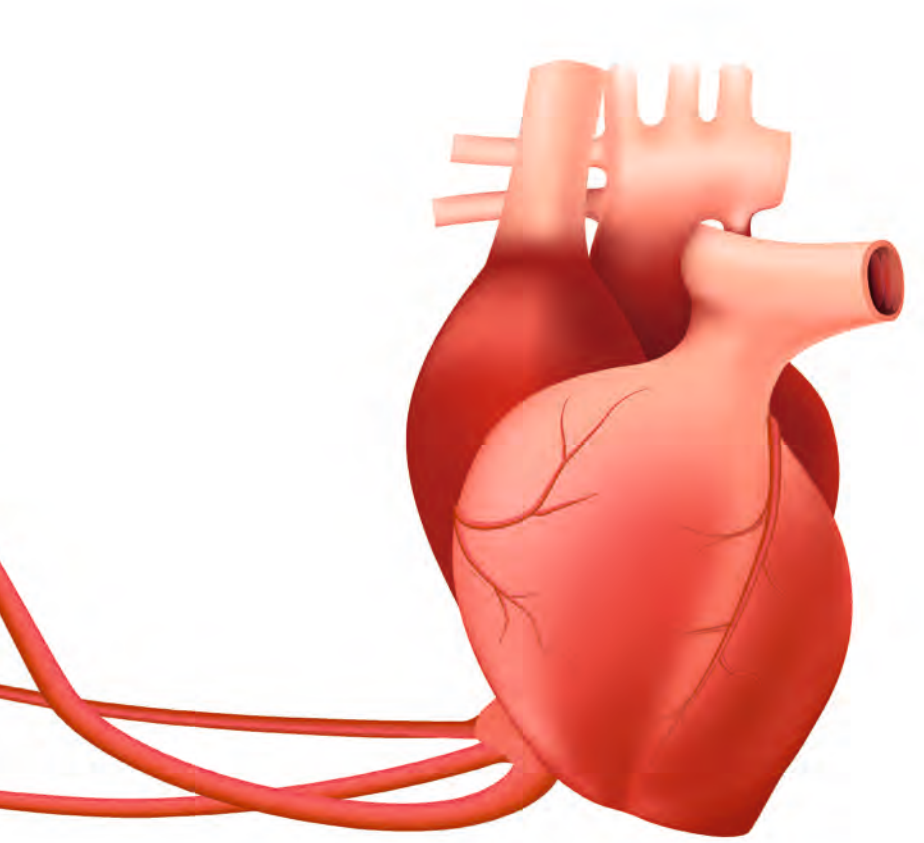
OPTIMIZED AND INDIVIDUALIZED MEDICINE IN HEART FAILURE THERAPY

"THE NEXT STEP FORWARD"



JESSE VEENIS

Optimized and individualized medicine in heart failure therapy "the next step forward"

Geoptimaliseerde en gepersonaliseerde behandeling in hartfalen zorg

"de volgende stap voorwaarts"

Jesse Feiko Veenis

Colofon

Optimized and individualized medicine in heart failure therapy
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1

General introduction and outlines of the thesis

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A brief history of heart failure

Over the last centuries, many discoveries and developments has contributed to our knowledge of heart failure, as shown in Figure 1. The ancient civilizations of China, Egypt, Greek, and the Roman Empire were the first to describe manifestations and symptoms most likely caused due to heart failure, with the earliest descriptions dating back to 2600 BC. [1-3] The oldest case identified with heart failure was most likely Nebiri, an Egyptian dignitary living during the 18th dynasty Pharaoh Thutmose III (1479 – 1425 BC). After discovering his remains, histological examination of the lungs showed signs of pulmonary edema, most likely caused by heart failure. [4]

The discovery and detailed description of the circulatory system by William Harvey in 1628 AD was probably the first big step in heart failure research. [5] This discovery led to new insights in the hemodynamics of the heart and provided new knowledge on the hemodynamic abnormalities associated with heart failure. Additional developments, such as the X-ray by Wilhelm Röntgen and the electrocardiogram by Willem Einthoven, as well as the introduction of cardiac catheterization and cardiac surgery, improved the understanding of heart failure. [6]

