support at primary implantation, INTERMACS, ischemic etiology and right ventricle (RV) function. RV function was classified as poor, moderate or good by two independent cardiologists, who individually classified the RV based on echocardiography and right heart catheterization using earlier published methods.⁽¹⁷⁾ Within the JM, both the effect of the predicted sST2 and

the predicted change in sST2 at the time of the event (the instantaneous slope) on the primary and secondary outcome were assessed. As a sensitivity analysis, a multivariate JM analysis, was performed, adjusted for serially measured NT-proBNP, with a \log_{10} transformation of NT-proBNP and a natural spline with a knot at 90 days. In this multivariate JM similar covariates as in the primary analysis were adjusted for.

In literature, patients that receive a heart transplantation, including patients that were listed as high urgent, are usually censored. Hence, we performed a sensitivity analysis similar to the primary JM analysis, now also censoring for urgent HTx.

To assess whether post-operative sST2 trajectories vary in patients on different types of LVAD support (HVAD, HM3), we fitted another separate linear mixed effect (LME) model similarly to the LME model in the JM analysis, and added device type as a fixed variable. Significance of the prediction of the sST2 trajectory by device type was assessed using a χ^2 -log likelihood test comparing models with and without the predictor device type.

Pre- and post-operative sST2

To assess the correlation between pre-operative sST2 and post-operative sST2, pre-operative sST2 levels and predicted sST2 levels at the end of the follow-up were visualized in a scatterplot. Moreover, to quantify this relationship, the Spearman correlation coefficient of the pre-operative sST2 and predicted sST2 at the end of the follow-up or at the time of the event was calculated in all patients that were included in the primary JM analysis and of whom pre-operative sST2 was available. The flowchart of patients that were included for each of the analysis is displayed in the graphical abstract. Model assumptions of both linear mixed models and Cox regression were checked. P-values < 0.05 were considered significant. Results are presented as median and inter-quartile range (IQR) for continuous variables and as number or percentages for categorical variables. All analyses were performed using R version 3.6.3.

RESULTS

Between 2015 and January 2022 237 patients received either HVAD or HM3 as a primary LVAD implantation at the University Medical Center Utrecht. Baseline characteristics of all patients with and without post-operative sST2 measurement(s) are presented in Table 1, with complete covariates for all patients. The median age at implantation was 56 years (IQR: 16 years) and 65% of the patients were male. Most

patients had non-ischemic cardiomyopathy as underlying disease (70%). The median follow-up time was 25 months (IQR: 33 months), during which 61 (26%) patients died after a median of 10 months (range: 0-69 months). Table 2 shows the causes of death. 8 patients (3%) received urgent HTx after a median of 26 months (range: 1-66 months), 15 patients (6%) received normal HTx after a median of 36 months (range: 11-64) and no patients were weaned from LVAD support. Three patients received urgent HTx due to RV-failure. Other reasons were: obstructed outflow graft, recurrent driveline infection, recurrent pump thrombosis or recurrent untreatable symptomatic ventricular tachycardia's (leading to RV-failure). Right heart failure > 30 days after surgery was diagnosed in 26 patients (11%). None of these patients were treated by a right ventricular assist device (RVAD) implant.

Table 1: Baseline characteristics of all patients (n=237).

		All patients n=237
Age (years)		56 [46-62]
Male sex n(%)		155 (65.4)
Ischemic etiology n(%)		72 (30.4)
Dilated etiology n(%)		149 (62.9)
BMI (kg/m ²)		24.5 [21.8-27.5]
BSA (m ²)		1.94 [1.80-2.09]
Right ventricle-function	Poor n(%)	36 (15.2)
	Moderate n(%)	126 (53.2)
	Good n(%)	75 (31.6)
Device type	HeartWare n(%)	84 (35.4)
	HeartMate3 n(%)	153 (64.6)
INTERMACS	1 n(%)	54 (22.8)
	2 n(%)	71 (30.0)
	3-7 n(%)	112 (47.3)
Pre-operative temporary support n(%)		42 (17.7)
Pre-operative diabetes n(%)		34 (14.3)
Pre-operative eGFR (ml/min/1.73m ²)		62 [46-87]
Pre-operative Bilirubin (μmol/L)		19 [13-32]

Table 2: Causes of death of all patients.

Type of death	Number of patients n (%), total = 61
Device malfunction	3 (4.9)
Infection	10 (16.4)
Multi-organ failure	12 (19.7)
Neurological	13 (21.3)
Right heart failure	9 (14.8)
Other	14 (23.0)

Pre-operative sST2

sST2 was measured pre-operatively (<30 days before surgery) in 86 patients, with a median of 57 ng/ml (IQR: 57 ng/ml). Figure S1 depicts a boxplot of the pre-operative sST2 in patients that reached the primary endpoint and patients that did not. Supplemental table S1 shows the baseline characteristics of patients with and without pre-operative sST2. Patients with pre-operative sST2 level more often had a good RV-function, were more frequently implanted with a HM3, were less often on temporary mechanical support and were more often classified as INTERMACS 3-7. Figure 1 depicts the Kaplan-Meier survival of patients with high (>35 ng/ml in 64 patients) or normal (≤ 35 ng/ml in 21 patients) pre-operative sST2 levels. Survival of patients with normal or elevated pre-operative sST2 levels did not differ significantly ($p=0.22$). The sensitivity analysis with a cut-off of ≤ 27 ng/ml included 72 patients with elevated levels and 14 patients with normal sST2 levels (figure S2). Similar to the primary Kaplan-Meier analysis, survival was not significantly different between the two groups ($p=0.14$).

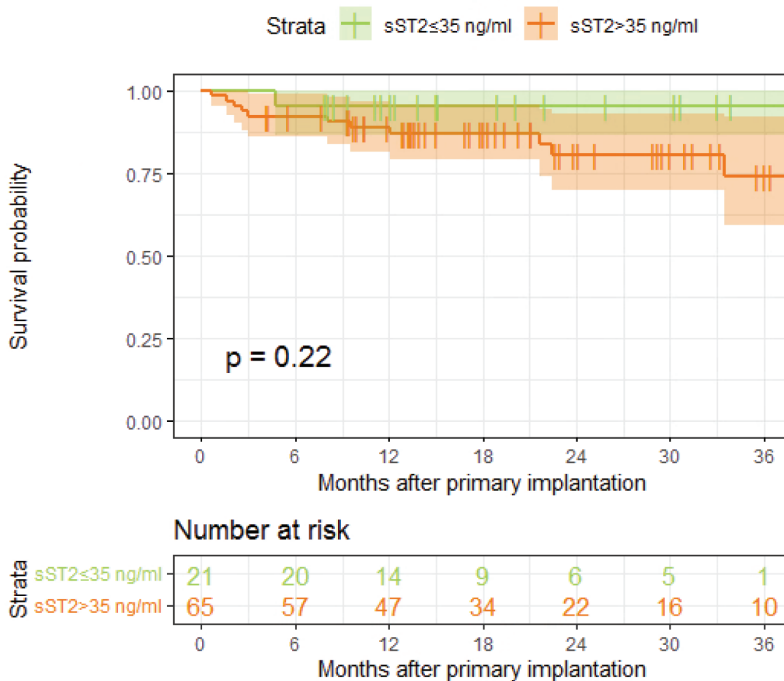


Figure 1: Kaplan–Meier survival of patients with a normal (≤ 35 ng/ml) or elevated (> 35 ng/ml) pre-operative soluble suppression of tumorigenicity-2 (sST2) level.

Post-operative sST2

In total, 1573 post-operative sST2 levels were measured in 199 patients, with a median of 29 ng/ml (IQR: 21 ng/ml). 38 patients out of 237 had no post-operative sST2 measurements, of which the majority died early. Figure 2 depicts the post-operative sST2 measurement and its predicted trajectories of four random cases. The median square error of the predicted sST2 trajectories by the LME was 4.5 ng/ml. All predicted sST2 trajectories are displayed in Figure S3, separated for patients with and without event (death, urgent HTx, right heart failure or no event). The intracluster correlation coefficient of post-operative sST2 was 0.73, so 73% of the variation observed in post-operative sST2 is explained by differences between patients, and the remaining 27% is a result of variation within patients over time. Figure 3 shows a heatmap sorted by highest sST2 level in the entire post-operative sST2 measurement set, visualizing both primary and secondary endpoints and the height of the sST2 level for all patients. The majority of the patients that reached the primary (survival) and secondary outcome (right heart failure) are concentrated in the lower part of the figure, with higher sST2 levels over time, suggesting that patients that reached the primary outcome have higher sST2 values. To test this finding, Joint Model (JM) analysis was performed, which confirmed the predictive value of time-dependent sST2 for survival with HR = 1.20 (95% CI: 1.10-1.30, $p < 0.01$) for a 10 unit increase in sST2 (Table 3). In addition, time dependent sST2 was a predictor for right heart failure as well, with a HR of 1.22 (95% CI: 1.07-1.39, $p = 0.01$) for a 10 unit increase. A sensitivity analysis where we censored for urgent transplantation, instead of considering it a proxy for mortality, confirmed the significant relation between time-dependent sST2 and survival, with a HR of 1.18 (95% CI: 1.08-1.30 $p < 0.01$) for a 10 unit increase of sST2. Thus, higher expected levels of sST2 at a point in time are predictive for a worse survival. We also investigated whether the instantaneous dynamics sST2 values at the time of the events would be more predictive than the time-dependent predicted values. However, the predicted instantaneous change in sST2 at the time of the event was not an independent predictor of survival (HR: 0.99 (95% CI: < 0.01 - > 10.0 , $p = 0.99$) nor of right heart failure (HR: 1.15 95% CI: < 0.01 - > 10.0 , $p = 0.94$).

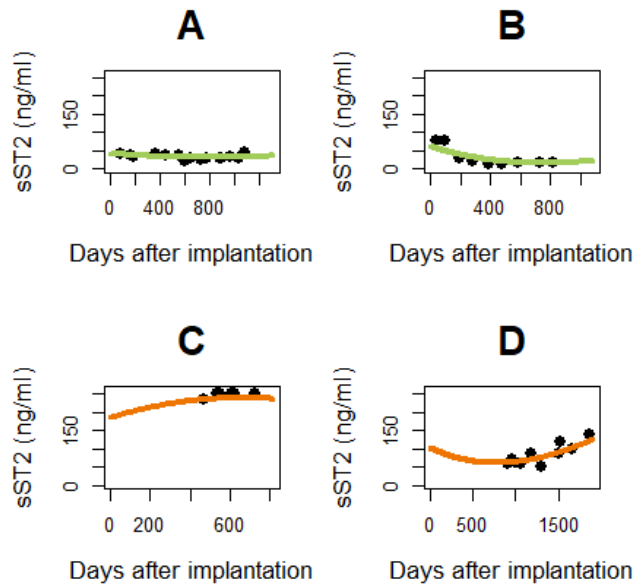


Figure 2: Trajectory of post-operative soluble suppression of tumorigenicity-2 (sST2) levels in four patients. The black dots indicate the sST2 measurement, and the predicted sST2 trajectory by the linear mixed effects model is depicted by the colored line for patients (A and B) without event (A and B) or patients that reached the primary endpoint (C and D).

Table 3: Joint model results for soluble suppression of time-dependent tumorigenicity-2 (sST2) and survival and right heart failure.

	Survival		Right heart failure	
	Hazard Ratio[95% CI]	p-value	Hazard Ratio[95% CI]	p-value
Age at implantation	0.99 [0.96-1.02]	0.58	1.00 [0.96-1.03]	0.83
Sex (1=male)	1.32 [0.59-3.07]	0.53	1.30 [0.43-4.29]	0.69
Ischemic etiology	1.13 [0.46-2.89]	0.83	0.52 [0.11-1.90]	0.37
BMI (kg/m ²)	1.06 [0.98-1.13]	0.11	0.97 [0.87-1.08]	0.57
RV-function	0.78 [0.46-1.32]	0.36	1.18 [0.53-1.39]	0.71
INTERMACS	1.02 [0.67-1.50]	0.92	0.52 [0.26-1.01]	0.06
Time-dependent sST2	1.20 [1.10-1.30]	<0.01	1.22 [1.07-1.39]	0.01

CI: confidence interval, BMI: body mass index, RV: right ventricle.

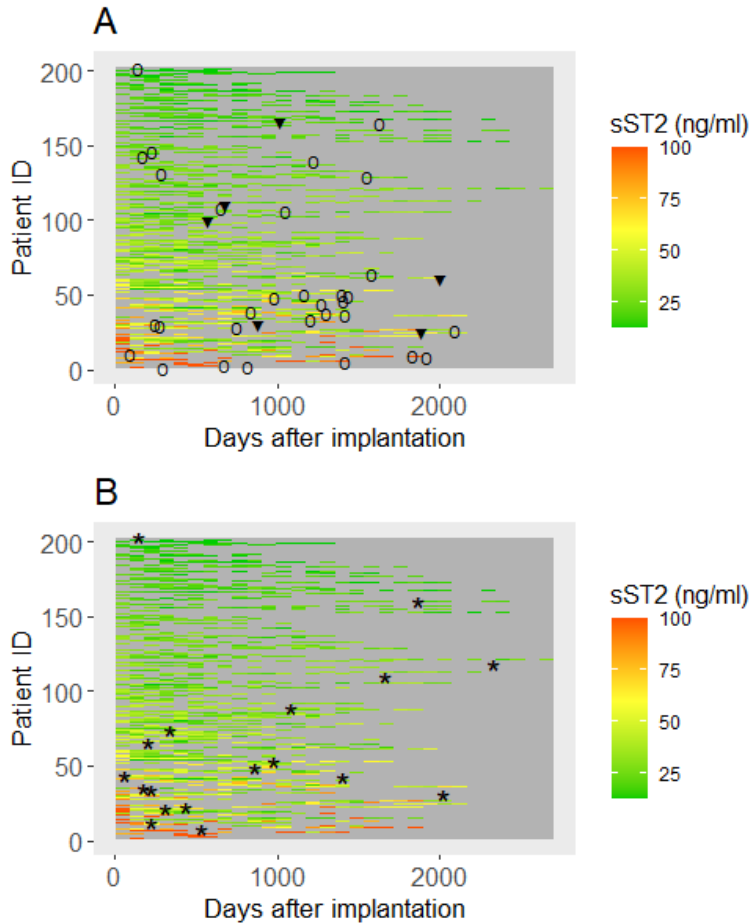


Figure 3: Heatmap for death or urgent heart transplantation (A) and right heart failure (B) of all post-operative soluble suppression of tumorigenicity-2 (sST2) levels, sorted by highest value. The triangle (▼) indicates urgent heart transplantation, the circle (O) indicates death and the asterisk (*) indicates right heart failure.

In total, 1851 post-operative NT-proBNP levels were measured in 191 patients, with a median of 1457 ng/ml (IQR: 2095 ng/ml). Figure S4 depicts a histogram of all NT-proBNP values. In addition, the log₁₀-transformed NT-proBNP levels are displayed. Multivariate JM analysis, adjusted for serially measured NT-proBNP, showed a significant relationship with mortality and urgent HTx with HR 1.19 (95% CI: 1.00-1.42, $p=0.05$) per 10 unit increase of time-dependent sST2. As an example, this means that the HR is 1.19 for an sST2 of 30 instead of 20 ng/ml sST2. For RHF the relationship was not significant after adjustment for NT-proBNP, with HR 1.22 (95% CI: 0.94-1.59, $p=0.14$) per 10 unit increase. In the multivariate JM,

the HR of time-dependent NT-proBNP for mortality was 3.22 (95% CI: 0.62-16.5, $p=0.14$) for a NT-proBNP level that is 10 times higher. As an example, this implies a HR of 3.22 for an NT-proBNP of 2000 instead of 200 pg/ml. For RHF, the HR of time-dependent NT-proBNP was 2.18 (95% CI: 0.28-14.2, $p=0.42$) for a NT-proBNP level that is 10 times higher in the multivariate JM.

In addition, we explored the potential role of device type as a possible confounder for survival.(17)(18) In a sensitivity analysis using LME with device type as additional fixed effect, device type was not a significant predictor of the trajectory of sST2 ($p=0.26$).

Finally we studied the relation between pre-operative sST2 and predicted post-operative sST2 at the event or end of the follow-up (figure S5). The Spearman correlation coefficient of pre-operative sST2 and predicted post-operative sST2 at the end of the follow-up was 0.05 ($p=0.63$).

DISCUSSION

In this study on long term serial sST2 measurements in a large group of patients on LVAD support, we demonstrated that time-dependent sST2 levels after LVAD implantation are predictive for mortality and RHF. The time-dependent sST2 level was predictive for both right heart failure and mortality, whereas the instantaneous increase of sST2 at the event or end of the follow-up was not a significant predictor. In addition, time-dependent sST2 is a significant predictor for mortality independently of time-dependent NT-proBNP (graphical abstract). sST2 trajectories did not differ between patients on different types of LVAD support. We found no significant difference in survival on LVAD in patients with and without elevated pre-operative sST2 levels.

sST2 has been studied extensively in general heart failure patients for more than a decade(5). Vark et al. studied the prognostic value of serial sST2 measurements in patients with acute heart failure and suggested that an increase or stabilization of sST2 levels may be useful in daily practice for stratification or to monitor treatment.(11) Moreover, sST2 is an independent risk factor for hypertensive left ventricular hypertrophy.(19) Repeated sST2 measurements provide independent prognostic information in addition to NT-proBNP in patients with acute heart failure. As NT-proBNP is a biomarker indicating volume overload, while sST2 is a marker of remodeling, inflammation and cardiac fibrosis, the two biomarkers are complementary.(11)(20)(21) sST2 levels may be increased in other, mostly

inflammatory-associated diseases such as COPD, pneumonia or sepsis.(22) However, in contrast to NT-proBNP, sST2 is independent of important prognostic factors such as age, sex, BMI, hypertension, smoking, prior myocardial infarction or renal dysfunction(23)(24)(25)(26) and only modestly positively correlated with NT-proBNP.(24) In a systematic review, Janssen et al. concluded that natriuretic peptides before LVAD implantation are not predictive of all-cause mortality.(27) On the other hand, Bellavia et al. showed that higher pre-operative levels of NT-proBNP were associated with a higher risk of post-LVAD RHF.

Recently, some short-term studies on sST2 were performed in patients with end-stage heart failure on LVAD support (9)(26). In a prior pilot study, we reported sST2 analysis in 38 patients with end-stage heart failure both before and up until 6 months after LVAD implantation. sST2 was elevated in patients just before LVAD implantation and decreased to normal values within three to six months after primary LVAD surgery. No difference was observed between male and female patients.(9) In contrast, Denfeld et al. found a different sST2 trajectory in 79 male and 19 female patients within the first 6 months after LVAD implantation, whereas fairly similar trajectories in symptoms were demonstrated from pre- to 6 months post-implantation. Female patients showed an initial increase after implantation, followed by a decrease, whereas male patients showed an overall decrease.(28) In the current study, none of the covariates including sex were independent predictors for adverse outcome in addition to longitudinal sST2 measurements.

Our study revealed no significant relation between the instantaneous slope of sST2 and neither primary or secondary outcome. This is in line with the findings of Vark et al. who found no significant relationship between the instantaneous slope of sST2 and all-cause mortality and HF rehospitalization in HF patients.(11) However, the relationship may be diminished due to the limited monitoring frequency or relatively low number of patients with increasing levels of sST2, which therefore might have led to an underestimation of the effect slope by the linear mixed model. To the best of our knowledge, we were the first to evaluate the predictive value of serially measured sST2 in patients on long-term LVAD support independently of NT-proBNP. For the current study we used a JM approach, to allow for analysis with irregular and longitudinal sST2 measurements and different types of outcome. JM allows for individual variation, due to the use of a random effect for both the intercept and time in the linear mixed effect models.(14) In addition, it allows for evaluation of the effect of an instantaneous slope in the biomarker of interest in addition to the predicted instantaneous value at the time of the event (or end of the follow-up). To deal with the competing risks, we used two cause-specific Cox models in the JMs. The cause-specific hazard function indicates the hazard rate of

an event in subjects who are currently free of events.(29) Within JM we were also able to adjust for important covariates, including serially measured NT-proBNP.

Limitations

This study has some limitations. sST2 was not measured at fixed intervals in all patients from the start in 2015. Therefore sST2 measurements in some patients were irregular or absent. Pre-operative sST2 levels were present in a relatively small subset of patients (86/237), including patients that were more stable at the time of implant, regarding INTERMACS and RV-function. So, less severe patients were included for this analysis, which could have affected the results (e.g. underestimation of the effect). Therefore, this cannot directly be extrapolated to the whole LVAD population. To deal with missing and irregular data, we used a JM approach that estimates the trajectory of post-operative sST2 levels. Due to the relatively low number of events, we were not able to distinguish predictive values specific for different types of cause of deaths. Possibly, the association between time-dependent sST2 and RHF after adjustment for serially measured NT-proBNP did not reach statistical significance due to a relatively small patient cohort. The majority of the population was Caucasian and therefore the results cannot be extrapolated to other ethnicities. In addition, the maximum number of covariates in the JM is related to sample size. Increasing patient numbers would allow for additional clinically relevant parameters, such as early post-operative heart rate or the diurnal pattern of sST2.(30)(31) Lastly, the current study is hypothesis generating. Additional studies are warranted before sST2 is recommended to be widely used as a predictive parameter in daily clinical routine for LVAD patients.

Future

Now that the predictive role of sST2 both early and late after LVAD implantation has been established, the question rises how often and at which moments sST2 should be measured. Since high frequency monitoring results in high costs and patient burden, future research is warranted to define the optimal monitoring frequency. Repeated echocardiography and pump parameter evaluation is suggested for patients with persistently high sST2. In addition, it is recommended to investigate whether sST2 responds to interventions such as heart failure medication or pump speed adjustment. Also, future studies with higher frequency sST2 measurements in a larger patient cohort should define a cut-off value for LVAD patients, being a specific subgroup of HF patients. The current study focused on repeatedly measured sST2 and identified it as a crucial biomarker, independently of NT-proBNP, but prediction models can be enhanced in the future by adding other biomarkers or clinical and echocardiographic variables. Altogether, early interventions in LVAD patients with elevated sST2 levels may assist in preventing complications.

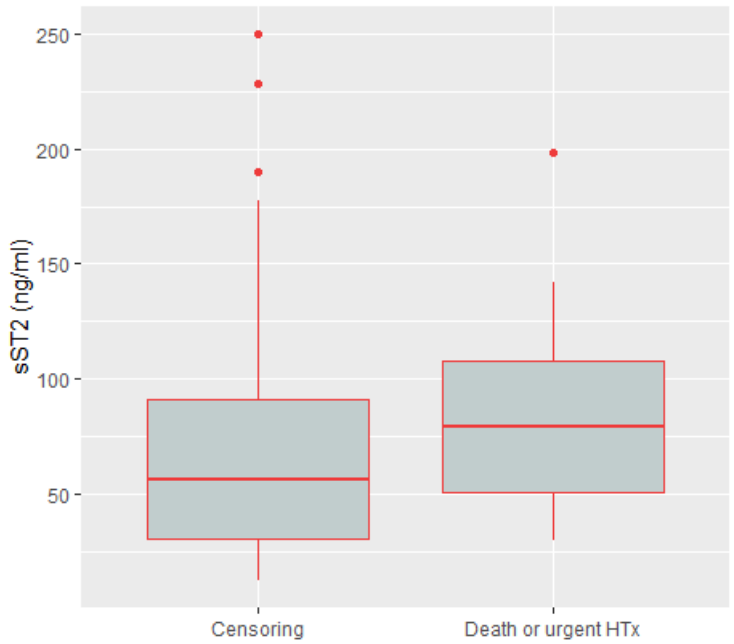
In conclusion, sST2 predicts all-cause mortality and right heart failure after LVAD implantation. Moreover, sST2 is a predictor for mortality independently of NT-proBNP. The time-dependent level of post-operative sST2 is predictive, in contrast to the instantaneous change in sST2 at the time of the event or end of the follow-up. sST2 trajectories after LVAD implantation do not cluster per type of LVAD. A closer follow-up can be appropriate in patients with high sST2 levels. Further research is warranted into the optimal monitoring frequency, the mechanisms of elevated sST2 in LVAD patients and possible targeted interventions.

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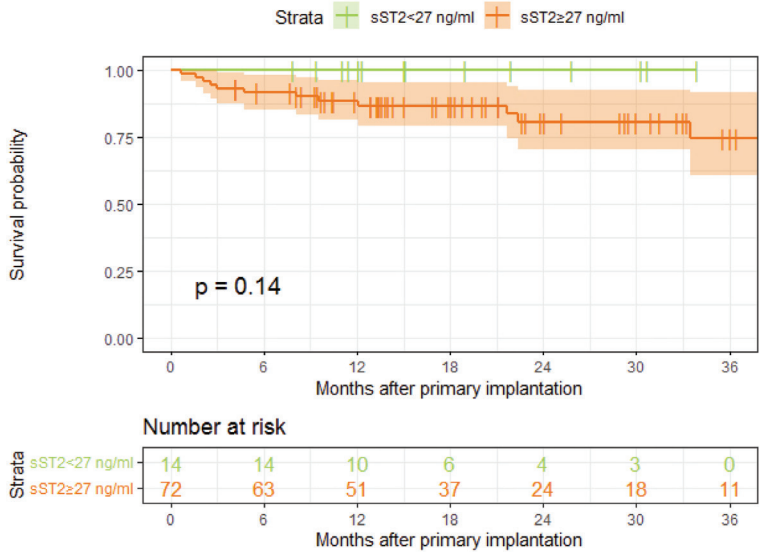
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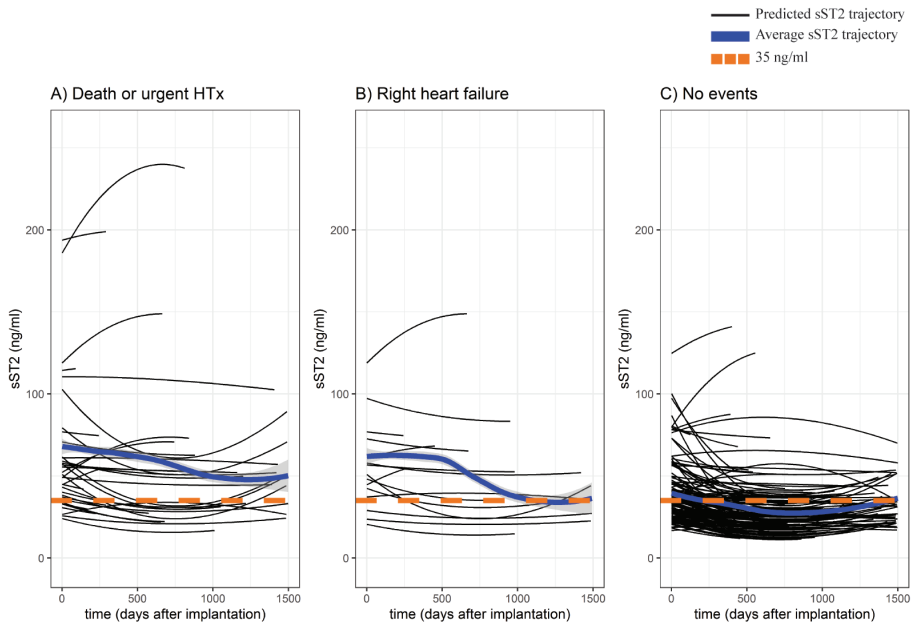
SUPPLEMENTARY MATERIAL



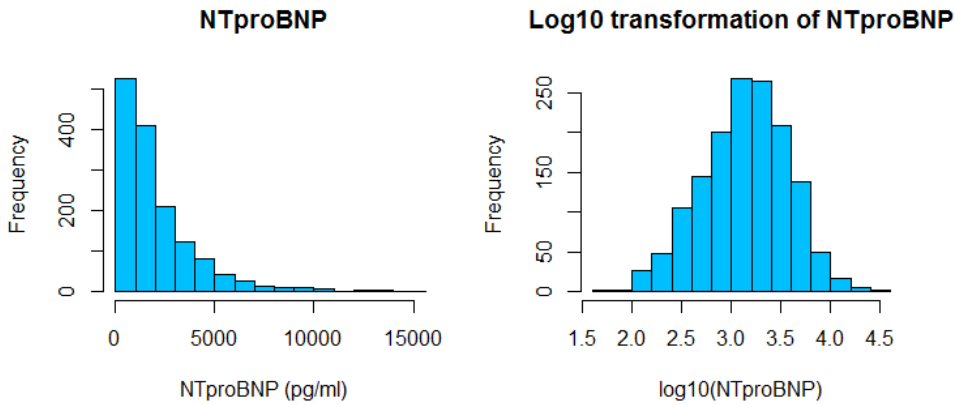
Supplemental Figure 1: Pre-operative soluble suppression of tumorigenicity-2 (sST2) of patients that died or underwent urgent heart transplantation and patients that were censored.



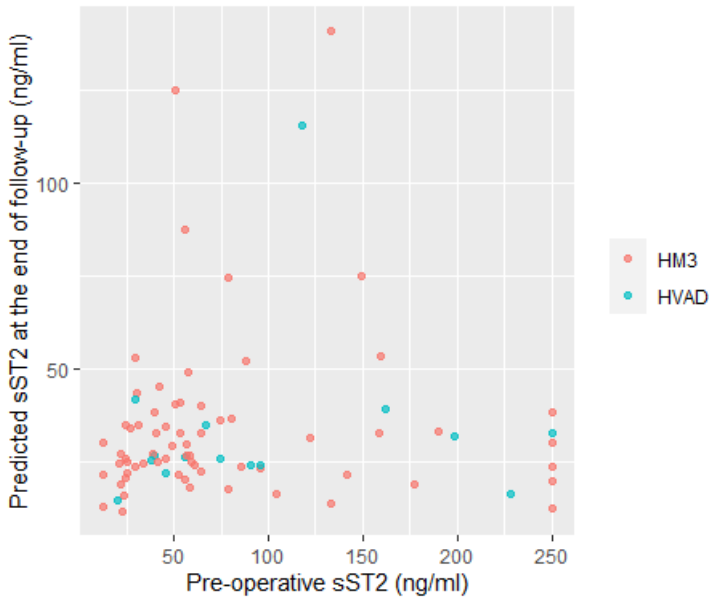
Supplemental Figure 2: Kaplan–Meier survival of patients with a normal (<27 ng/ml) or elevated (≥28 ng/ml) pre-operative soluble suppression of tumorigenicity-2 (sST2) level.



Supplemental Figure 3: Predicted post-operative individual soluble suppression of tumorigenicity-2 (sST2) trajectory of patients that died or received urgent heart transplantation (HTx) in (A), patients suffering from right heart failure in (B) and patients without primary or secondary outcome in (C). The “normal” cut-off value (35 ng/ml) is indicated by the dashed orange line, and the smoothened sST2 trajectory is depicted in blue.



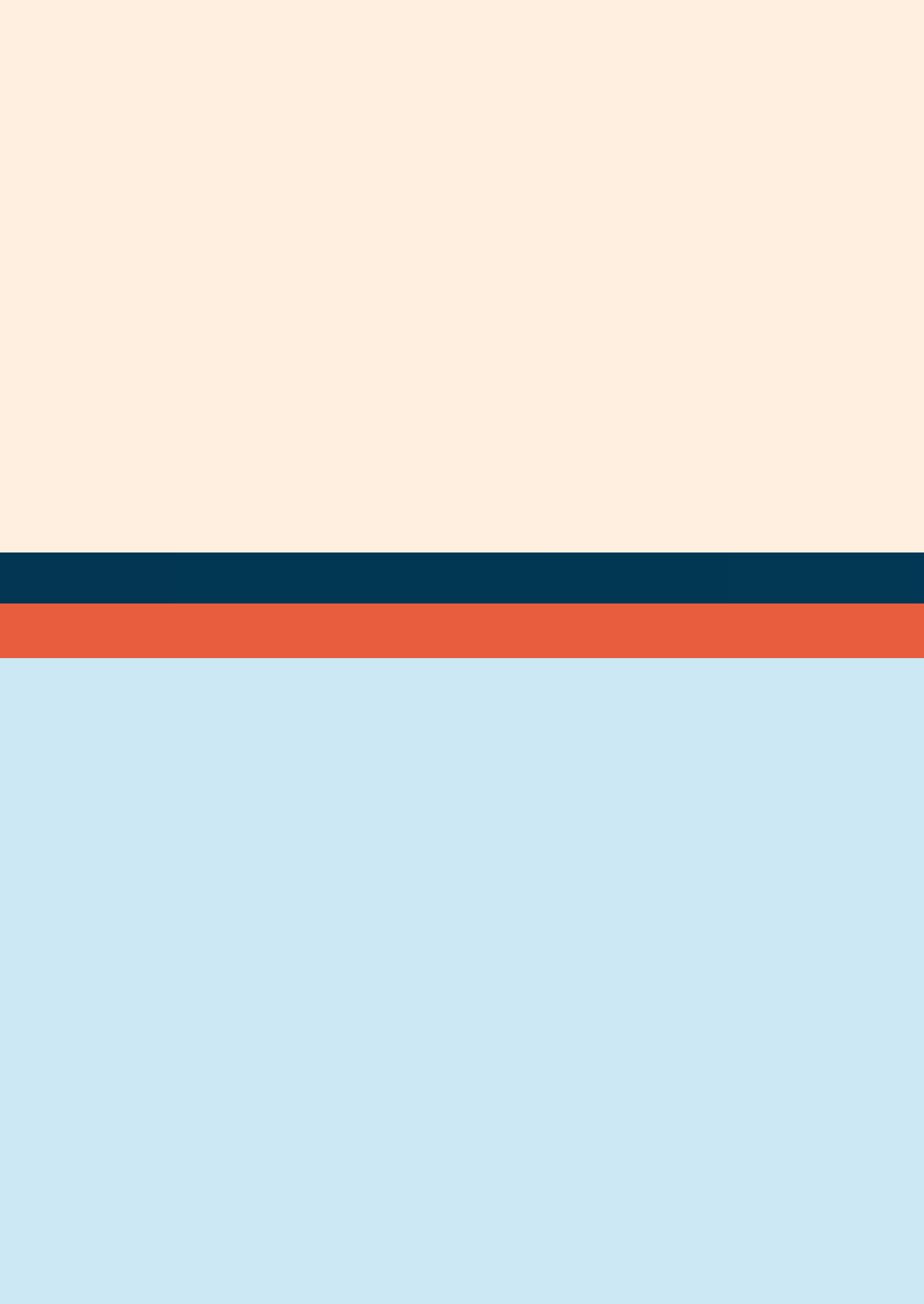
Supplemental Figure 4: Histogram of all included NT-proBNP values (left) and histogram of all log10 transformed NT-proBNP values (right).



Supplemental Figure 5: Relation between pre-operative soluble suppression of tumorigenicity-2 (sST2) and predicted post-operative sST2 at the event or end of follow-up categorized for device type.

Table S1: Baseline characteristic stratified for patients with and without pre-operative sST2

		Patients without pre-operative sST2 n=151	Patients with pre-operative sST2 n=86	p-value
Age (years)		57 [47-62]	55 [43-61]	0.35
Male sex n(%)		95 (62.9)	60 (69.8)	0.36
Ischemic etiology n(%)		49 (32.5)	23 (26.7)	0.44
BMI (kg/m²)		24.7 [22-28]	24.4 [22-27]	0.93
Right ventricle-function	Poor n(%)	29 (19.2)	7 (8.1)	<0.01
	Moderate n(%)	82 (54.3)	44 (51.2)	
	Good n(%)	40 (26.5)	35 (40.7)	
Device type	HeartWare n(%)	68 (45.0)	16 (18.6)	<0.01
	HeartMate3 n(%)	83 (55.0)	70 (81.4)	
INTERMACS	1 n(%)	43 (28.5)	11 (12.8)	<0.01
	2 n(%)	49 (32.5)	22 (25.6)	
	3 n(%)	59 (39.1)	53 (61.6)	
Pre-operative temporary support n(%)		35 (23.2)	7 (8.1)	<0.01



CHAPTER 8

Data-driven monitoring in patients on left ventricular assist device support

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ABSTRACT

Introduction

Despite an increasing population of patients supported with a left ventricular assist device (LVAD), it remains a complex therapy, and patients are frequently admitted. Therefore, a strict follow-up including frequent hospital visits, patient self-management and telemonitoring is needed.

Areas covered

The current review describes the principles of LVADs, the possibilities of (tele) monitoring using non-invasive and invasive devices. Furthermore, possibilities, challenges and future perspectives in this emerging field are discussed.

Expert Opinion

Several studies described initial experiences on telemonitoring in LVAD patients, using mobile phone applications to collect clinical data and pump data. This may replace frequent hospital visits in near future. In addition, algorithms were developed aiming to early detect pump thrombosis or driveline infections. Since not all complications are reflected by pump parameters, data from different sources should be combined to detect a broader spectrum of complications in an early stage. We need to focus on the development of sophisticated but understandable algorithms and infrastructure combining different data sources, while addressing essential aspects such as data safety, privacy and cost-effectiveness.

INTRODUCTION

The number of patients receiving a left ventricular assist device (LVAD) continuously increases due to the limited number of donor hearts and the increasing population of patients with end-stage heart failure.(1)(2) LVADs were initially implanted as a bridge to transplantation, but were also established as destination therapy driven by technical enhancements and tremendous improvement in patient survival.(3) Nevertheless, LVAD patient care remains very complex, and patients are frequently admitted for serious complications.(4) A strict follow-up including frequent outpatient clinic visits and patient self-management is therefore required. A multidisciplinary team with cardiologists, cardiothoracic surgeons, physician assistants, nurse practitioners, VAD coordinators, and social workers collaborate to provide complex LVAD patient care.(5) Nevertheless, up to 80% of the patients are readmitted within the first year after implantation.(6) Therefore, telemonitoring may further improve clinical outcome in LVAD patients by early detection of deterioration. In addition it could also reduce the number of unnecessary hospital visits. This is especially beneficial for patients who have a long travel distance to an LVAD center. Telemonitoring may improve the quality of life of patients on LVAD support, while being a cost-effective method. LVAD patients can be monitored on different aspects, such as LVAD controller parameters, blood pressure, pacemaker, implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT), coagulation values and medication and further parameters and findings that can be transmitted by a smartphone such as driveline photo's or activity.(7) The aim of the current review is to discuss the possibilities of such methods and initial experiences of telemonitoring in LVAD patients. At first, a short introduction on LVADs is provided and lastly, possibilities, challenges and future perspectives in this emerging field are discussed.

LEFT VENTRICULAR ASSIST DEVICE

Figure 1 depicts all components of an LVAD. The implanted components are the inflow cannula, which is implanted into the apex of the left ventricle (LV) and an impeller that circulates blood towards the outflow graft connecting to the aorta. The pump is connected via a driveline to an external controller with two batteries. The controller can be attached to a monitor, which allows for data retrieval. The speed of the pump is set by clinicians and optimized using echocardiography. Currently, most patients have a HeartMate 3 (HM3, Abbott, Chicago, IL, USA) or HeartWare (HVAD, Medtronic, Minneapolis, MN, USA), which was recently withdrawn from the global market.(8) Those commonly used LVADs store the speed of the rotor, the

power, the calculated flow, the pulse index (PI) or pulsatility, alarms and events. HM3 has an intrinsic pulse mode aiming to reduce blood stasis in the pump and minimizing thrombus formation.(9) Both HM3 and HVAD alarm if the flow drops below the pre-set threshold mostly at 2.5 L/min, and HVAD alarms if the power is > 2 Watts above the average power.