The treatment of heart failure patients has developed rapidly over the last 200 years. In the beginning, bloodletting, bed rest, inactivity, and fluid restrictions were the only treatment options available. Later, diuretics and digitalis were used for the therapy of heart failure, followed by other pharmacological drugs, such as renin-angiotensin system (RAS)-inhibitors (consisting of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), beta-blockers and mineral corticoid receptor antagonists (MRAs). Since the 1960s, advanced treatment options such as heart transplantation and circulatory support using a left ventricular assist device (LVAD) surgery became available. [6, 7] Despite all these advances, heart failure management still faces many significant challenges that need to be addressed.

Heart Failure

Currently, heart failure is defined as a complex clinical syndrome characterized by typical signs and symptoms such as elevated jugular venous pressure, pulmonary crackles, peripheral edema, and complaints of breathlessness. These signs and symptoms are caused by a structural and/or functional cardiac abnormality resulting in reduced cardiac output and/or elevated intracardiac pressures. [8]

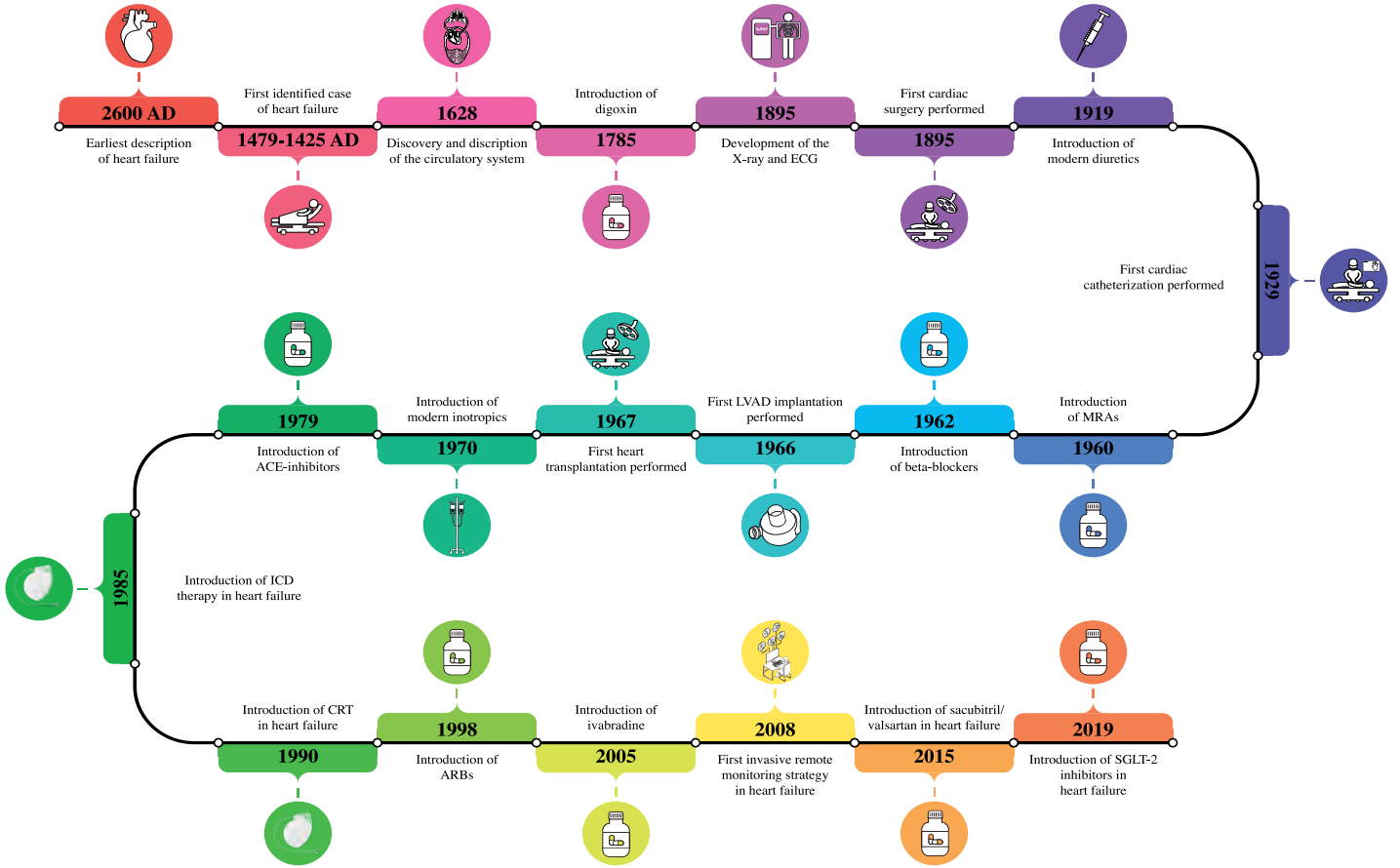

Figure 1. Graphical summary of the major discoveries and developments in heart failure research

Heart failure can be divided based on the left ventricular ejection fraction into heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF), according to the most recent 2016 European Society of Cardiology Guidelines for heart failure. [8]

Due to an aging population and better survival of cardiovascular diseases, such as acute myocardial infarction, more and more patients are diagnosed with heart failure. Approximately 1-2% of the European population is diagnosed with heart failure, and 26 million adults live with heart failure worldwide, and these numbers are expected to rise even further. [9, 10] Heart failure remains strongly associated with high morbidity and mortality, despite the introduction of new treatment options. [11] The one-year survival of heart failure patients is approximately 80%, while only 26% are still alive ten years after their initial diagnosis. [12] During this period, heart failure patients are frequently hospitalized, and their quality of life is significantly reduced due to limitations in their physical and social activities. [9, 13, 14]

Heart failure significantly affects the lives of heart failure patients. Additionally, it places a significant and increasing burden on hospital and healthcare systems due to the rising prevalence of heart failure with high morbidity, mortality, and hospitalization rates. Therefore, adequate treatment according to the guidelines based upon clinical evidence is crucial to improve patient outcome and wellbeing as well as to reduce the economic impact.