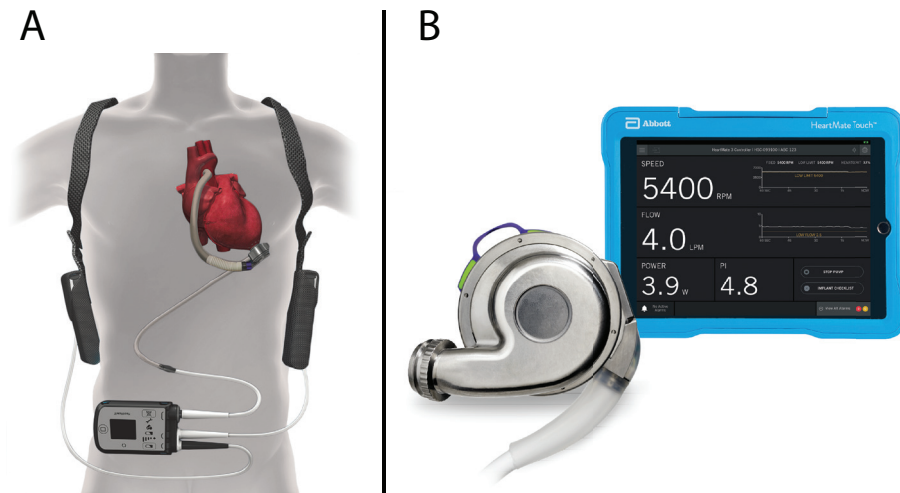


Figure 1: A: The left ventricular assist device and its components: inflow graft, pump, outflow graft, driveline, controller and batteries in twofold. B: In-hospital monitor. Permission for the use of those figures was granted by Abbott.

MONITORING OF LVAD PUMP PARAMETERS

LVAD pump parameters are currently mostly monitored in hospital at the outpatient clinic. Those are crucial for clinical assessment, as they are often affected in case of abnormalities. LVAD pump parameters are stored and can be retrieved by connecting the controller to a monitor. Currently it is impossible to retrieve data remotely due to the requirement of the physical attachment to the monitor located in-hospital. Data storage is rather limited, i.e. one sample every 15 minutes for HVAD or maximal 256 samples for HM3. In contrast, both the HeartAssist 5 (HA5, MicroMed Cardiovascular, Inc., Houston, TX, USA) and aVAD (ReliantHeart Inc., Houston, TX, USA) allow for telemonitoring. Both axial flow devices contain an ultrasonic flow probe on the outflow graft. Patients connect to a portable console to transmit the data to a secured central server using standard cellular network. Caregivers can assess the data on a website. A ten-second high resolution and real-time waveform

can be requested.(10)(11) Even though those devices are not implanted on a large scale, since axial flow devices have been proven to be inferior to centrifugal pumps, their possibility to remotely assess pump parameters should be recognized in future LVAD designs.(12) Although the diagnosis of complications in LVAD patients is never solely based on pump parameters, it is a valuable tool in the clinical assessment (table 1). Notably, not all complications are reflected by the pump parameters.

Despite the low occurrence, a much feared complication in patients on LVAD support is pump thrombosis (PT). The risk for thrombosis after LVAD implantation increases due to the exposure to foreign surfaces and regions of blood stasis. Cessation reduction of anti-platelet therapy to treat major bleeding may increase the risk of a thromboembolic event.(13) In addition, poorly controlled hypertension results in a decreased LVAD flow, which can also contribute to thrombus formation, that may result in PT or an ischemic stroke.(14) Several studies focused on the development and evaluation of algorithms, aiming for detection of pump thrombosis at an early stage.(15)(16)(17)(18)(19) The prevailing variable that was monitored in those algorithms is the pump power. During the development of pump thrombosis, the formation of a blood clot results in a surge in power consumption since it tries to maintain the set speed, and will also cause a falsely elevated pump flow estimation.(18)(19) Although for example HVAD has a standard-of-care threshold to detect “High Watt” alarms, more sensitive settings for pump power may enable earlier detection. Slaughter et al. developed an algorithm based on four detectors, including short and longer trends, comparing power to population norms, and a detector for the initial phase where no patient-specific estimates were present. Testing the algorithm retrospectively, they identified pump thrombosis on average four days before clinical presentation, with a sensitivity of 85%.(15) In addition to trends in pump power, the circadian rhythm of pump parameters may add valuable information. Consolo et al. showed that patients gain physiological circadian (24-hour) rhythmicity in their pump parameters during the initial post-operative period, which remains stable in the long term. The circadian rhythm is diminished during the early stages of pump thrombosis, providing the opportunity to detect pump thrombosis at an early stage. After the resolution of the thrombus, a stable circadian rhythm reemerges.(16) However, enabling the incorporation of the circadian rhythm into an algorithm requires high resolution datasets. A thrombus may also arise in the outflow graft, resulting in an outflow graft obstruction. In addition, the outflow graft can be obstructed by kinking of the graft or external compression of the graft. Commonly it results in a decrease in flow over several weeks, but may also abruptly cause a decreased flow.(20)

On the other side of the spectrum there is an increased bleeding risk, which instead may lead to a decreased power, flow and increased PI (table 1). Also, the circadian rhythm of power and flow may diminish.(21) It can have several causes, such as intrinsic coagulopathies or over-anticoagulation for example due to liver congestion. Moreover, there is an increased risk for a bleeding event following treatment of a thrombotic event due to cessation of anticoagulation therapy.(22) However, bleeding complications such as a hemorrhagic stroke are not caused by anticoagulation therapy alone, as a supra therapeutic INR is neither necessary nor sufficient to cause a hemorrhagic stroke.(23) In addition, patients on LVAD support often suffer from acquired von Willebrand syndrome, where the Von Willebrand Factors (VWF) are structurally misshaped due to increased shear stress, leading to an increased bleeding risk. Bleeding in the gastro-intestinal tract (GI) often occurs at the location of an arteriovenous malformation (AVM) that arise as a consequence of diminished pulsatility.(24) No studies specifically focused on detecting such patterns in pump power, but algorithms developed for pump thrombosis may be applicable as well.

In addition to bleeding and thrombosis risks, patients are at risk of right ventricular (RV) failure, which may occur early after implantation or in the long term.(25) The right ventricle output needs to match the increased flow generated by the device. The optimal pump speed is determined using echocardiography to ensure that the septum is in the midline. With a septal shift towards the left side, the efficiency of the RV contraction is negatively affected, since the contribution of the septum to RV contraction is diminished, which needs to be compensated by the RV free wall, leading to failure.(26)(27) If RV failure leads to a significant reduction in preload for the left ventricle, it is accompanied by a reduced LVAD pump power and flow. However, diagnosis is mostly done using echocardiography.

Other important complications that may be reflected by pump parameters and occur as a consequence or aggravate after LVAD implantation are ventricular arrhythmias (VAs) and atrial arrhythmias (AA). VA occurs in 20-60% of the patients and is more frequently diagnosed in the initial postoperative period with a U-shaped incidence over time.(28) Fibrosis, ischemia, inotropic and vasopressor medication, or suction events may cause VAs. Suction is the occurrence where the septum occludes the inflow cannula, caused by a mismatch in preload and pump speed, resulting in a sudden drop in pump flow. When de instantaneous and 15-second average PI differ by more than 45%, a so called "PI-event" is stored and the speed drops to its pre-set low speed, and increases gradually to the normal speed. Gross et al. revealed high suction rates in clinically stable outpatients which reveals the importance of the development of early detection algorithms, since

suction may lead to irritation of cardiac tissue and arrhythmias.(29) Moreover, an algorithm was built to early detect suction, which can be used as a diagnostic tool or as an automatic physiological controller.(30) Both suction and arrhythmias result in a decreased power and flow, and may cause either increased or decreased PI.

MONITORING MEDICATION ADHERENCE

Patients on LVAD support require anticoagulation medication. The current guidelines recommend a vitamin K-antagonist (e.g. warfarin) and aspirin with an international normalized ratio (INR) target range of 2.0-3.0.(31) Optimizing anticoagulation is challenging, since there is a small therapeutic range between bleeding and thrombotic risks in LVAD patients.(32) INR is measured several times per week to monitor anticoagulation status. The workflow of INR measurement differs per center and country and may even differ within centers. It may comprise self-monitoring (self-testing), self-management (self-testing and self-dosage), or it is managed by an anticoagulation management clinic or service.(33) Self-management of INR after intensive training by experienced staff is superior regarding the time in the therapeutic range when compared to telemedical-based INR management.(34) Self-management of INR is not standard care yet and may not be suitable to all patients. Some centers have experience in structured phone consultation or using mobile apps where INR measurements are transmitted. In addition to INR as a tool to monitor the effect of anticoagulation, the mean arterial pressure (MAP) is important to follow-up, since a higher MAP is associated with an increased risk of stroke during LVAD support.(35)(36)(37) Therefore, blood pressure management is very important, and experts recommend to maintain the MAP below 85 mmHg.(38) Therefore, many patients receive Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers. To check whether the blood pressure lowering medication is sufficient, the MAP is measured. Blood pressure measurement is challenging in patients on continuous flow LVAD, due to a diminished pulsatility. Therefore, the MAP is preferably measured using a Doppler or a slow cuff device.(39) Slow cuff devices were reported to perform most optimally.(40) The majority of patients do not have such device at home and therefore MAP is often only measured at the outpatient clinic or transmitted via a mobile phone application.

Table 1: Complications that may occur in patients on left ventricular assist device support (LVAD), including the change in LVAD parameters and diagnosis that may, but not per se, occur.

Complication	LVAD pump parameters				Diagnosis
	Power	Predicted Flow	Actual flow	Pulsatility index	
Major bleeding	↓	↓	↓	↑	Hemoglobin level, endoscopy, CT-scan
Pump thrombosis	↑	↑	↓	↓	Hemolysis (serum lactate dehydrogenase 2.5 times upper limits of normal range), echocardiography, LVAD pump data
Outflow obstruction	↓	↓	↓	↓	Echocardiography, Computed Tomography scan(66), LVAD pump data
Right ventricular failure	↓	↓	↓	↑	Echocardiography, elevated central venous pressure
Arrhythmias	↓	↓	↓	↓ or ↑	Electrocardiogram
Suction	↓	↓	↓	↑	LVAD pump data
Hypertension	↓	↓	↓	↑	Blood pressure measurement
Aortic insufficiency	↑	↑	↑	↓	Echocardiography
Hemorrhagic or ischemic stroke	≈	≈	≈	≈	Computed Tomography scan
Driveline infection	≈	≈	≈	≈	Signs of infection, C-reactive Protein and culture of exit site

MONITORING USING NON-INVASIVE DEVICES

Even though telemonitoring has been recognized as a relevant topic, telemonitoring programs for LVAD patients have not been implemented on a large scale yet.(7) A few studies evaluated the feasibility of telemonitoring using mobile phone applications or structured phone consultations and their effect on patient outcomes in patients on LVAD support.(41)(42)(43)(44)

Casida et al. developed an application for LVAD patients to improve self-management and allow caregivers to monitor their patients remotely.(41) The application's content included questions on the functionality of the LVAD system and its components, evaluation of LVAD parameters, symptoms, body weight, lab tests, driveline, the color of urine and stool, diet, and fluid intake allowance. They demonstrated that it was feasible for both patients and caregivers to use an app as a telemonitoring tool. Patients and caregivers reported high acceptability and usability scores. In addition, Patel et al. evaluated a virtual care platform for telemonitoring of LVAD patients.(44) Their platform included monitoring of LVAD parameters and medication adherence, a two-way messaging function and

educational videos (i.e., on troubleshooting). Patients who used the platform (n=25) had significantly less outpatient visits when compared to the control group (n=77), but no difference was found in 30-day readmission rates. Although 3 out of 25 patients showed engagement rates below 10%, the median overall engagement rate was 73%. No false alarm rate or burden was reported, and workload for healthcare professionals was not discussed. Although feasibility is demonstrated in small studies, additional research needs to expel long-term acceptance, usability, adherence and cost-effectiveness. Furthermore, Schmidt et al. developed a smartphone application where different relevant parameters can be sent daily to the LVAD center. Using the application, weight, INR, medication, symptoms and LVAD parameters and driveline photos can be evaluated at the hospital. They studied usability, acceptable and functionality of the application in 13 patients for four weeks. Usability was scored 4.8 out of 5 by patients and the software was stable. Most alarms were caused by deviations in INR. They acknowledge that larger and long term studies are required to prove its added value, also to test the impact on the psychological aspect of patients.(45)

Comparable to mobile phone applications, telephone-based monitoring strategies have been reported.(42)(43) Although in literature structured telephone consultation solely is not considered as telemonitoring, it is considered valuable in order to (further) develop telemonitoring strategies. For example, the algorithm developed by Schlöglhofer et al. that determines the level of patient severity(42), can directly be transferred to application based telemonitoring and are considered a valuable step towards more automated assessment of relevant LVAD-related data. They developed a standardized telephone intervention algorithm, where patients were called every two weeks. Nurses used a flowchart with questions on pump parameters and general well-being, INR, weight MAP, temperature, dyspnea, peripheral edema, and the driveline.(42) Patients were randomized into either the intervention arm or the control arm. A high patient acceptance was reported in the intervention arm. In 42.5% of the calls a problem was identified, regarding elevated blood pressure, edema, INR outside the therapeutic range or exit-site problems. The additional workload for nurses was not discussed. Despite the small size of their study, with only 25 patients in the intervention group, the study touched upon the possibilities of additional monitoring of LVAD patients, with a significantly better survival in the intervention arm. Cost-effectiveness was not assessed in their study and remained to be investigated. In addition, Mariani et al. developed a phone-based monitoring strategy during the initial coronavirus disease 2019 (COVID-19) outbreak.(43) Patients were allowed to enter the monitoring program after extensive training. During a weekly phone call, questions were asked following a developed questionnaire including COVID-related questions in addition to LVAD-

specific questions on flow, speed, power, INR, weight, and driveline status. If necessary, the patient sent a photo of the driveline exit site via email or by phone. The pandemic may have accelerated the development of such programs. To improve the workflow of sending driveline photo's, an application was developed by Lüneburg et al., who used a machine learning algorithm to classify photos of driveline exit sites in either no infection, mild infection, or severe infection. Driveline infections are associated with an increased risk of sepsis, ischemic stroke and mortality.(46)(47)(48)(49) The algorithm that was built by Lüneburg et al. included assessing out-of-focus images, segmentation of the driveline, prediction of the region of interest, and infection classification. Their infection classification algorithm had an accuracy of 67%. Although in typical machine learning applications, 90% or higher accuracy is expected and desired, their algorithm performed better than pure visual recognition by nurses.(50) Its performance is expected to increase with larger datasets. Such tools may be used to pre-select cases that certainly need priority. Future prospective studies are warranted to prove the effectiveness of such algorithms.

In addition to mobile phone strategies, other non-invasive devices may be used to early detect adverse events. Kaufmann et al. studied the possibilities of acoustic measurements in LVAD patients and demonstrated that a sound peak in a specific frequency band correlates with the presence of thrombi inside the pump. In addition, an increase of 75% in the sound amplitude of the rotary frequency indicates pump thrombosis. They concluded that analysis of the acoustic spectrum of an LVAD using a microphone is a reliable method to detect pump thrombosis.(51) In addition, Boilson et al. showed alterations in the amplitude of higher-order harmonics in patients on HMII support diagnosed with pump thrombosis.(52) Those acoustic measurements were performed in-hospital. In contrast, Mainsah et al. analyzed acoustic measurements at home, where patients were instructed to perform 1-minute recordings weekly.(53) It remains to be investigated whether such acoustic methods contribute to the current practice. Detection of gradual increase in pump power or spikes in pump power may also identify pump thrombosis at an early stage without the need of an additional device. These methods should be compared in future studies. Another aspect that can be monitored non-invasively is activity. Although not studied extensively, two case examples were shown where the activity level of LVAD patients dropped several weeks before readmission.(21) However, these were only case reports and larger-scale studies are required to prove their feasibility and additional value.

MONITORING USING IMPLANTABLE DEVICES

In addition to non-invasive tools, invasive or implantable devices may be used to remotely monitor LVAD patients. Although not frequently used in combination with LVADs, the safety and feasibility of the CardioMEMS (Abbott Inc, Atlanta, GA, USA) in LVAD patients have been demonstrated.(54) The CardioMEMS, which measures pulmonary artery pressure, provides daily insight into a patient's fluid status, enabling optimization of patients prior to LVAD implantation. In addition, pulmonary artery pressure lowering medication can be monitored. Several complications such as tamponade, aortic valve regurgitation, pump thrombosis, right heart failure or significant hemodynamic arrhythmias will lead to either congestion or reduced pulmonary artery pressure, which may be detected using the CardioMEMS sensor.(55) Likewise, it allows for telemonitoring after LVAD implantation. Zhou et al. incorporated a pressure sensor into the LVAD inlet in an experimental set-up. This enables a direct measure of the left ventricle function during LVAD support.(56) They stated that this is the start of a closed loop speed control based on left ventricular pressure. Although pressure sensors or flow probes may provide valuable information, durability and reliability should be tested extensively in-vivo. The more components a device includes, the more prone it is to malfunctioning and failure. Future studies are warranted to prove its added value. Noteworthy, cost-effectiveness is not touched upon yet, and we may need to focus on more accessible and noninvasive telemonitoring tools first.

Almost 80% of the patients on LVAD support have also an ICD implanted, either with or without CRT.(57) In addition to heart rhythm, heart rate variability and thoracic impedance are measured. This provides an additional source of data to integrate with pump parameters to develop a prediction model for adverse events. Bartoli et al. described a case where intrathoracic impedance measured by a pacemaker increased preceding suction events, low flow alarms, and worsening of heart failure symptoms. (58) HeartLogic (Boston Scientific, Massachusetts, USA) developed an algorithm to early detect deterioration in heart failure patients and is available in both ICDs and CRTs.(59) The algorithm uses the first and third heart sounds, thoracic impedance, respiration rate, tidal volume, heart rate, and activity. Feasibility was shown in two patients on LVAD support.(60) Further research is needed to study the added value of monitoring LVAD patients using systems like HeartLogic. Combining an algorithm such as HeartLogic and pump parameters could further improve the prediction of adverse events, although limitations exist due to different vendor systems to integrate data flows into a real-time predictive model.

CONCLUSION

The interest in telemonitoring as addition to the current clinical follow-up for LVAD patients has increased over the last decade. Despite broad recognition of its importance, telemonitoring in LVAD patients has not yet been fully explored nor integrated into standard care. We provided an overview of different strategies aiming to early detect adverse events. In addition to standard clinical care, mobile phone applications or phone-based strategies, other implanted or non-invasive devices, and sophisticated algorithms may further improve both quality of life and survival in patients on LVAD support. A future challenge is to develop the infrastructure that enables to integrate data from different sources and vendors. Sophisticated, modular and patient-specific algorithms are desired to further optimize LVAD patient care. Large scale implementation studies are needed across different healthcare systems to optimize LVAD care pathways. Finally, additional studies are warranted to address the cost-effectiveness of such telemonitoring strategies.

EXPERT OPINION: CHALLENGES AND FUTURE PERSPECTIVES

In the current review we described the necessity of (tele)monitoring for LVAD patients, its current forms and initial experiences. Figure 2 summarizes aspects that can be monitored in LVAD patients. Several studies were discussed showing initial experience with additional forms of monitoring patients outside hospital, utilizing phone based applications, structured telephone intervention or invasive devices. In addition to its potential to improve survival and quality of life of LVAD patients, telemonitoring could also reduce healthcare costs by diminishing the number of unplanned readmissions by early detection and intervention. In future, this may reduce the number of hospital visits. However, at the moment, experts suggest to use telemonitoring as a substitute to rather than replacing routine clinical visits. (45)(38)(61) Moreover, completely replacing personal contact with medical staff was not considered as a good development.(45) Although telemonitoring for LVAD patients seems feasible, we need to overcome several barriers.

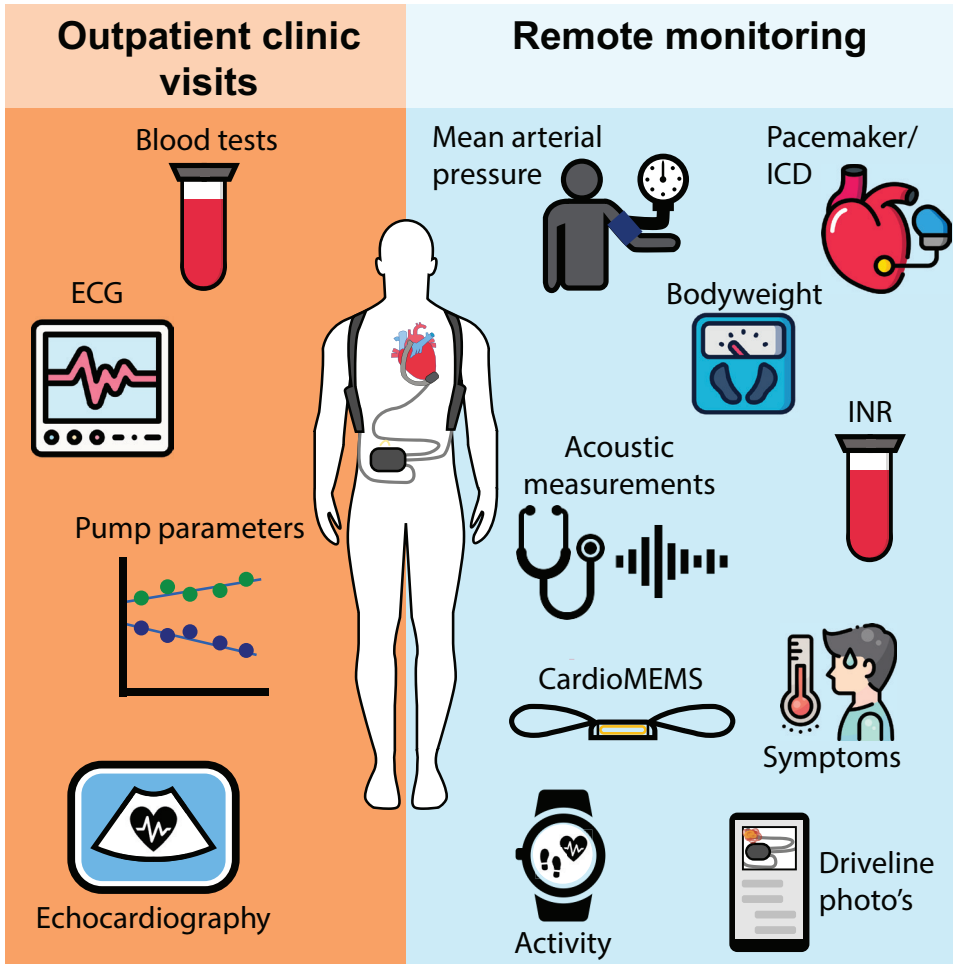


Figure 2: Aspects that can be monitored in patients on left ventricular assist device support.

One of the main barriers is the development of the data infrastructure. This requires a major investment both in resources and time, while cost-effectiveness remains to be proven. Advancements in the development and implementation of telemonitoring for LVAD are lagging behind compared to the general heart failure population, since patient groups are relatively small. Therefore, it receives less attention, while LVAD patients may especially benefit from telemonitoring due to the complexity and risk of LVAD therapy. In addition because LVAD patients already have several sensors as of their implanted devices that result in parameters that can be monitored.⁽⁶¹⁾ Experience in telemonitoring programs used in other patient groups may benefit the realization of such methods specifically for LVAD patients. Researchers should collaborate with different LVAD-centers, but also with industry. This is expected

to accelerate development and implementation of telemonitoring techniques. Due to the limited patient numbers per center, we should set-up multi-center studies to collect larger data-sets that can be used to further improve algorithms that can be used in telemonitoring methods. Application-based telemonitoring methods offer other advantages beyond telemonitoring of patients, such as centralized communication between nurses and patients. This may improve efficiency and therefore reduce the workload. However, initially, the workload is expected to increase. This may be a hurdle for healthcare providers. We do not expect major barriers for patients, since several studies on mobile phone applications that were discussed showed good patient acceptance. Though, larger long-term studies on long-term patient adherence are required. Also, a mobile phone application can be used to send a push notification to all patients and general instruction and educational videos can be uploaded in the app, so that patients can easily access those multiple times. This would further enhance self-management, an essential element in LVAD care. Telemonitoring may require active patient participation or could include automatic transfer of data. On the one hand, it is favorable if there is no need for active patient participation since this may lead to poor adherence and therefore reduces its potential.⁽⁴⁴⁾ On the other hand, by actively asking patients to participate, i.e. asking questions on symptoms, they may gain a deeper understanding of normal and abnormal situations and further improve self-care. In addition, temporarily quitting active participation in telemonitoring systems may also be predictive of deterioration. Although phone-based telemonitoring and applications were proven feasible, telemonitoring strategies can be further enriched using sophisticated algorithms for the early prediction of abnormal situations.⁽⁴¹⁾⁽⁴²⁾⁽⁴³⁾⁽⁴⁴⁾

An extensive effort is still required before algorithms can be used prospectively (figure 3). Improvement in appropriate and early notification of abnormalities without having too many alarms is needed, as alarm fatigue will hamper the successful implementation of a new monitoring strategy. Algorithms are ideally personalized and dynamic, where decisions in the trade-off between sensitivity and false alarm rate are critical. Improvements in early pump malfunction detection is a prerequisite for the success of telemonitoring in LVAD patients. Those algorithms can be improved using high-density data. Data storage on the most currently used LVADs is limited, complicating the development of prediction algorithms. A miniaturized data recorder was developed to solve this, enabling high-density pump data retrieval from HVAD. Such high density data allows us to study the mechanisms of suction and the relationship between suction and tachyarrhythmia. Even more sophisticated algorithms could make use of continuous data, with waveform analysis. Those waveforms offer much more valuable information than

just average values of power, flow and PI, to estimate the left ventricle function. (31) For example, Grinsteil et al. showed that the ventricular filling phase slope of the HVAD flow waveform correlates with the pulmonary capillary wedge pressure. (38) This would also help in the development of LVAD speed control systems in the future, to reduce suction rates. Another challenge, is to monitor pump parameters online. Despite major progress in the development of algorithms, the majority is tested retrospectively and not used prospectively. Ideally, a system is developed that automatically sends pump parameters for example to a smartphone, that in turn sends it to a secured server that enables healthcare providers to assess the patient's status. Security and privacy may be at risk and should therefore be addressed appropriately, i.e. by encrypting patient data. A possible solution for security and privacy of telemonitoring data suggested by Taralunga et al. is a block chain enabled framework.(62) Another important aspect that needs to be arranged is assigning additional staff in telemonitoring centers to assess alarms and monitor LVAD patients remotely.(61) Since the implementation of telemonitoring directly results in additional costs, cost-effectiveness studies are warranted. With increasing numbers of patients on LVAD support, a regional or national monitoring center with trained personnel could filter the false alarms.

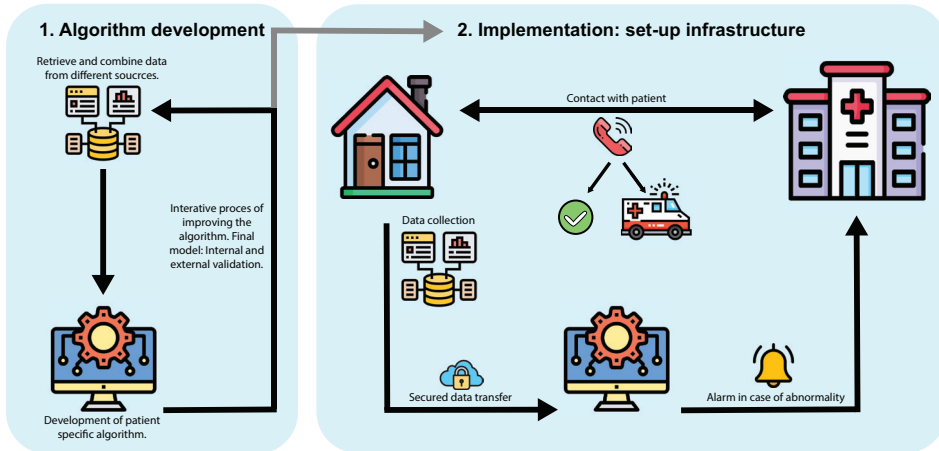


Figure 3: Steps needed before implementation and prospective usage of telemonitoring using sophisticated algorithms.

As described, most algorithms that use LVAD parameters were developed aiming to early detect PT, because it is a very severe condition and it directly affects pump parameters. Although it is a very severe condition, the incidence of pump thrombosis is very low in the contemporary LVADs.(12) Thus, we should also focus on predicting

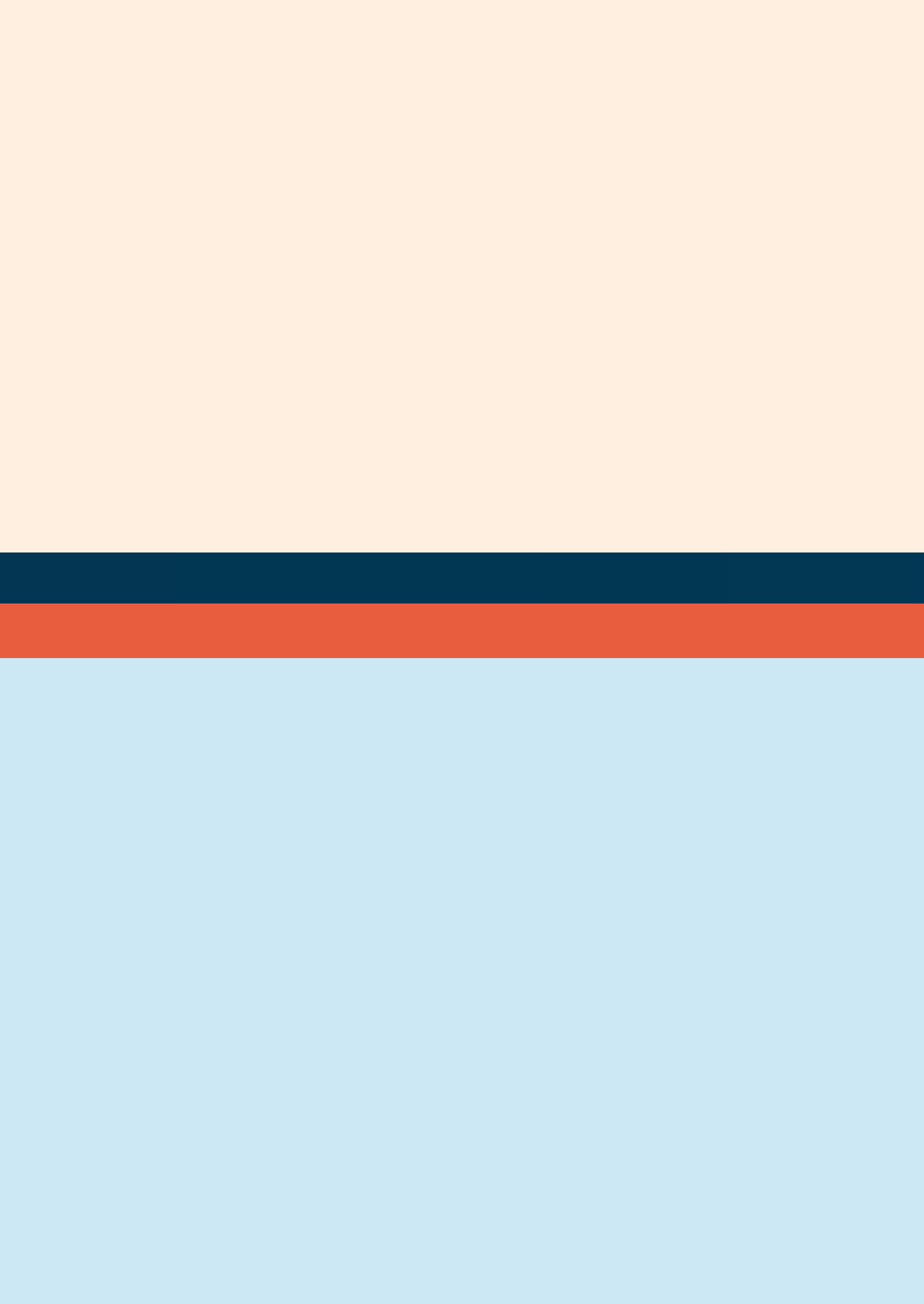
other complications. However, not all complications will be reflected by the LVAD pump parameters. Therefore, algorithms to monitor LVAD patients should not only comprise LVAD data, but also data from additional sensors, implanted devices or wearables in addition to data generated in-hospital. As technology advances, more data will be generated outside the hospital. Patients may for example not only monitor INR at home, but other biomarkers may be collected in the future using finger prick tests. In addition, we should consider focusing on blood pressure measurement and control at home, since blood pressure is not adequately controlled in more than a third of all patients on LVAD support.(63) Combining different data sources may be challenging. A seamless incorporation with hospital patient record systems is desired, as this will save time and will improve user experience for healthcare providers, also recognized by Reiss et al.(64) An open source platform such as RADAR-base is needed. It enables the integration of data streams from various sources such as wearables, which may benefit the success of implementation.(65) Algorithms need to be developed that combine input from those different sources. Progress is being made in the development of algorithms using pump parameters. The next step is combining those pump parameters with clinical data as displayed in figure 2. In such a way, clinical decision making can be improved. Though, we should first prove the added value in larger studies. In conclusion, we strongly believe that we need to focus on the development of the infrastructure utilizing sophisticated but understandable algorithms combining different data sources, while addressing important aspects such as data safety, privacy and cost-effectiveness.

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CHAPTER 9

Monitoring pump parameters to detect cardiac arrhythmia and major bleeding admissions: A proof-of-concept

Submitted

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ABSTRACT

The number of patients on left ventricular assist device (LVAD) support increases due to the growing number of patients with end-stage heart failure and the limited number of donor hearts. Despite improving survival rates, patients frequently suffer from adverse events such as cardiac arrhythmia and major bleeding. Telemonitoring is a potentially powerful tool to early detect deteriorations and may further improve outcome after LVAD implantation. Hence, we developed a personalized algorithm to remotely monitor HeartMate3 (HM3) pump parameters aiming to early detect unscheduled admissions due to cardiac arrhythmia and major bleeding. The source code of the algorithm is publicly available. The algorithm was optimized and tested retrospectively using HM3 power and flow data of 120 patients, including 29 admissions due to cardiac arrhythmia and 14 admissions due to major bleeding. Using a true alarm window of 14 days prior to the admission date, the algorithm detected 59% and 79% of unscheduled admissions due to cardiac arrhythmia and major bleeding, respectively, with a false alarm rate of 2%. The proposed algorithm showed that the personalized algorithm is a viable approach to early identify cardiac arrhythmia and major bleeding by monitoring HM3 pump parameters. External validation is needed and integration with other clinical parameters could potentially improve the predictive value. In addition, the algorithm can be further enhanced using continuous data.

INTRODUCTION

Left ventricular assist device (LVAD) implantation is an established treatment for patients with advanced heart failure. LVADs are primarily implanted as a bridge to transplant, but are also used as destination therapy in patients not eligible for heart transplant.(1) Despite improving survival rates after third generation LVAD implantation, with a five-year survival of 58.4%, patients frequently suffer from adverse events such as cardiac arrhythmia and major bleeding.(2)(3)(4) Between 20-60 % of all patients experience ventricular arrhythmia after LVAD implantation and major bleeding occurs at a rate of 0.48 per patient-year. LVAD care is complex and patients frequently suffer from adverse events.(5)(6) Hence, LVAD patients visit the outpatient clinic multiple times per year for a clinical and technical assessment and the surveillance between those visits relies purely on an alarm in case of a low flow (flow < 2.5 L/Min) and self-management by the patient. This may lead to late detection of complications. Therefore remote monitoring tools that enable early detection of LVAD related complications are desired to start early treatment.(6)(7) So far, only limited work has been done on remote monitoring of pump parameters. (6)(8)(13) Earlier studies have indicated that monitoring power to identify pump thrombosis (PT) in patients on HeartWare (HVAD) support can provide results with high sensitivity (ranging from 85% to 100%) and high specificity with a low rate of false alarms (0.15 events per patient-year).(10)(14)(15) However, due to the global market withdrawal of HVAD, HeartMate 3 (HM3) has become the most implanted LVAD underscoring the necessity for investigations into algorithms applicable for HM3. Since PT is a very scarce complication in HM3 patients, occurring in 1.4% of HM3 patients within 2 years after implantation, algorithms should also be able to detect other more common complications such as cardiac arrhythmia and major bleeding.(16) As these complications may affect power or flow values, monitoring of these parameters provide the opportunity for timely diagnosis and treatment. (8) Therefore, we aimed to develop and test a remote personalized monitoring algorithm to early detect the admission due to common adverse events (cardiac arrhythmia and major bleeding), based on the HM3 pump power and flow values.

MATERIALS AND METHODS

This single-center retrospective study was approved by the local ethics committee of the University Medical Centre Utrecht (UMCU) in the Netherlands (METC:20-195) who waived the need for informed consent. The study was conducted in accordance with Good Clinical Practice and the 2002 Declaration of Helsinki.

Patient cohort

Between December 2015 and December 2021 157 patients were implanted with HM3 in the UMCU. The follow-up was until February 2022. Measurements during index admission were removed from the analysis. Patients with a follow-up of less than 180 days were excluded, in addition to patients with more than 25% missing pump parameter data during follow-up.

Primary endpoint

The primary endpoint was unscheduled admission due to cardiac arrhythmia and major bleeding, as defined by the INTERMACS definitions. For the development and evaluation of the algorithm, the patients were split into groups. Patients without any unplanned LVAD related admission were called the “stable-LVAD patient” group. Patients with admissions due to cardiac arrhythmia or major bleeding were called the “non-stable patients” group. Patients with unplanned LVAD-related admissions other than cardiac arrhythmia or major bleeding were excluded. For the analysis, pump data on 180 days preceding the cardiac arrhythmia and major bleeding admissions were included.

Pump Data

HM3 pump parameter data were manually retrieved during outpatient visits and admissions. These files contain pump speed (RPM), motor power (Watts), pulsatility index (PI), flow (L/Min), and hematocrit (HCT). HM3 can store 256 measurements before data is overwritten. At our centre, pump parameters are usually stored every 12 hours. In some hospitalized patients, data was retrieved at a higher frequency. Hence, measurement frequency varies between patients. Therefore, data was down sampled to two samples per day with an interval of 12 hours for each patient to reach agreement between patients. Logfiles were converted to CSV and compiled into a database.

Personalized algorithm

A summary of the steps in the personalized algorithm is provided in this section. The algorithm screens for irregular observations in power and flow by patient-tailored thresholds. Initially, a linear mixed effects (LME) model is employed, which

incorporates both the cross-sectional pump parameters of “stable-LVAD patients” and the longitudinal data of each patient. This produces a personalized mean pump value that is dynamic and reflective of the patient’s stable historical baseline. Our study included 53 patients from the “stable-LVAD patient” group in our general cohort. We hypothesize that this group provides a precise estimation of the mean and variance of stable situation in LVAD patients.

During the calibration period (30 days), data from “stable-LVAD patients” is used, and thresholds are continuously updated and tailored to the patient. In addition, patient-specific thresholds are updated after LVAD pump speed change. In the final step, real-time measurements are subtracted from the patient-specific mean. These residuals show how much a pump parameter deviates from the predicted value. The residuals are smoothed using an exponentially weighted moving average (EWMA). The EWMA control chart determines the lower-control-limit (LCL) and upper-control-limit (UCL). If the smoothed values exceed control-limits, the algorithm alarms. An illustration of how the personalized algorithm operates is depicted in figure 1.

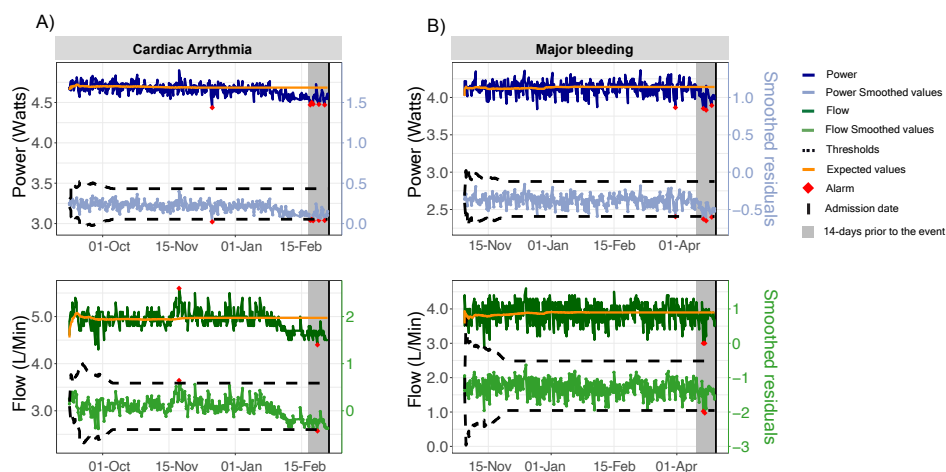


Figure 1: Personalized thresholds and out-of-control measurements for two patients with cardiac arrhythmia (panel A) and major bleeding (panel B) when monitoring flow and power is considered. 14 days prior to the admission is visualized as shaded grey area. Both two events detected when monitoring flow or power.