Pharmacological treatment of heart failure

Nowadays, many pharmacological treatment options are available in heart failure management, and the European Society of Cardiology Guidelines for heart failure provides clear treatment recommendations for HFrEF patients. [8] All HFrEF patients should be treated with a RAS-inhibitor in combination with a beta-blocker, and an MRA should be added if indicated. Additionally, diuretics could be used to reduce signs and symptoms of congestion, and newly pharmacological agents such as angiotensin receptor neprilysin inhibitors (ARNIs) could be used instead of a RAS-inhibitor. Ivabradine could be added to the treatment in HFrEF patients with sinus rhythm and a heart rate of 70 beats per minute or higher.

It has been demonstrated that adherence to these guidelines significantly improves the prognosis and quality of life of HFrEF patients [8, 15], and reduces the number of heart failure related hospitalizations. [16] Therefore, the implementation of the guidelines could be used

as a benchmark for the quality of care. However, the implementation of these guidelines appears to be challenging, with relatively low adherence to the guidelines, as demonstrated in recent registries. [14, 17, 18] Additionally, the prescribed dosages are often much lower than recommended by the guidelines. [17, 19] However, the optimal up titration strategy is still up for debate, and it remains unclear whether the guideline-recommended dose is the ideal dose for each patient category. Side-effects, such as symptomatic hypotension and degradation of the renal function might be introduced when HF drugs are dosed to high.

Monitoring of the heart failure patient

In addition to adequate treatment, monitoring of heart failure patients is needed to detect deterioration leading to hospitalization and improve patient outcomes. Several monitoring strategies can be applied, including patient self-care, monitoring during outpatient clinic visits, or remote monitoring. [8] Patient self-care is a cornerstone of heart failure management. Patients are instructed to use the prescribed medication, implement lifestyle recommendations, and regularly monitor themselves for signs and symptoms of deterioration of heart failure, such as an increase in weight or dyspnea. Unfortunately, these clinical symptoms occur relatively late before heart failure decompensation, and hospitalization might not be avertable. [20] Additionally, many patients do not perform self-monitoring as frequently as necessary. [21] Another monitoring option could be monitoring visits at the outpatient clinic. However, this is very time consuming for the patient and places a substantial burden on the hospital recourses.