The following parameters in the personalized algorithm need to be tuned: coefficient of the width of the control limits during the calibration phase and after the calibration varied between 1 and 5, with steps of 1. The smoothing parameter

varied between 0.2 to 0.8 with step of 0.2.

Comparison with other algorithms

Since HM3 data is overwritten after 256 rows, it was not possible to retrieve all low flow alarms. Therefore, we could not compare our algorithm with the current situation (low flow alarms). Hence, we compared the personalized algorithm with three “simple” algorithms, namely absolute and relative thresholds, and the moving average convergence-divergence (MACD) algorithm.

Absolute and relative thresholds

Absolute thresholds were determined by calculating the average of each pump parameter during the calibration period. The absolute thresholds are determined with a variation from the mean. An alarm is raised when real-time measurements exceed the thresholds. Patient-specific thresholds for each pump parameter fixed over time. To obtain the thresholds:

$$\text{Absolute threshold} = \mu_{1:c} \pm K$$

Where $\mu_{1:c}$ is the mean in the calibration period (14 days) and K varied between 0.1 and 2 with steps of 0.1 L/min for flow 0.1 Watts for power.

The relative threshold method considers previous pump measurements during a specified time window (varying from 2 to 14 days with a step of 1 day).(11) In contrast to the absolute thresholds, the standard deviation (sd) is updated after each new measurement. The threshold solely relies on the sd of each patient, and it is equal to

$$\text{threshold}_{i,j} = sd_{i,j} * n$$

where i is the i -th patient and j is the j -th relative threshold. n was varied of 0.1-3 with a step of 0.1. If the absolute daily difference of the flow/power measurements exceeds the thresholds, the algorithm will trigger an alarm.

Moving average convergence-divergence (MACD) algorithm

The third algorithm is the MACD. MACD considers deviation between two exponentially weighted moving averages (EMA), a short and long-time span. The algorithm is sensitive to trends instead of short increases, and it triggers an alarm once the MACD line exceeds a predefined threshold. MACD has been implemented for monitoring heart failure patients. (17-18) Short and long-term time windows were varied between 1 to 10 and 10 to 14, respectively with thresholds of 0.1 to 1 L/min and Watts for flow and power, respectively.

Evaluation and definition of alarms

The performance indices to evaluate and compare the algorithms were the percentage of detected events and false alarm rate (FAR) for power and flow. All algorithms were applied to power and flow of the “non-stable group” patients. The following definitions were used:

- *True-Positive (TP)*: An alarm is labeled as a true-positive alarm if it is triggered 14 days before an admission.
- *False-Positive (FP)*: An alarm is labeled as a false-positive alarm if it is triggered more than 14 days before an admission.
- *Detection rate/ Recall*: Fraction of events detected among all admissions.
- *False Alarm Rate (FAR)*: It is defined as the number of false-positive per patient using:

$$FAR = \frac{FP}{\text{Follow-up period}}$$

Alarms within the first 14 days were ignored for all algorithms because of calibration of the parameters. For false positives, we considered four different scenarios, where the average FPR ranged between 0.5% to 2%.

RESULTS

23 out of 157 patients on HM3 support had more than 25% missing data and were therefore excluded from the analysis. 14 patients were excluded because of having less than 180 days of measurement when only two samples per day were selected. In total 120 patients were included containing $n = 53$ from “stable-LVAD” patient group and 67 patients from “non-stable patients” group, yielding total patient year of approximately 354. Table 1 shows the baseline characteristics of these patients. The median age of the patient cohort was 58 [IQR: 73] years and 65.8% were male. For the evaluation of all algorithms, 29 admissions related to cardiac arrhythmia and 14 admissions because of major bleeding were included for evaluation (figure 2).

The personalized algorithm in cardiac arrhythmia detected around half of admissions when monitoring power and 35% when monitoring flow with a FAR of 0.5%. For a FAR of 2%, the detection rate of the personalized algorithm increased to 59 and 57%, for power and flow monitoring respectively. Comparing the performance of power and flow in detecting cardiac arrhythmia admissions, the personalized algorithm revealed that power surpasses flow throughout the FAR scenarios. Flow monitoring with MACD achieved a detection rate of 37%, which was higher when compared to absolute thresholds. Using relative thresholds was more effective

in detecting cardiac arrhythmia admissions for both power and flow (48% and 42%, respectively) in scenarios with higher FARs in comparison to the absolute thresholds (31% and 37%, respectively) (figure 3).

Table 1: Baseline characteristics of all patients (n=120)

All HeartMate 3 implants		n=120
Age (years) [IQR]		55.0 [14.5]
Sex n (% male)		79.0 (65.8%)
Ischemic etiology n (%)		31 (25.8%)
BSA (m ²) [IQR]		1.96 [0.30]
BMI (kg/m ²) [IQR]		24.9 [5.97]
Primary HeartMate3 implants		n =114
eGFR (ml/min/1.73 m ²) [IQR]		64.8 [40.0]
Bilirubin (μmol/L) [IQR]		24.9 [18.0]
Right ventricle function	Poor n (%)	13 (11.4%)
	Moderate n (%)	58 (50.9%)
	Good n (%)	43 (37.8%)
Temporary support n (%)		12 (10.5%)
INTERMACS	1 n (%)	7 (6.1%)
	2 n (%)	37 (32.4%)
	3-7 n (%)	58 (50.9%)
Diabetes Mellitus n (%)		16 (14.0%)

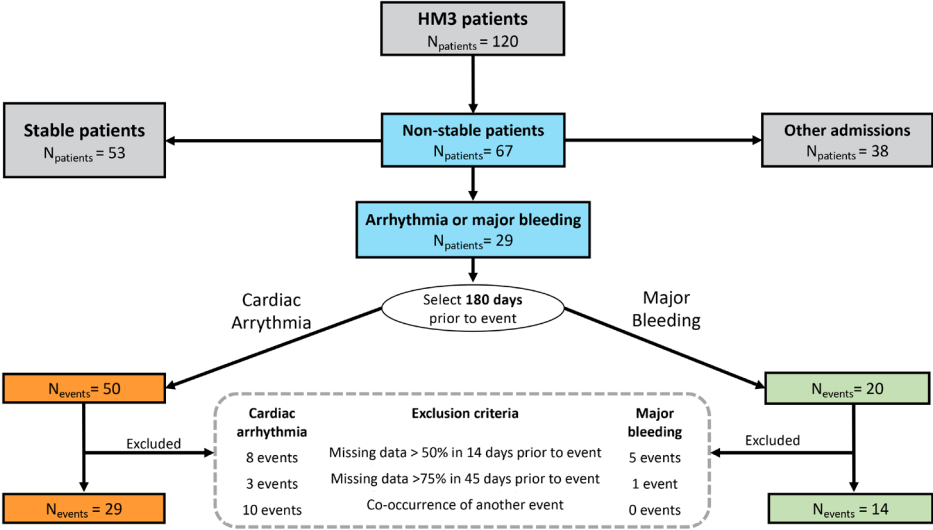


Figure 2: Flowchart of included patients and admissions due to cardiac arrhythmia and major bleeding

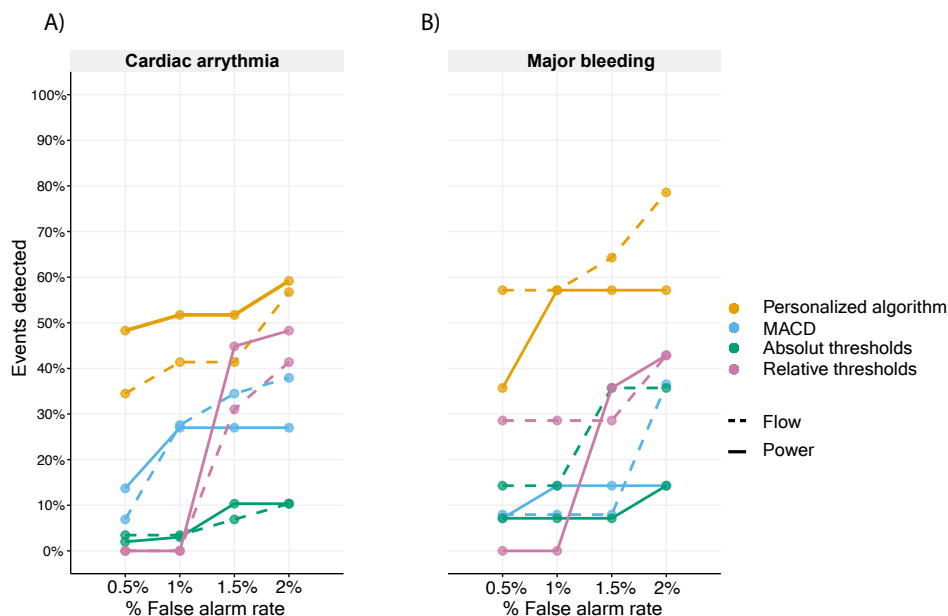


Figure 3: Detection rate comparison of the methods based on different FAR for cardiac arrhythmia (panel A) and major bleeding (panel B). Dashed lines represent flow and solid lines represent power monitoring.

The highest rate attained by the personalized algorithm in detecting major bleeding admissions was in flow monitoring (79%), whereas with power the detection rate was lower (57%). The performance of the other algorithms was lower than the personalized algorithm regarding major bleeding admissions.

The median number of days of the first alarm before the admission due to cardiac arrhythmia or major bleeding was 6.5 (IQR: 7.0) days and 7.0 (IQR: 7.5) respectively. Supplemental figure 1 displays the first alarm in the 14 days window prior to the admission for personalized algorithm. Supplemental figure 2 shows the FAR of all patients for an average FAR of 2% for power and flow, split up in admissions due to cardiac arrhythmia and major bleeding. A large variation in the number of false alarms per patient was found (range 0.005 to 18%). 10 out of 22 patients in the cardiac arrhythmia group had a high false alarm rate of more than 2%. The FAR for the “stable-LVAD” patient group was 1.62%.

DISCUSSION

Remote monitoring of LVAD pump parameters, as a supplement to outpatient clinic visits, may improve clinical outcomes by early detection of adverse events. In this proof-of-concept study, we developed and tested a personalized algorithm on HM3 parameters. 59% and 79% of the cardiac arrhythmia and major bleeding admissions were detected by the algorithm, with a false alarm rate of 2%.

The performance of the personalized algorithm was evaluated by the number of true and false alarms. Alarms within 14 days before an endpoint were assigned as a true positive alarm. The definition of this two-week window was determined by a clinical expert team and was needed because of the retrospective nature of the study. Alarms prior to this window were labeled as false positives but could be related to the admission. On the other hand, an alarm during this window can be unrelated to the admission but is counted as a true positive. Hence, prospective testing is needed to confirm the algorithm's performance. There is a trade-off between detection power and number of false alarms. Wider thresholds increase detection power but come along with more false alarms. The detection power was shown for various false alarm rates. It is important to reduce nonactionable alarms to prevent alarm fatigue, which can increase health care professionals' and jeopardize patient safety.⁽¹⁹⁾

Several patients had a relatively high number of false alarms, which may occur after a shift in pump parameters. For example, power and flow shift in their baseline after a pump speed change. Therefore, the personalized algorithm recalibrates patient-tailored thresholds after a change in pump speed. In addition, progressive worsening or medication changes that affect preload or afterload of the heart can affect the baseline of a patient's pump parameters. A VAD coordinator may update the personalized algorithm in such situations, in case of a stable patient. This could reduce the number of false alarms during prospective usage. The personalized algorithm is not updating continuously, i.e., at every new data-point, as slow upward or downward trends in the pump parameters remain undetected.

The primary endpoint used to evaluate the personalized algorithm was defined as admissions due to cardiac arrhythmia or major bleeding. Possibly, not all these admissions were accompanied by detectable changes in power or flow. Hence, the performance of the personalized algorithm may be interpreted as relatively low. However, the current situation, where the LVAD alarms in case of a low flow (i.e., 2.5 L/min), can be improved by patient tailored thresholds that help to detect trends.

Comparison with existing literature

Previous research on the prediction of complications after LVAD implantation using pump parameters mainly focused on pump thrombosis (PT) only in HVAD patients. (15)(20)(21)(22) Slaughter et al. tested a power tracking algorithm yielding a high sensitivity of 85.7%.(20) Krysinski et al. achieved high sensitivity and specificity of 100% in detecting PT events by monitoring power.(15) The sensitivity and specificity of these studies are high since PT events drastically affects pump power. In addition to the LVAD power itself, the circadian rhythm of the power was of interest in previous literature. The circadian rhythm HVAD power is diminished at early stages of PT, unlocking the potential to early identify PT prior to clinical symptoms.(21)(22) It was not possible to incorporate the circadian rhythm in the personalized algorithm due to HM3's limited data storage.

Strengths and limitations

We were the first to retrospectively test a patient-tailored monitoring algorithm for HM3 pump parameters considering two common adverse events: cardiac arrhythmia or major bleeding. It is an important addition to the current literature, as previous research mainly focused on the detection of PT. The current study has several limitations. At first, our method was evaluated using two daily samples and must be fine-tuned to higher frequency or continuous data-streams. Secondly, the study included a relatively small patient cohort using retrospective analysis. Third, we were not able to compare the performance of the personalized algorithm with the current monitoring system (low flow alarms) since all low flow alarms were overwritten after 256 rows. Hence, we compared our algorithm to other algorithms.

Future research

Several steps are required before clinical application of the personalized algorithm. First, higher frequency pump data for HM3 is needed to fine-tune the algorithm. Consolo et al. showed that during post-operative recovery, HVAD patients develop circadian rhythmicity, which remains stable in the long-term.(21) Their findings suggested that including circadian variability (CV) provides unprecedented prediction power to detect PT events. Possibly, the circadian rhythm in pump parameters is informative as well with respect to cardiac arrhythmia or major bleeding events. To test this hypothesis, we need higher frequency data. The Snoopy HM3, a non-invasive device, was developed to retrieve high-frequency HM3 data(1 sample per second).(23) This allows optimization of the algorithm applicable for online monitoring. Moreover, these high frequency datasets enable the possibility to incorporate the circadian rhythm, as power and flow show a nocturnal decrease. (24) In addition to varying thresholds throughout the day, the circadian rhythm itself may be used as a predictive tool.(21)(22)

Additional clinical data can be used to further improve the detection power of monitoring algorithms for LVAD patients, since not all admissions are preceded by a substantial change in pump parameters.(8) Clinical data such as mean arterial pressure (MAP), lab values (i.e. sST2) could be used to provide additional clinical context.(25) Moreover, either non-invasive (i.e. activity trackers, heartrate monitoring) or invasive devices (i.e. CardioMEMS, ICDs and pacemakers) may provide valuable data.(8) Other data sources could be used to influence the strictness of the personalized algorithm.

Importantly, infrastructure of the telemonitoring approaches must be set up, which can hamper clinical implementation.(8) Ideally, the algorithm is incorporated into the HM3 enabling “online monitoring” of continuous data streams. Additionally, data should be transferred to the hospital, enabling remote assessment of the patient by the VAD coordinators.

CONCLUSION

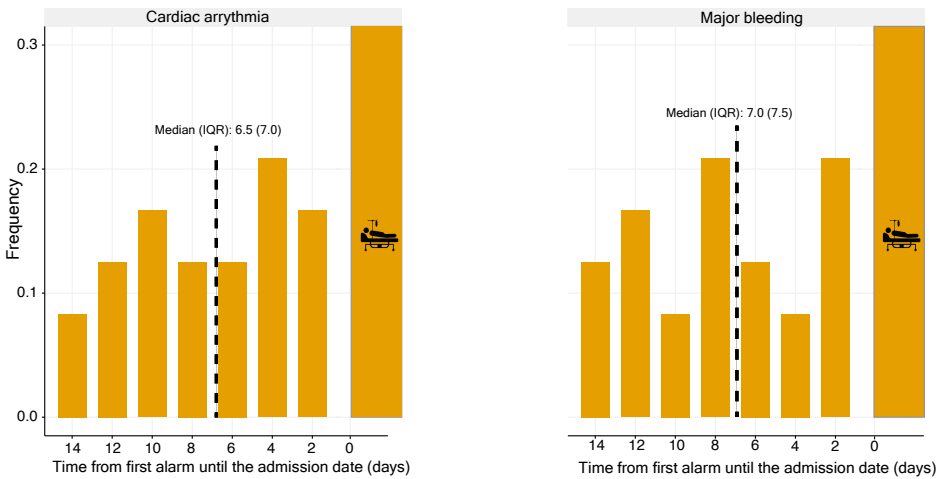
Remote monitoring of pump parameters in patients on HM3 support is a potential powerful tool to early detect adverse events. This proof-of-concept study proposes a personalized algorithm applied to HM3 parameters to detect cardiac arrhythmia and major bleeding. The performance of the developed algorithm showed an improvement compared to simple other algorithms, however, several admissions remained undetected. Further improvement using higher frequency data accommodating circadian fluctuation, a larger study size with a prospective design is warranted.

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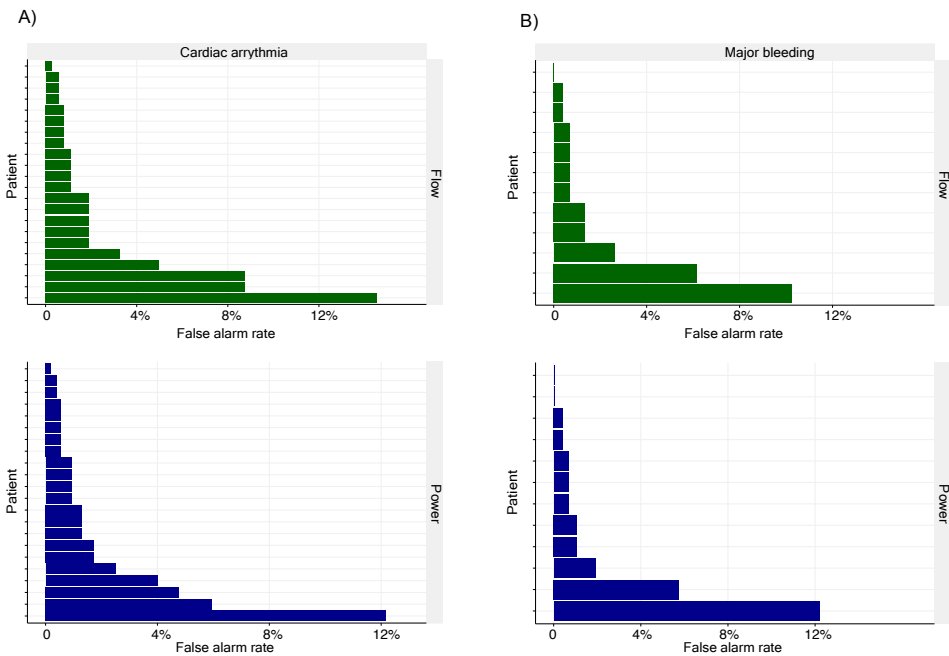
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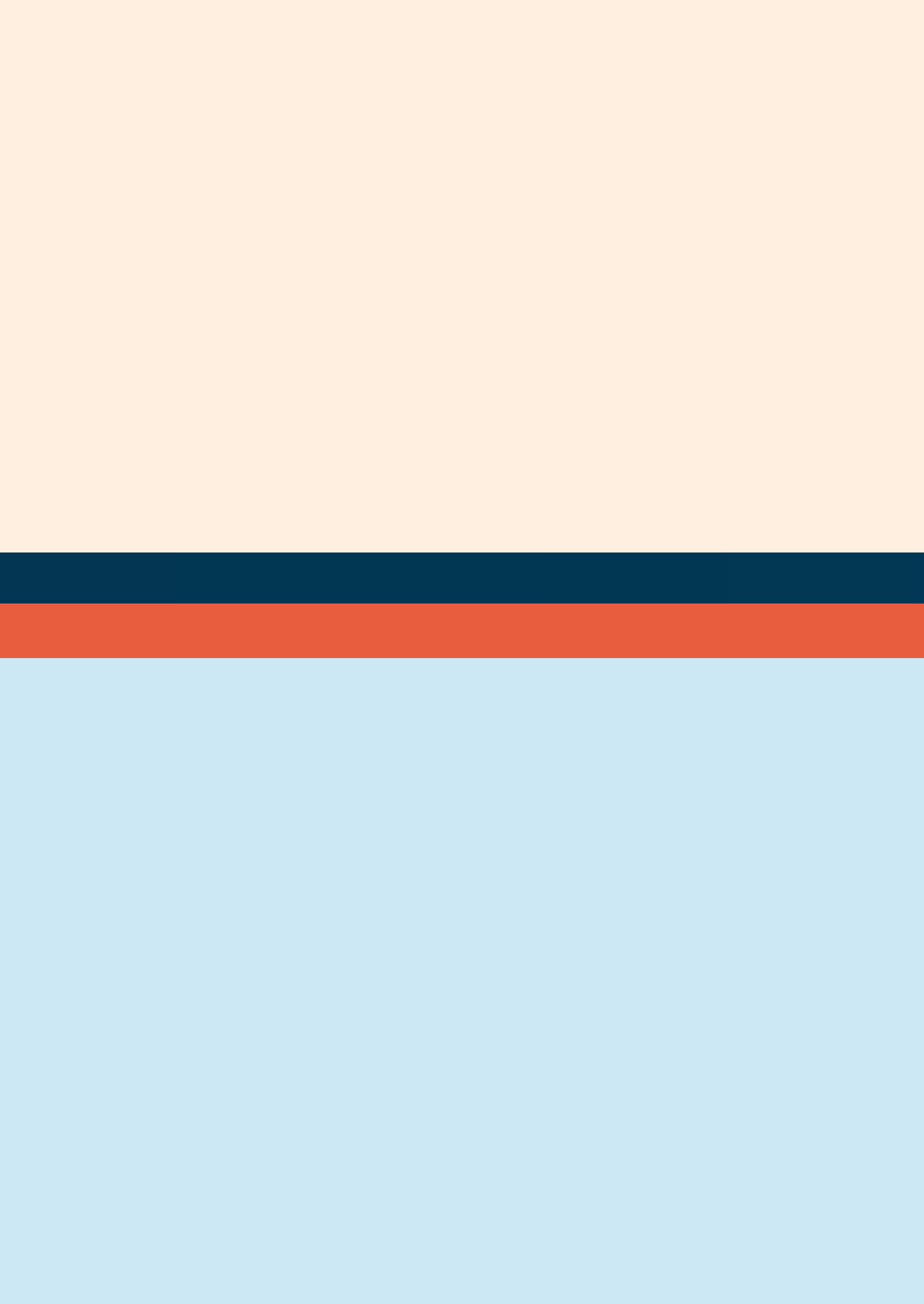
SUPPLEMENTARY MATERIAL



Supplemental Figure 1: Day of the first alarm within the 14-day window prior to the admission due to cardiac arrhythmia (A) and major bleeding (B).



Supplemental figure 2: False alarm rate per patient for cardiac arrhythmia (A) and major bleeding (B) admissions for flow and power, respectively.



CHAPTER 10

Circadian rhythms in pump parameters of patients on contemporary left ventricular assist device (LVAD) support

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ABSTRACT

Background

Circadian rhythms in blood pressure and heart rate (HR) are often disrupted in patients with advanced heart failure. Previous research showed a restored circadian rhythm in pump parameters in patients on HeartWare (HVAD) type left ventricular assist device (LVAD). Circadian patterns in HeartMate3 (HM3) were not studied before, which is important for the development of LVAD monitoring algorithms. Hence, we aimed to describe circadian patterns in HM3 parameters and their relation to patterns in HR.

Methods

18 HM3 patients were included for this study. HM3 data was retrieved at a high frequency (one sample per one or two hours) for 1-2 weeks. HR was measured using a wearable biosensor. To study overall patterns in HM3 parameters and HR, a heatmap was created. A 24h cosine was fitted on power and HR separately. The relation between the amplitude of the fitted cosines of power and HR was calculated using Pearson correlation.

Results

A higher between-patient variability was found in the circadian rhythm of flow and PI when compared to power. 83% of the patients showed a significant circadian rhythmicity in power ($p < 0.001-0.05$), with a clear morning increase. All patients showed significant circadian rhythmicity in HR ($p < 0.001-0.02$). The amplitudes of the circadian rhythm in power and HR were not correlated (Spearman correlation of 0.19 ($p = 0.44$)).

Conclusions

A circadian rhythm of pump parameters is present in the majority of the patients on HM3 and is suggested to consider in algorithms to monitor pump parameters.

PURPOSE

The circadian rhythm in blood pressure and heart rate (HR) is often disrupted in patients with severe heart failure (HF).(1) Previous research in HeartWare (HVAD) patients suggests that a circadian rhythm in pump parameters is restored within several weeks after left ventricular assist device (LVAD) implantation.(2) The circadian rhythmicity is affected in early stages of pump thrombosis, which offers the potential for early detection by using algorithms that remotely monitor pump parameters.(3) Since the withdrawal of HVAD, most patients are implanted with HeartMate 3 (HM3). Circadian patterns in HM3 parameters patients have not been studied before. Hence, we aimed to describe circadian patterns in HM3 parameters and their relation to circadian patterns in HR.

MATERIALS AND METHODS

This investigator-initiated prospective study was performed in the University Medical Centre Utrecht. The study was approved by the local ethics committee of our centre (METC: 20-195). Patients with two hospital appointments within 14 days were asked for written consent.

Study set-up

At the first study appointment, HM3's data storage was changed to one sample per 1-2 hours instead of two samples per day (which is the standard setting, as data is automatically overwritten after 256 samples). A Philips wearable biosensor was applied to the patient's chest to measure HR with a sample frequency of 1 Hz. It's data was automatically and securely transferred via Bluetooth to a mobile phone that was provided to the patient. Due to a limited battery life of four days, the patient was instructed to replace the sensor at home. During the second study appointment, LVAD and biosensor data were retrieved.

Statistics

HM3 pump parameters (power, flow, pulsatility index (PI)) and the HR were normalized by subtracting the mean and dividing by the standard deviation of each patient. The amount of available HM3 data and HR data was calculated per patient. HR data was down-sampled to one sample per hour by taking the mean. To study overall patterns, normalized and averaged HM3 pump data and HR were depicted in a heatmap of 24 hours. Subsequently, the amplitude of the circadian rhythm in power and HR was studied, as well as their relationship. A 24-hour cosine was fitted on the normalized power and HR. The Spearman correlation coefficient between

the amplitude of these fitted cosines was calculated. P-values were adjusted for multiple testing using the false discovery rate method, and a p-value of <0.05 was considered as statistically significant. R Version 3.6.3 was used for analysis.

RESULTS

Between June 2021 and December 2022 18 patients were included for the study after a median of 12 months after primary LVAD implantation. Table 1 shows all baseline characteristics. The median age was 58 years (IQR: 24 years) and 22% patients had ischemic etiology. The HM3 speed ranged from 5000-5700 and was constant throughout the study. The median time of combined available LVAD and biosensor data was 138 hours [IQR: 57 hours] per patient, as displayed in Figure 1. Figure 2 depicts a heatmap of all averaged and normalized values of power, flow and PI for all patients. All patients demonstrated a clear increase in power in the morning. Visually, a higher between-patient variability was found in the circadian rhythm of flow and PI when compared to power. 15 out of 18 patients (83%) showed a significant circadian rhythmicity in power (p-values ranging from <0.001 to 0.05). For HR, all patients showed a significant circadian rhythmicity (p-values ranging from <0.001 to 0.02). Supplemental Figure S1 and S2 display the individual circadian rhythm and fitted cosine of power and HR. The spearman correlation between the amplitude of the fitted cosine on power and HR was 0.19 (p=0.44), so the degree of the circadian rhythm in power and HR were not correlated. Nevertheless, the time of the onset of the increase in power and HR seems to be congruent in both parameters.

Table 1: Baseline characteristics of all patients.

Variable median [IQR] or n(%)		All patients (n=18)
Age (years)		57.5 [24.0]
Male sex n(%)		8 (44)
Etiology - ischemic n(%)		4 (22)
Etiology - dilated n(%)		13 (72.2)
BMI (kg/m ²)		22.1 [4.1]
BSA (m ²)		1.85 [0.27]
INTERMACS n(%)	1	1 (6)
	2	4 (22)
	3-7	13 (72)
Pre-operative temporary support n(%)		0 (0)
Pre-operative eGFR (ml/min/1.73m ²)		79 [42]
Pre-operative bilirubin (μmol/L)		15 [10]
Poor RV- function n(%)		1 (6)
Start study (number of months after implantation)		12 [3]

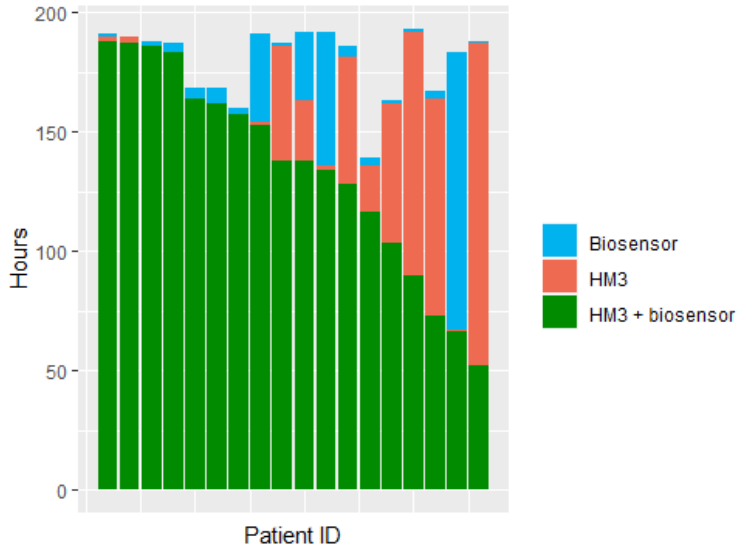


Figure 1: Data availability in hours per patient for HeartMate 3 parameters, biosensor or combined.

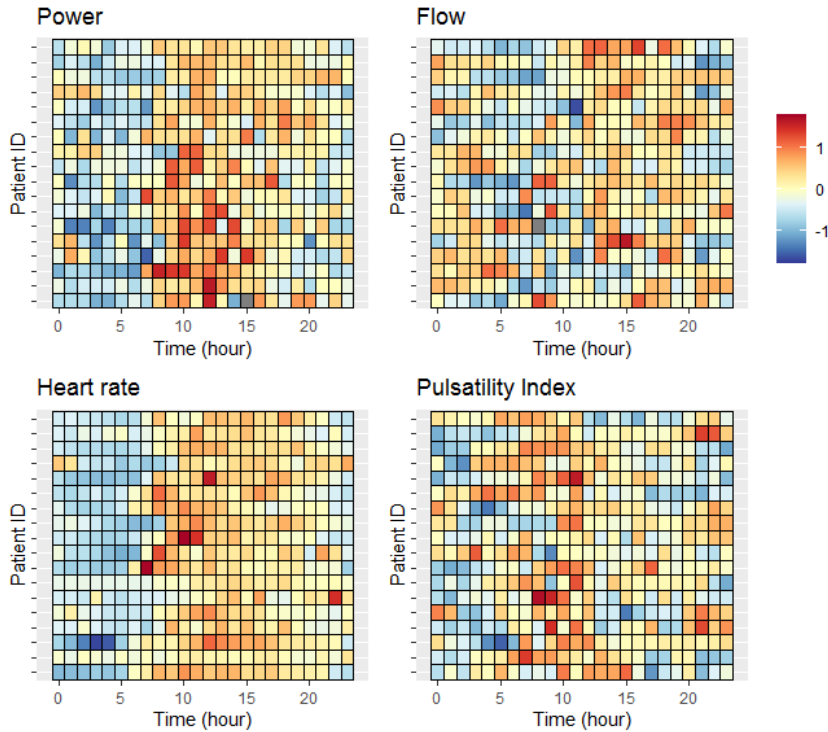


Figure 2: Circadian rhythm of pump parameters (Power, Flow and Pulsatility Index) and heart rate. Patients (on the y-axis) are sorted on the highest normalized average power.

DISCUSSION

We aimed to study the circadian rhythm in HM3 parameters and its relationship with the circadian pattern in HR. The majority of the patients on HM3 LVAD support (83%) showed a circadian rhythm in power, with an increase in the morning. Albeit with a variable degree, all patients showed a circadian rhythm in HR with decreased values at night. The amplitude of the circadian rhythm in power and HR was not correlated.

In contrast to the constant HM3 speed, pump parameters fluctuate throughout the day. They are affected by the preload and afterload of the heart, which can be affected by alterations in for example medication, fluid balance, activity or adverse events. For example, Consolo et al. showed that at early stages of pump thrombosis the circadian rhythm in power is disrupted.(3) In our study, three patients did not demonstrate a significant circadian rhythm in power. One of these patients was admitted due to septic arthritis in the knee one week after the study, which may have affected the circadian rhythm of the pump parameters. However, a causal relation cannot be proven. No correlation between the amplitude of the circadian rhythm in power and HR was demonstrated. This may be caused by the relatively small sample size. Alternatively, other intrinsic factors such as systemic vascular resistance may play an important role.

In contrast to our results, Castagna et al. demonstrated that only 4 out of 29 (14%) of their patients on HeartMate II support showed a nocturnal reduction in HR, defined as a reduction of >10% in HR during the night.(4) These differences may be explained by the different methods used or due to different patient populations. Moreover, intrinsic differences between HMII and HM3 may play a role. 90% of their LVAD patients were prescribed a beta-blocker, which may partly be responsible for the reduced circadian rhythmicity in HR. Both patient populations are relatively small, so a larger cohort is needed to confirm these findings.

The current study is limited by several factors. Some patients had missing data because of an error in data transmission of the biosensor or automatic overwriting of the HM3 data. However, in all patients, a minimum of 52 hours was available, which was considered to be sufficient for the current analysis. Although our cohort was small, in concordance with previous studies on circadian rhythms in LVAD, our findings are relevant as it is the first description of circadian rhythm in HM3 pump parameters.

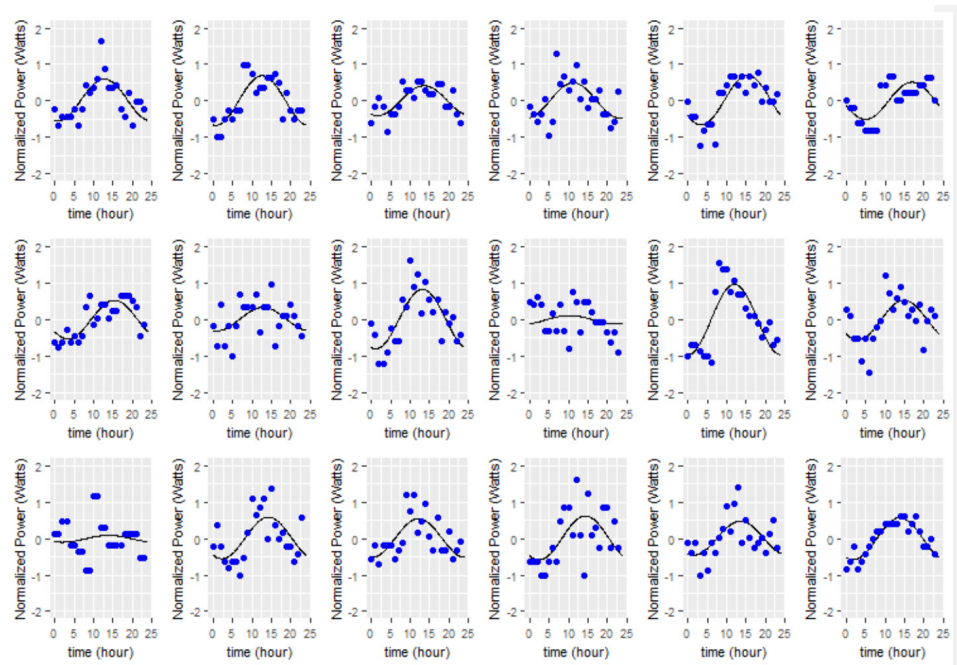
Since the withdrawal of HVAD from the global market in June 2021(5), HM3 is the most commonly implanted LVAD. Current study findings are relevant for the development of algorithms to (remotely) monitor HM3 parameters to early identify deterioration.(6) Algorithms should on one hand adjust for the circadian rhythm, for example with higher patient-specific alarm thresholds for power/flow during the day when compared to the night. On the other hand, the circadian rhythm itself can be included as a predictor. Lastly, these findings are potentially relevant for clinical practice.

Concluding, a circadian rhythm of pump parameters, especially power, is present in the majority of the patients on HM3 and is suggested to consider on a patient level in algorithms to monitor pump parameters.

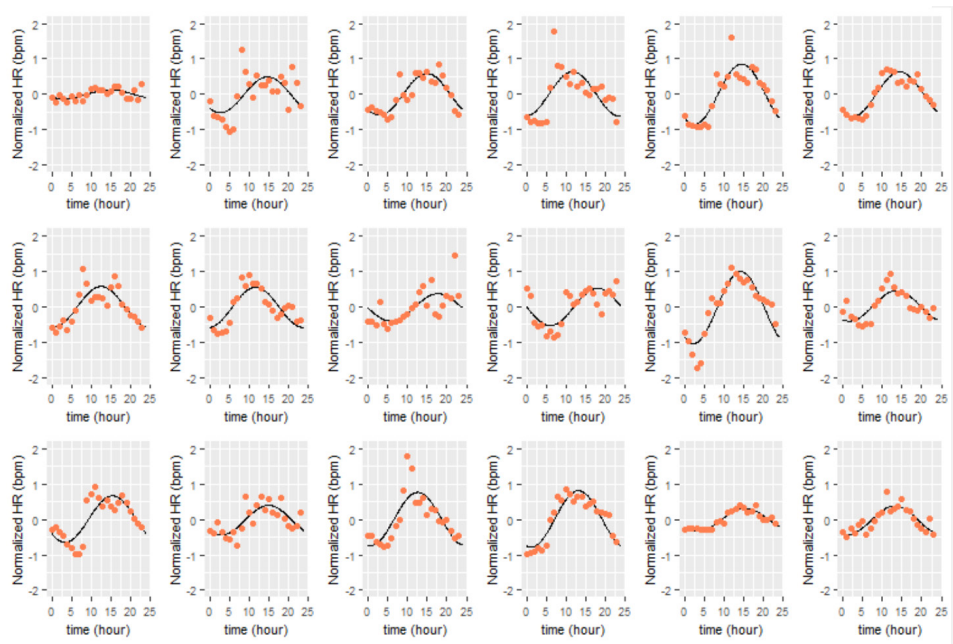
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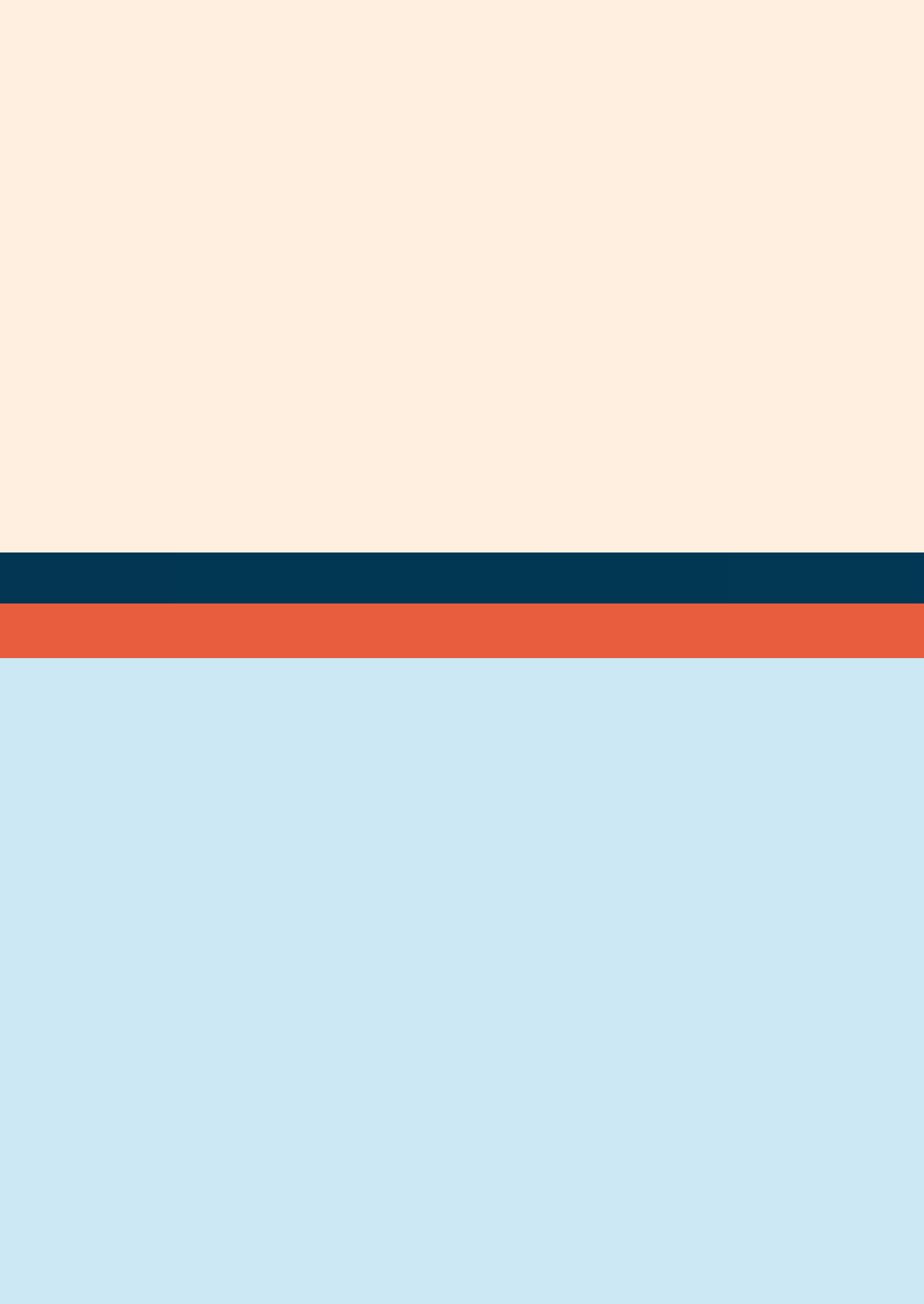
SUPPLEMENTARY MATERIAL



Supplemental figure 1: Normalized and average power values of individual patients depicted in each panel (blue dots). The black line indicates the estimated value predicted by the cosinor model.