Alternatively, remote monitoring facilitates monitoring of the patient's status at home. Three main remote monitoring strategies are currently used, (1) non-invasive remote monitoring using, (2) remote monitoring of implantable cardioverter-defibrillator or cardiac resynchronization therapy devices, and (3) remote hemodynamic monitoring using implantable devices. [20, 22, 23] Each monitoring strategy has its specific advantages and disadvantages, and the optimal remote strategy is still up to debate.

End-stage heart failure

Patients with heart failure can become refractory for pharmacological therapy and develop end-stage heart failure. End-stage heart failure is a severe condition, with an estimated 1-year survival of 60% and a median survival of 18 months when treated with optimal medical therapy. [24] In these patients, advanced treatment options are indicated. Heart transplantation is considered to be the gold therapy option in end-stage heart failure patients. However, due to a shortage of available heart donors, left ventricular

assist device therapy is increasingly used as a bridge to transplantation. [25] Additionally, a left ventricular assist device can be used as destination therapy in patients who are not eligible for heart transplantation.

An left ventricular assist device is implanted during open-heart surgery. An inflow cannula connects the pump with the left ventricle, and an outflow cannula forms the connection between the pump and the thoracic aorta. The pump supports the left ventricle by pumping blood out of the left ventricle into the aorta and the rest of the circulatory system.

Experience with left ventricular assist device therapy has increased significantly over the last years, and essential technological improvements have led to a significant improvement in the overall survival of left ventricular assist device patients. [26] However, many patients remain affected by left ventricular assist device related complications, including right ventricular failure, acute kidney injury, and major bleeding events. [25-28] Frequent monitoring could aid in improving the overall outcome of left ventricular assist device patients. Unfortunately, the left ventricular assist device only provides static pump parameters, which can only be monitored during outpatient visits. Additional monitoring tools, especially remotely monitoring strategies, are needed to improve the left ventricular assist device management. Left ventricular assist device management remains very complex and faces many challenges that need to be addressed to improve patient outcome further. The effects of patient demographics such as age and sex, as well as concomitant procedures, including procedures of the aortic valve, on the overall survival remains unclear. Furthermore, iron deficiency is a common comorbidity in chronic heart failure patients, associated with reduced survival. However, the prevalence of iron deficiency in patients with end-stage heart failure is still unknown.

Aims and outlines of this thesis

As previously described, several significant challenges should be addressed to individualize and optimize heart failure management further. Therefore, the purpose of this thesis was four-fold: (A) to analyze the current quality of heart failure care in The Netherlands and identify patient groups in which heart failure care could be optimized; (B) to assess the impact of remote hemodynamic monitoring in chronic heart failure patients; (C) to determine the safety and feasibility of remote hemodynamic monitoring in left ventricular assist device patients; and (D) to optimize left ventricular assist device management.

A. Assess the current quality of heart failure care in The Netherlands and identify patient groups in whom heart failure care could be optimized

In the first part of this thesis, prescription rates and prescribed dosages are investigated in chronic heart failure patients as an indication of the quality of heart failure care in The Netherlands. The clinical profiles and prescription behavior in different subgroups of the Dutch heart failure population were investigated to increase our insight into the heart failure treatment in Dutch heart failure outpatient clinics. Additionally, these insights might be used to optimize and individualize the heart failure treatment of Dutch chronic heart failure patients.

B. Assess the impact of remote hemodynamic monitoring in chronic heart failure patients

In the second part, the potential impact of remote hemodynamic monitoring by using an implantable device in chronic heart failure patients was investigated. Additionally, the daily hemodynamic impact of interventional cardiac procedures, such as MitraClip, are investigated, which provides a unique insight into the hemodynamic changes pre- and post-valvular procedures.