Supplemental figure 2: Normalized and average heart rate values of individual patients depicted in each panel (orange dots). The black line indicates the estimated value predicted by the cosinor model.



CHAPTER 11

General discussion

Heart failure (HF) is a growing public health issue and a leading cause of morbidity and mortality. (1)(2)(3) A subset of chronic HF patients progresses into an advanced HF stage, showing persistent symptoms despite optimal therapy.(4) The role of left ventricular assist device (LVAD) therapy has become more prominent due to the permanent shortage of donor hearts and the increased number of patients on the waiting list. Despite remarkable improvement in survival and quality of life after LVAD implantation, patients are frequently re-admitted because of serious complications.(5) Research brought many advancements in advanced heart failure therapy. Yet, continuous research throughout the whole process of LVAD therapy (figure 1) is required to further optimize outcome. The studies described in this thesis have been focused on device type selection, the identification of LVAD patients at risk and monitoring of patients after implantation. Hence, we aimed to contribute to risk stratification and early detection of deterioration. In this chapter, the main findings of this thesis will be summarized and interpreted. Challenges and implications in the field of LVADs will be addressed and recommendations for future research will be discussed.

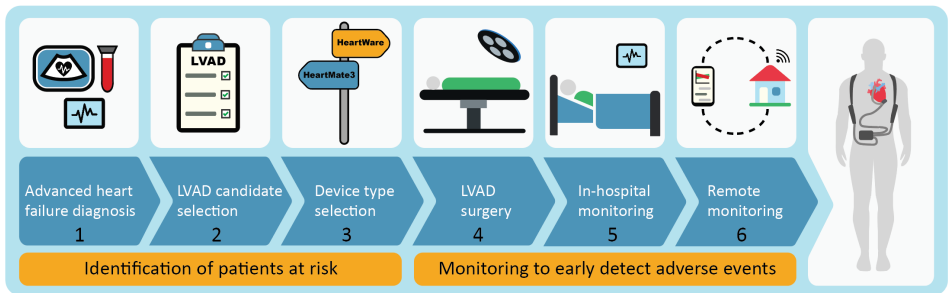


Figure 1: Process before and after left ventricular assist device (LVAD) implantation.

Device type selection and outcome

After extensive testing of the patient on LVAD candidacy, clinicians face the question which LVAD type to use. Since HeartWare (HVAD) is withdrawn from the global market in June 2021, HeartMate3 (HM3) is the most implanted LVAD. (6) Discussions regarding the optimal device have dominated research in the past years. The MOMENTUM and ENDURANCE supplemental trials showed a better or equal survival of patients on HeartMate 3 (HM3) or HeartWare (HVAD) support compared to the previous commonly used device: HeartMate II (HMII).(7)(8) In contrast, no RCT was set-up to compare clinical outcome after implantation of the third generation devices: HVAD and HM3. Manufactures were reluctant to initiate such one-to-one comparisons, as the results could eliminate them. In addition,

prospective studies are time-consuming and come with high costs due to the high administrative workload and months of preparation. A new framework to embed clinical trials in routine care could be used in future to overcome these drawbacks. (9) It will reduce the burden of trial administration, improved generalizability of results and ease implementation into clinical practice. Compared to prospective studies, retrospective studies can be conducted in a shorter time frame and can be investigator-initiated. In our centre (University Medical Centre Utrecht), both HVAD and HM3 were implanted since the introduction of the HM3 in 2015. This enabled us to perform a retrospective single centre study comparing survival and important complications in Chapter 2. Since device type was not randomized, the two patient groups differed in their baseline characteristics. There was a tendency towards the decision for HVAD in smaller patients and patients on extracorporeal membrane oxygenation (ECMO) support. We hypothesized that a worse outcome after HVAD implantation when compared to HM3 was caused by unfavorable patient characteristics. Therefore, propensity score (PS) matching was used, to obtain two comparable groups. Even after PS-matching survival in HM3 patients was better compared to HVAD, although not statistically significant. In addition, we found a worse complication profile in patients on HVAD support. Similar findings were demonstrated in three other retrospective studies, who all used slightly different methodologies.(10)(11)(12) Those single centre studies are hampered by the limited numbers of patients, ranging from 26 to 100 in each patient group. Accordingly, multi-centre or registry studies come into view. Registries such as INTERMACS and EUROMACS collect valuable data of many LVAD implanting centres in the United States and Europe, respectively. A EUROMACS registry study analyzed 722 PS-matched patients and found a non-significant difference in survival of patients on HVAD and HM3 support, but confirmed a worse complication profile after HVAD implantation.(13) Pagani et al. included 2800 PS-matched patients from the INTERMACS registry and demonstrated a worse 1-years survival for patients on HVAD support.(14) Those studies are of great importance due their impressive large patient numbers. Nevertheless, they are limited by several factors such as missing specific variables. More importantly, they included all centres that implanted either HVAD or HM3 and did not adjust for centre specific effects. Centres may differ in patient selection, volume or experience, which are difficult factors to adjust for, but may heavily affect clinical outcome. In retrospective studies it is of paramount importance to maximally reduce bias. To overcome both the limitation of small patient cohorts in our single centre study and the disadvantage of those registry-based studies, we initiated a multicenter study in Chapter 3, including centres that implanted both devices. Similar to our analysis in Chapter 2, we used PS-matching and added “centre” as a covariate for matching. We demonstrated a better survival in patients on HM3 support in 458 matched patients. Moreover, we

found that patients more often suffered from ischemic strokes and pump thrombosis after HVAD implantation. Thus, hemocompatibility of HM3 seems advantageous. HM3 has an artificial pulse, a wider rotor housing and a fully magnetically levitated rotor that may be responsible for the reduced thrombotic events.(15) The difference in baseline characteristics of HM3 and HVAD patients across centres, together with the different outcomes in single centre studies highlight the need for our multicenter approach. However, we should not underestimate the power of registry based studies. They enable inclusion of large patient populations, which is often a limitation in LVAD research due to the low number of implants per centre. Concluding, single centre, multi-centre and registry-based studies all bring their own advantages and limitations and therefore complement each other, in addition to prospective studies.

The withdrawal of HVAD from the market resulted in a new challenge: how can we determine which HVAD patients benefit from a HM3 exchange?(6) We aimed to identify which HVAD patients are at highest risk in Chapter 3, but were not able to answer this question based on the pre-operative information. Post-operative patient characteristics should be included in the decision to prophylactically exchange HVAD to HM3. An INTERMACS analysis showed a significantly higher mortality in HVAD patients that were exchange to HM3 when compared to continuous HVAD support.(16) However, this should be interpreted carefully, as patients in the exchange cohort were generally sicker and LVADs were exchanged for a specific cause. In the United States, patients on HVAD support are allowed to upgrade to an emergency status on the transplantation list. However, not all patients are eligible for transplant. As such, an exchange strategy could be beneficial, for which best practices recommendations regarding patient management and techniques for surgical exchange were recently published.(17) Peri-operative risks after HVAD to HM3 exchange such as stroke, bleeding or right heart failure should outweigh the risk of continued support on HVAD. This, however, should be determined on a patient level by a team of experts and shared decision making with the patient. Currently, several new LVAD types are under development. Hence, we will probably face similar questions in the future. To prevent a delay in comparing two or more devices, the methodology of our multi-centre study is suggested for future studies as well. Registry data can be used as well, though a sensitivity analysis including centres that implant both devices is advised. In the meantime waiting for the introduction of new technologies, research continuous to improve clinical outcome of patients on HM3. Recently, the follow-up of HM3 patients included in the MOMENTUM trial demonstrated a five years survival of 58.4%.(18) Our study in Chapter 4 confirmed this 5-year survival (54%) using real-world data.

Complications after LVAD implantation

Aiming to maximize the duration of LVAD support, quality of life should not be left out of consideration. LVAD patients are frequently admitted for serious complications that may heavily reduce their quality of life: 80% of the patients is readmitted within the first year after LVAD implantation.(19) Hence, pre-operative characteristics can be valuable to predict which patients are at high risk for specific complications. Right heart failure (RHF) remains a major challenge in patients on LVAD support. It can occur early after implantation or during long-term support. Early identification of patients at risk and early treatment may prevent deterioration. Therefore, there is an ongoing search for risk factors. The majority of the research focused on early RHF. Nevertheless, late onset RHF is recognized as a significant cause of morbidity and mortality.(20) In Chapter 5 we found that a higher BMI, longer ICU duration and a history of atrial fibrillation are associated with increased risk to develop late RHF. Additionally, we demonstrated that only 25% of the patients with early RHF developed late RHF. Previous research showed that pre-operative RV-failure increases the risk of early and persistent RHF, but not for new onset RHF.(21) Late RHF is therefore probably caused by other mechanisms than early RHF. Patients with a higher risk may need an intensified follow-up. Diuretics, pulmonary vasodilators, inotropes or anti-arrhythmic drugs may be used for the management of RHF. If insufficient, mechanical circulatory support for the right ventricle can be offered. However, biventricular assist device (BiVAD) support is a temporary solution, for example as a bridge to heart transplantation. Only a few cases that were supported for more than 12 months were reported, because outcome is generally poor.(22)(23) Additionally, patients on biventricular HM3 are limited by the necessity of two sets of external equipment and two drivelines. Although not routinely used in the Netherlands, a total artificial heart (TAH) such as the Syncardia or Carmat TAH are an option in case of biventricular failure. Up until now, TAH implantations were primarily done as a bridge to transplantation in patients ineligible for LVAD due to biventricular failure. Post-transplantation survival after Syncardia implantation was demonstrated to be worse when compared to patients on LVAD, BiVAD and patients without ventricular assist device support in a single centre study.(24) Moreover, a Registry based study revealed a worse post-transplant survival for patients on Syncardia, although insignificant ($p=0.06$). (25) Those studies comparing TAH to BiVAD or LVAD implantation were not randomized or prospective. Additionally no adjustment or PS-matching was performed. Large prospective studies are needed to find confirm current findings. However, these are logistically challenging due to a low number of patients implanted with a TAH. Challenges in the field of TAHs are durability, haemocompatibility, device size and high complication rates. So, significant improvements are required before the TAH may solve the permanent shortage in

donor hearts.

Medication use after LVAD implantation

In addition to right heart failure, bleedings and thrombotic events (i.e. strokes or pump thrombosis) are frequent problems after LVAD implantation. To prevent thrombotic events, current guidelines recommend using a combination of vitamin K antagonist (warfarin) and antiplatelet therapy (aspirin).(26) In addition to anticoagulation drugs, patients are often prescribed to take anti-arrhythmic drugs, blood pressure lowering drugs, diuretics, diabetes medication or lipid lowering drugs. Hence, many LVAD patients fulfill the criteria of hyperpolypharmacy, which is usually defined as the use of 10 or more different medications.(27)(28)(29) In contrast to the general HF population, in which hyperpolypharmacy was linked to a higher readmission rate(29), hyperpolypharmacy was not previously studied in patients on LVAD support. In Chapter 6 we showed that polypharmacy is highly prevalent in patients on LVAD support. We demonstrated that hyperpolypharmacy is associated with a higher mortality rate. Careful interpretation of these results is warranted, as a causal relationship cannot be confirmed. Despite adjustment for several important factors, hyperpolypharmacy may still reflect frailty of patients. So, to confirm this association future research is warranted, ideally in a prospective manner.

Not only the number of prescribed medications, but also the dose is of interest. The HeartMate3 improved haemocompatibility when compared to its predecessor HMII.(8) The work in this thesis confirms a better haemocompatibility of HM3 when compared to HVAD. An exploratory analysis of HM3 patients in the MOMENTUM 3 trial was conducted, comparing patients with usual dose (325 mg) to low-dose aspirin (81 mg), showing similar rates of bleeding and thrombotic events in both groups, after adjustment for age, sex and intended goal of support (bridge to transplant or destination therapy).(30) To confirm these initial findings, the ARIES HM3 trial was initiated, where they randomize patients to either vitamin K antagonist with or without aspirin (or placebo).(31) The results of this trial may reduce the number of bleeding events in patients on HM3 support, while minimizing thrombotic events.

Monitoring after implantation

In the previous section, we highlighted the added value of studies on risk stratification, device type selection and hyperpolypharmacy. As such, we contribute to identifying patients at a higher risk for adverse outcome. However, this will not inform us if and when specific complications or even death will occur on patient level. Hence, extensive patient monitoring is necessary after LVAD implantation.

Patients usually visit the outpatient clinic every three to four months. In addition to clinical symptoms, blood pressure measurement and technical assessment of the LVAD, labvalues are determined for a complete assessment of the patient's status. The severity of HF, liver function, renal function, infection parameters and blood parameters are tested. In addition to this standard set, there is a continuous search for new biomarkers. In Chapter 7 we studied the predictive value of soluble suppression of tumorigenicity 2 (sST2) in patients on LVAD support, which was demonstrated to be a prognostic indicator for all-cause death in patients with chronic heart failure.(32) We demonstrated no difference in survival in patients with normal (<35 ng/ml) and elevated pre-operative sST2 levels. However, the number of patients included in this analysis was relatively small (n=86). Therefore, larger studies are warranted. To deal with irregularly measured post-operative sST2 levels, a joint model (JM) was used to evaluate the relationship between time-dependent sST2 and right heart failure and mortality. We found a significant relationship between higher post-operative sST2 levels and right heart failure and mortality. Additionally, we demonstrated that sST2 also predicts all-cause mortality independently of NT-proBNP. In contrast to NT-proBNP, a marker of volume overload, sST2 is independent from important factors such as age, sex, BMI, hypertension or renal dysfunction.(33)(34)(35)(36) Although its mechanism has not been elucidated completely yet, it is known as a marker of fibrosis, remodeling and inflammation.(37) Hence, it seems a valuable addition to the lab values that are tested routinely. Larger studies are required to confirm our results. Future studies should inquire the optimal monitoring frequency of sST2. In addition, a cut-off for sST2 specifically for patients on LVAD support need to be determined. Additionally, the effect of heart failure medication or pump speed adjustment on sST2 and outcomes should be investigated.

In addition to lab values such as sST2, several other factors can be monitored in LVAD patients. We explored the possibilities of (remote) monitoring of patients on LVAD support in Chapter 8. Monitoring is done mainly in-hospital during regular outpatient clinic visits. However, in between those visits, several adverse events can occur. Therefore, remote monitoring or telemonitoring can be a valuable tool to early detect deterioration. Despite recognition of the importance of using remote monitoring for LVAD patients, it has not yet been explored completely nor integrated in the current workflow. Setting up the infrastructure for telemonitoring care pathways is a barrier for implementation. The workload initially increases, but may decrease after complete settlement. The LVAD patient cohort per centre is relatively small, which also hampers the introduction of such new methods into clinical care. Nevertheless, the LVAD pump parameters (power, flow and pulsatility index) provide great opportunity for remote monitoring of a patient's health

status. Several studies were performed to investigate the value of monitoring pump parameters to early identify pump thrombosis.(38)(39)(40)(41)(42) Although it is very important to early identify a dreadful complication such as pump thrombosis (PT), the ELEVATE registry showed that only 1.1% of the patients suffers from pump thrombosis in 5 years after contemporary LVAD (HM3) implantation.(43) Therefore, we should also focus on the early detection of other more frequent complications. The focus was mainly on HVAD due to its favorable data storage capacity. In chapter 9, we presented a proof-of-concept study, for which we developed an algorithm (PRECISION-LVAD) to monitor power and flow, aiming to early detect major bleeding and cardiac arrhythmia events. It performed better compared to simple algorithms in early detection with respect to both events, with a detection rate of 59% and 79% for cardiac arrhythmia and major bleeding admission respectively, for a false alarm rate of 2%.(44) These initial results are very promising, but further improvement is desired as false alarm fatigue may hamper the introduction of such tools. HM3's parameters and low flow alarms are overwritten after 256 rows. Hence, in our centre, two samples per day are generally stored. Higher frequency data or even continuous data could allow for further improvement of its performance. Waveform analysis offers much potential to retrieve information on the left ventricle status. The ventricular filling phase slope of the HVAD flow waveform was demonstrated to correlate with the pulmonary capillary wedge pressure.(45) Additionally, this higher frequency data enables the possibility to incorporate the circadian rhythm in prediction tools. Previous studies demonstrated a circadian rhythm in patients on HVAD support, which is diminished at early stages of pump thrombosis. In contrast, the circadian rhythm of HM3 pump parameters was not previously described, probably due its limited data storage. Therefore, in Chapter 10 we collected (two-)hourly data samples of 18 patients. We found that the majority of the HM3 patients demonstrate a circadian rhythm in pump parameters, especially in pump power. These findings are relevant for future studies on pump parameter monitoring. Algorithms such as PRECISION-LVAD could on one hand adjust patient tailored thresholds for the circadian rhythm, and on the other hand use it as a predictor.

Future recommendations

Based on the findings of the current thesis and the challenges that were faced, several recommendations will be made. Development of new devices for patients with advanced HF is key to further improve clinical outcome. LVADs could be improved on several aspects. For example adaptive speed control, which enables a higher cardiac output during activity. This could improve the quality of life of patients on LVAD support. Additionally, the possibility of wireless charging of the LVAD could lead to a great change in LVAD therapy. 27% of the patients suffer from

driveline infection within 2 years after implantation, despite careful instruction on daily driveline dressings.(46) Despite improvements in wireless power transfer technology, it remains difficult due to the high power required and the implantation depth. Such developments and CE or FDA approval are very time consuming in the field of high risk therapy.