C. Determine the safety and feasibility of remote hemodynamic monitoring in left ventricular assist device patients

In the third part, the safety and feasibility of remote hemodynamic monitoring pre- and post-left ventricular assist device surgery was studied to investigate its usefulness in preoperative risk prediction as well as preoperative optimization. This concept of combining two state of the art techniques, remote hemodynamic monitoring and left ventricular assist device therapy, together is completely novel. Furthermore, we studied the impact of remote hemodynamic monitoring during the outpatient phase, which provides new insights to optimized and individualized ventricular assist device management. Remote management in this patient group is still in its infancy.

D. Optimize left ventricular assist device management

The last part of this thesis focused on several challenges that still exist in patients requiring left ventricular assist device support to optimize their treatment further. Additionally, differences in overall survival and left ventricular assist device-related complications according to age, sex, and the usage of implantable cardiac electronic devices with a defibrillator was studied. Furthermore, the risks and benefits of concomitant aortic valve procedures during left ventricular assist device surgery was assessed as well. Finally, the prevalence of iron deficiency was studied.

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Age differences in contemporary treatment of patients with chronic heart failure and reduced ejection fraction

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Abstract

Background: Elderly patients are underrepresented in clinical trials but comprise the majority of heart failure patients. Data on age-specific use of heart failure therapy are limited. The European Society of Cardiology heart failure guidelines provide no age-specific treatment recommendations. We investigated practice-based heart failure management in a large registry at heart failure outpatient clinics.

Design and methods: We studied 8351 heart failure with reduced ejection fraction patients at 34 Dutch outpatient clinics between 2013 and 2016. The mean age was 72.311.8 years and we divided age into three categories: less than 60 years (13.9%); 60–74 years (36.0%); and 75 years and over (50.2%).

Results: Elderly heart failure with reduced ejection fraction patients (≥75 years) received significantly fewer beta-blockers (77.8% vs. 84.2%), renin–angiotensin system inhibitors (75.2% vs. 89.7%), mineralocorticoid receptor antagonists (50.6% vs. 59.6%) and ivabradine (2.9% vs. 9.3%), but significantly more diuretics (88.1% vs. 72.6%) compared to patients aged less than 60 years ($P_{\text{for all trends}}<0.01$). Moreover, the prescribed target dosages were significantly lower in elderly patients. Also, implantable cardioverter defibrillator (18.9% vs. 44.1%) and cardiac resynchronisation therapy device (14.6% vs. 16.7%) implantation rates were significantly lower in elderly patients. A similar trend in drug prescription was observed in patients with heart failure with mid-range ejection fraction as in heart failure with reduced ejection fraction.

Conclusion: With increasing age, heart failure with reduced ejection fraction patients less often received guideline-recommended medication prescriptions and also in a lower dosage. In addition, a lower percentage of implantable cardioverter defibrillator and cardiac resynchronisation therapy device implantation in elderly patients was observed.

Introduction

Chronic heart failure (HF) is a major healthcare problem, associated with a poor prognosis, high morbidity and mortality.[1] Optimising medical and device therapy according to the guidelines improves prognosis.[2] Therefore, adherence to the guidelines, such as the rate of drug prescription and dosage, are often used as benchmarks of quality of care. Approximately 1–2% of the global adult population is diagnosed with HF.[3] Due to an aging population and better survival of underlying heart diseases, these numbers are expected to rise even further.[4] Elderly patients are a major part of the HF population, with approximately 80% older than 65 years, and 40–50% even aged 75 years or older.[2,5]

In elderly patients, HF is the leading cause of hospitalization and is associated with high morbidity and mortality, resulting in an enormous burden on hospital resources.[6] Due to the high prevalence of comorbidities in elderly patients, optimising HF management remains even more challenging.[7] Until now, randomised clinical trials investigating HF therapy did not include large number of elderly patients,[8] with the exception of the SENIORS trial.[9] In fact, patients enrolled in these trials were on average 10 years younger than in daily clinical practice,[3] and elderly patients were clearly underrepresented. [10] A few registries have shown a lower prescription rate in the elderly but lack size.[8,11] Despite the ongoing discussion on optimal therapy in elderly HF patients, there is no European Society of Cardiology (ESC) recommended age-specific guidelines for HF treatment,[2] and data in groups of patients with advanced age are scarce.