Until new devices have entered the market, research can improve the current situation. We recommend a prospective study to collect higher frequency HM3 data using the Heartmate3 Snoopy.(47) This allows for the development of algorithms that incorporate the circadian rhythm. Since not all adverse events after LVAD implantation affect pump parameters, other parameters could be included as well: lab values (e.g. sST2, NT-proBNP, eGFR), mean arterial pressure (MAP) or INR. In addition, an activity tracker or wearable sensor to measure heartrate can be used to retrieve additional data at higher frequencies. Combining different data sources may be challenging regarding new infrastructure, but has the potential of further improving the performance of prediction algorithms. While using bigger data-sets to early detect deterioration, we should focus on false alarm reduction, especially with increasing numbers of patients on LVAD support. Just as important, the detection rate should be sufficient. This is a difficult trade-off.

A glimpse of the future: LVAD care in the next 10 years

In 10 years' time, we will have obtained a deeper insight and experience in remote monitoring of patients on LVAD support. A novel LVAD with extensive telemonitoring capabilities is available. In addition, it is equipped with additional sensors that allow for an accurate estimation of the flow. Based on multiple and large retrospective studies, it is easier to predict which patients are at a higher risk of adverse outcome. From one-size-fits all, we move towards patient tailored care, with a more intensive follow-up for specific patients. In addition, in some patients the intensity of follow-up visits can be reduced, provided that the patient is stable and the patient is eligible for telemonitoring. Furthermore, some (but not all) regular outpatient clinic visits can be replaced by virtual visits. Beforehand, all relevant information is sent to the nurse and cardiologist (figure 2). The new LVAD automatically transfers high density data to a local server on a daily basis. Pump parameters are monitored using a sophisticated algorithm and in case of an alarm, a snapshot of continuous data is stored and can be sent. In addition, patients are asked to fill in a questionnaire, have their blood levels tested at a local institute and to upload a photo of any relevant information (exit site, technical aspects, symptoms). All necessary information is uploaded in the electronic health record (EHR), and if possible or desired the follow-up visit is via a videocall. A patient or healthcare provider can always request to have an in-hospital visit. Based on

all available information (e.g. medical history), an artificial intelligence (AI) based algorithm is used as an advice for further examinations, for example to determine the timing of the next follow-up visit.

In between those virtual and in-hospital visits, telemonitoring is used to early identify deterioration. The strictness of telemonitoring is determined on a patient level and may change over time. Using a personalized algorithm, false alarm are reduced, while maintaining a high detection rate. Within the hospital, the telemonitoring department is the initial contact for all non-emergency alarms. Personnel is trained to act on the alarms, and timely refer for an emergency or expedited hospital visit. An intense collaboration between research and industry will accelerate future developments. Artificial Intelligence has obtained a larger role in LVAD patient care.

Too much trust in AI could be harmful. It will therefore never completely substitute a doctor/nurse, who can interpret the complex situation of an LVAD patient. Explainable AI may guide physicians in decision making. A human touch is needed for interpretation and empathy, especially in very sick patients. Healthcare providers and patients are involved at different stages throughout the implementation of new (telemonitoring) tools, for a smooth implementation. Furthermore, referral centres are more aware of the importance of early referral to LVAD-implanting hospitals. Patients that are referred at an early stage can be monitored remotely to determine the optimal moment of implantation.

Concluding remarks

In this thesis, we aimed to contribute to the identification of patients at high risk and the possibilities of (remote) monitoring of patients. Telemonitoring is a potential powerful tool to further improve clinical outcome in patients on LVAD support. The initial investment can be a burden, but is necessary to reduce workload and costs in future. Despite several challenges in this field, it should not prevent us from moving forward and further explore possibilities to improve outcome of advanced HF patients.

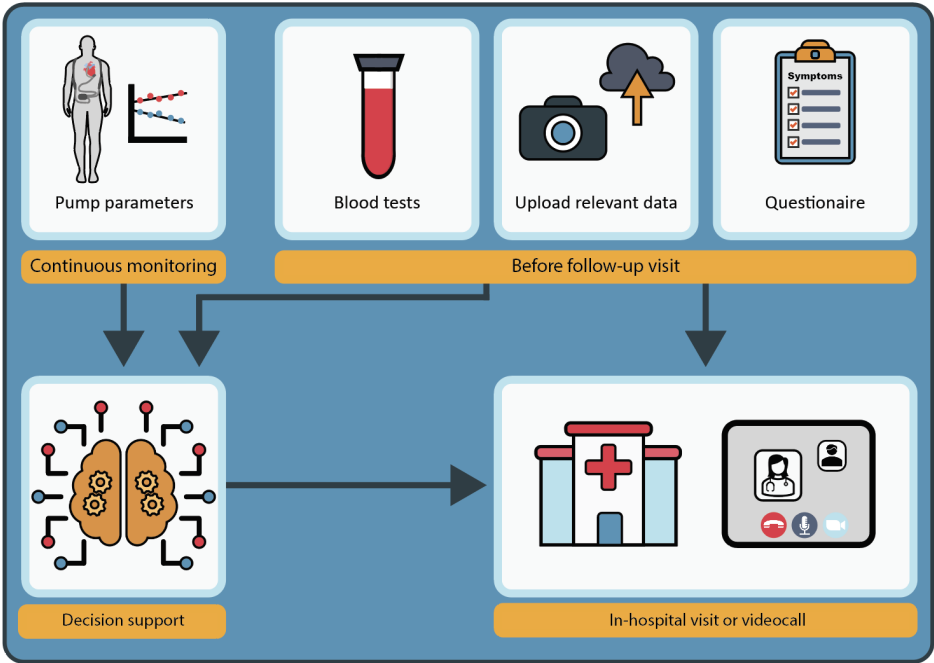


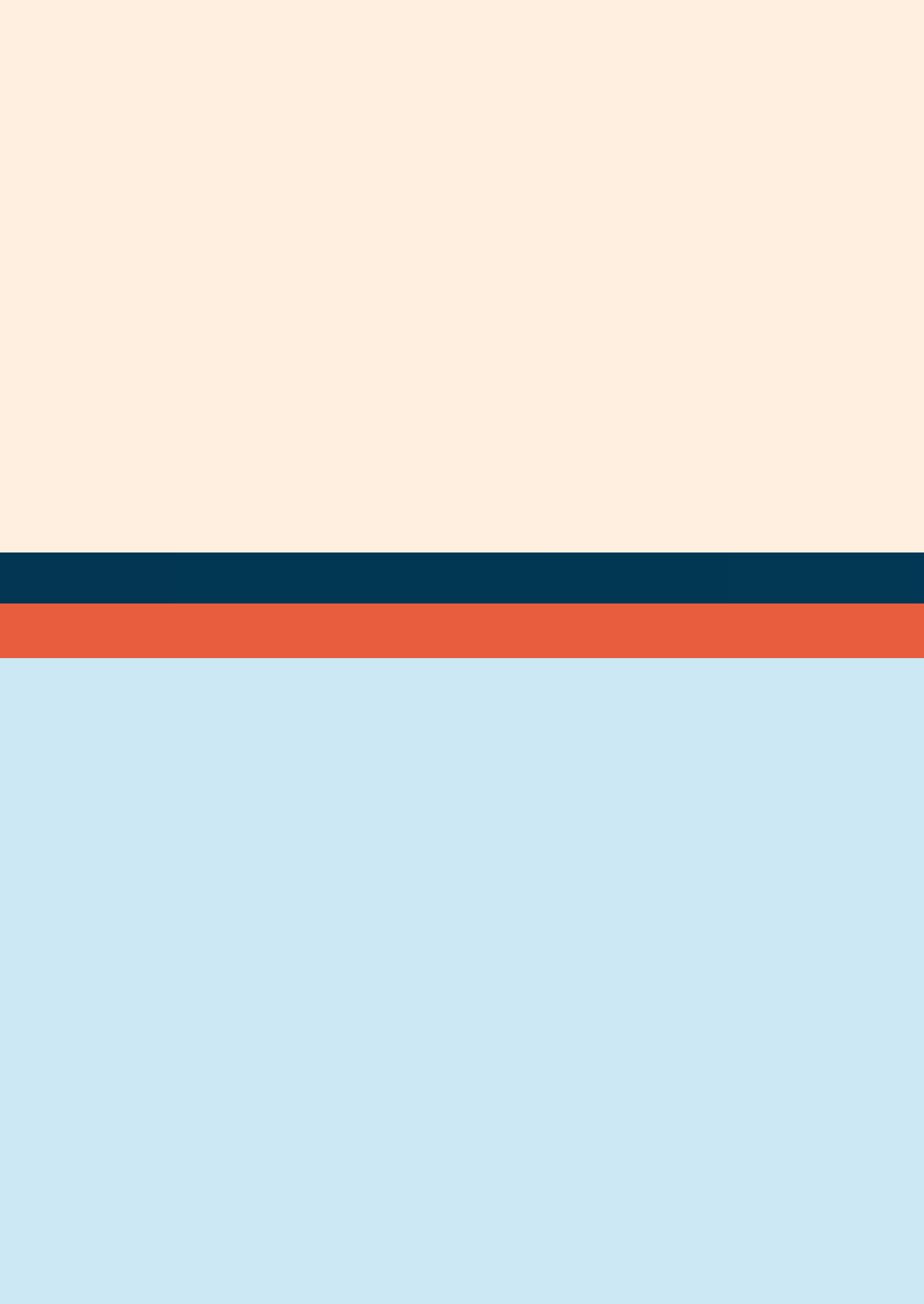
Figure 2: Flow-chart of the process before a regular follow-up visit (either in-hospital or online).

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APPENDICES

**Nederlandse samenvatting
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NEDERLANDSE SAMENVATTING

Hartfalen is een wereldwijd probleem dat 1-2% van de mensen treft. Het is geassocieerd met een grotere kans op overlijden, lagere kwaliteit van leven en brengt hoge zorgkosten met zich mee. Hartfalen wordt veroorzaakt door een structurele of functionele afwijking aan het hart, wat er toe leidt dat het hart onvoldoende bloed wegpompt. In zeer ernstige gevallen kan medicatie de klachten van hartfalen niet verminderen. Een harttransplantatie is voor die patiënten de “gouden standaard”. Er is echter een permanent tekort aan donorharten en een groeiend aantal patiënten op de transplantatie wachtlijst. Daarom is de behandeling met een steunhart (left ventricular assist device, LVAD) de afgelopen decennia steeds belangrijker geworden. Een steunhart is een pomp die continu bloed vanuit de linker kamer naar de aorta (de grote lichaamsslagader) pompt. Therapie met een steunhart wordt gebruikt als overbrugging naar een harttransplantatie, maar ook als eindbehandeling.

Ondanks sterk verbeterde overleving na een steunhart implantatie, treden er vaak onverwachte complicaties op zoals bloedingen, stolselvorming, beroertes, infecties, of het falen van de rechterkant van het hart. Er zijn veel belangrijke wetenschappelijke studies gedaan in de afgelopen jaren, maar het blijft het lastig om te voorspellen welke patiënten een hoger risico lopen op bepaalde complicaties. Vroegtijdig voorspellen van achteruitgang maakt het mogelijk om behandeling eerder te starten, wat kan leiden tot beter uitkomsten. Daarom was het doel van deze thesis tweeledig. Ten eerste hebben we patiënten geïdentificeerd die een hoger risico lopen op ernstige complicaties. Ten tweede hebben we de mogelijkheden van “telemonitoring” na steunhart implantatie onderzocht. Telemonitoring is het op afstand toezicht houden van patiënten die niet op dezelfde locatie zijn als de zorgverlener.

Als patiënten de screening voor een steunhart succesvol hebben doorlopen, kan de steunhartoperatie (soms met spoed) gepland worden. Het LVAD behandelteam staat voor een belangrijke keuze: welk type steunhart wordt er geïmplantéerd? Op dit moment wordt alleen de HeartMate 3 (HM3) geïmplantéerd. Echter, tijdens de start van ons onderzoek was er nog een (vergelijkbaar) type steunhart op de markt: HeartWare (HVAD). In het Universitair Medisch Centrum Utrecht (UMCU) werden vanaf 2015 zowel de HVAD als de HM3 geïmplantéerd, omdat het destijds niet duidelijk was welk steunhart beter was. Daarom hebben wij in **hoofdstuk 2 en 3** de uitkomsten na HM3 en HVAD implantatie vergeleken. Na het maken van twee vergelijkbare groepen, zagen wij dat de kans op overlijden, beroerte en stolselvorming in het steunhart kleiner is na HM3 implantatie. Daarnaast hebben we

onderzocht of het mogelijk is om te ontdekken welke HVAD patiënten een grotere kans hebben op ernstige complicaties en daarom baat zouden hebben bij een operatie waarbij de HVAD vervangen wordt door de HM3. Preoperatieve informatie bleek echter niet voldoende voor het maken van de keuze voor een vervanging. Het voordeel van de HM3 ten opzichte van de HVAD moet opwegen tegen de risico's van zo'n vervangende operatie, wat per patiënt beoordeeld moet worden. In **Hoofdstuk 4** is de lange termijn overleving (5-jaar) na een HM3 implantatie onderzocht. De gevonden overlevingskans van 54% in onze Europese populatie van alle geïmplanteerde patiënten is vergelijkbaar met de 5-jaars overleving in de Momentum3 trial, een grote Amerikaanse gerandomiseerde studie op het gebied van de HM3.

In **Hoofdstuk 5** hebben we gekeken naar risicofactoren voor een belangrijke complicatie die bij veel patiënten op lange termijn optreedt: laat rechterkamer falen. Dit houdt in dat de rechterkant van het hart niet meer in staat is om het tempo van het rondpompen van het steunhart aan de linkerkant van het hart bij te houden. Uit onze studie bleek dat patiënten met een hogere BMI, een langere IC-duur na steunhartoperatie en een geschiedenis van boezemfibrilleren voorafgaand aan de steunhart operatie een grotere kans hebben op het ontwikkelen van laat rechterkamer falen.

Twee andere belangrijke en ernstige complicaties na een steunhart implantatie zijn bloedingen en stolselvorming. Patiënten met een steunhart krijgen antistollingsmedicatie voorgeschreven, omdat het contact van hun bloed met "vreemd" materiaal het risico op stolselvorming verhoogt. Daarnaast kan het nodig zijn om medicatie te krijgen tegen hartritmestoornissen, bloeddrukverlagers, plasmedicatie, diabetes medicatie of cholesterolverlagers. Hyperpolyfarmacie (het gebruik van meer dan 10 medicamenten) komt dan ook regelmatig voor bij patiënten met een steunhart. In **Hoofdstuk 6** zagen we dat hyperpolyfarmacie voorkomt bij 34.8% van de steunhart patiënten. Ook liet de studie een verband zien tussen hyperpolyfarmacie en een hogere kans op sterfte, waarbij gecorrigeerd is voor belangrijke parameters.

Patiënten met een steunhart komen meerdere keren per jaar op de polikliniek voor een uitgebreide check. Tussen deze ziekenhuis bezoeken door, worden patiënten niet in de gaten gehouden op een nood-alarm van het steunhart na, welke afgaat bij onvoldoende bloed dat wordt rondgepompt. Omdat de behandeling met een steunhart grote risico's met zich mee brengt, is er behoefte aan extra monitoring (op afstand) om vroegtijdig achteruitgang op te sporen. Monitoring na steunhartimplantatie kan bijvoorbeeld met bepaalde biomarkers, gemeten in het

bloed. Daarom richt **Hoofdstuk 7** zich op de relatie tussen een bepaalde biomarker (soluble suppression of tumorigenicity-2, afgekort met sST2) en uitkomsten op de lange termijn, wat nooit eerder onderzocht is in steunhartpatiënten. Het mechanisme van sST2 is niet volledig bekend, maar uit studies blijkt dat hogere sST2 waarden gerelateerd zijn aan cel schade in het hart. Onze studie liet een significante relatie tussen een hogere sST2 gemeten na de operatie en mortaliteit en laat rechterkamer falen. Voordat sST2 kan worden ingezet in de zorg bij steunhart patiënten, moet er onderzocht worden wat de optimale frequentie is om het te meten en wat de juiste afkapwaarden zijn.

Naast regelmatige controle van bepaalde biomarkers, kunnen patiënten op afstand worden gemonitord met behulp van telemonitoring. Telemonitoring wordt veel gebruikt bij patiënten met hartfalen, waarbij patiënten bijvoorbeeld dagelijks hun lichaamsgewicht, bloeddruk en hartslag moeten meten. Ondanks de erkenning voor de potentiële toegevoegde waarde van telemonitoring bij patiënten met een steunhart, is het een onbekender terrein. Daarom hebben wij in **Hoofdstuk 8** een uiteenzetting gepresenteerd over de ervaring, mogelijkheden en de uitdagingen van telemonitoring bij patiënten met een steunhart. Het steunhart slaat bepaalde waarden op, bijvoorbeeld de energie die het nodig heeft om de pomp te laten draaien, of de berekende hoeveelheid bloed die het rondpompt. Er zijn verschillende studies gedaan waarbij deze waarden gemonitord worden met een voorspelmodel om vroegtijdig stolselvorming in de pomp te detecteren. Omdat niet alle complicaties te voorspellen zijn op basis van pompwaarden, is het interessant om verschillende bronnen van data te combineren.

Er zijn op dit moment geen voorspelmodellen die specifiek gericht zijn op het monitoren van de pompwaarden van de HM3, het steunharttype dat tegenwoordig grootschalig wordt gebruikt. Daarom hebben we in **Hoofdstuk 9** een patiënt specifiek voorspelmodel gemaakt dat de HM3 pompwaarden monitort. Vergeleken met andere “simpelere” modellen, zijn we hiermee beter in staat om grote bloedingen of hartritmestoornissen op te sporen. De kwaliteit van dit voorspelmodel kan verder worden verbeterd door het gebruik van extra data. Op dit moment worden de pompwaarden slechts twee keer per dag opgeslagen. Op die manier is het niet mogelijk om de variatie gedurende de dag mee te nemen in het voorspel model. Omdat het bekend is dat de variatie in de pompwaarden wordt beïnvloed in een vroeg stadium van bepaalde complicaties (stolselvorming in het steunhart), is het belangrijk om te onderzoeken of het meenemen hiervan het voorspelmodel verbetert. Als eerste stap hebben we voor de studie in **Hoofdstuk 10** extra pompwaarden en de hartfrequentie van 18 patiënten verzameld, waarmee het patroon van de pompwaarden gedurende de dag in kaart gebracht kon worden.

Er was 's ochtends een duidelijke toename te zien van de hartfrequentie en de hoeveelheid energie die de HM3 gebruikt. Het meenemen van dit variërende patroon in toekomstige voorspelmodellen kan de uitkomst mogelijk verder verbeteren. In **Hoofdstuk 11** bediscussiëren we onze resultaten en worden deze in perspectief geplaatst. Belangrijke uitdagingen en nieuwe mogelijkheden worden beschreven.

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Breteler, M. J. M., KleinJan, E., Numan, L., Ruurda, J. P., Van Hillegersberg, R., Leenen, L. P. H., Hermans, M., Kalkman, C. J., & Blokhuis, T. J. (2020). Are current wireless monitoring systems capable of detecting adverse events in high-risk surgical patients? A descriptive study. *Injury*, 51, S97–S105. <https://doi.org/10.1016/j.injury.2019.11.018>

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CURRICULUM VITAE

Lieke Numan was born 2th of February 1994 in Sneek, the Netherlands. She was raised by her parents Dick and Anja with her two sisters. After graduating from high school (CSG Bogerman, Sneek) in 2012 she moved to Enschede to study Technical Medicine at the University of Twente. After she finished her bachelor thesis, she moved to Gothenburg to study at Chalmers University of Technology, where she attended several Biomedical Engineering courses. Upon her return



to Enschede she started her master “Medical sensing and stimulation”, where her interest for research in (remote) monitoring and cardiology further developed. Thereafter, she performed medical internships at the lung department of the University Medical Centre (UMC) Groningen, clinical neurophysiology and pediatric urology department of the UMC Utrecht and Luscii in Amsterdam. For her master thesis she conducted a clinical feasibility study on home monitoring in patients after esophagectomy surgery. In 2019 she graduated as a technical physician. She continued her path to start a PhD program under supervision of prof. dr. Asselbergs, dr. Linda van Laake and dr. Emmeke Aarts at the cardiology department of the UMC Utrecht. These joint efforts resulted in the scientific work provided in this thesis.

After finishing her thesis, Lieke will start a new position at ZonMw as a program manager focussing on digital healthcare.