Therefore, we investigated age-related differences in HF therapy in a large-scale cross-sectional registry in 34 Dutch HF clinics, reflecting actual practice-based HF care at outpatient clinics including large numbers of elderly patients.

Methods

The design and methods of the CHECK–HF (Chronisch Hartfalen ESC – richtlijn Cardiologische praktijk Kwaliteitsproject HartFalen) registry have been published in detail elsewhere.[12,13] Briefly, the CHECK–HF registry consists of 10910 patients with chronic HF from a total of 34 participating Dutch centres, participating in the inclusion for this cross-sectional observational cohort. Between 2013 and 2016, all centres included patients diagnosed with HF according to 2012 ESC guidelines on HF,[2] based

on symptoms and echo parameters, who were seen at the outpatient HF clinic (96%) or general cardiology outpatient clinic (4%) if no specific HF clinic was present.

Baseline patient characteristics, aetiology of HF, comorbidities, basic echocardiographic and electrocardiographic parameters, laboratory markers, pacemaker, implantable cardioverter defibrillator (ICD) and cardiac resynchronisation therapy (CRT) treatment, as well as prescription rates of medication (drug name, dosage and frequency and total daily dose), were recorded. Furthermore, contraindication and intolerance rates were collected.

Ivabradine was only considered indicated on top of optimal treatment with beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs) (or angiotensin II receptor blockers (ARBs)) and mineralocorticoid receptor antagonists (MRAs) (or ARBs), and if patients were in sinus rhythm, left ventricular ejection fraction (LVEF) of 35% or less, heart rate of 70 beats/minute or greater and were still symptomatic (New York Heart Assocation (NYHA) ≥II), or already received ivabradine. Target doses of guideline-recommended HF therapy are presented in Supplementary Table 1.

Based on echocardiographic results, patients were classified based on LVEF or visual assessment of the function of the left ventricle function as heart failure with reduced ejection fraction (HFrEF, LVEF <50% (n=8360 (76.6%))), and according to 2016 ESC HF guidelines as heart failure with mid-range ejection fraction (HFmrEF) (LVEF 40–49% (n=1574 (14.4%))) in those with available measurement of ejection fraction. In addition, HFpEF was classified as LVEF of 50% or greater in 2267 (20.8%) patients. In 274 (2.5%) patients, recording of the left ventricular function in the database was insufficient to classify patients into HF type, in nine patients (0.1%) age was missing in the database, and they were excluded from this analysis. In the current analyses, we focus on age-related treatment differences in guideline recommended HF therapies, including device therapy and lifestyle interventions, in HFrEF and HFmEF patients only.

Statistical analysis

Continuous data are expressed as mean value±SD or median and interquartile range, depending on the distribution of the data, and compared by the one-way analysis of variance (ANOVA) or Mann–Whitney U-test. Categorical data are expressed as counts and percentages, and compared by the Pearson chi-square test. In order to investigate whether the observed age-related differences were independent of potential clinical predictors, univariable and multivariable logistic regression were used. Results of these

regression analyses are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). A two-sided P value of 0.05 was considered statistically significant.

In model 1, we adjusted for gender only. In model 2, we further adjusted for NYHA and LVEF. In model 3, we further included all comorbidities which were significantly related to the outcome variable at statistical level P value less than 0.05 using stepwise entry method in binary logistic regression. In the specific device therapy-related analysis, QRS duration was an additional variable in univariable analysis we included by entry method in the models. Age was entered per 10 years into the models.

In a total of 8.9% of all predicting values data were missing. These missing data were imputed using multiple imputation. If the missing variables showed a monotone pattern of missing values, the monotone method was used, otherwise, an iterative Markov chain Monte Carlo method was used with a number of 10 iterations. A total of five imputations was performed, and the pooled data were analysed. The imputed data were only used for the multivariable analysis. For all reported data of the multivariable analysis, we compared crude and imputed P values as well as the ORs and CIs in order to analyse whether imputation changed the results, and if no significant changes occurred we only presented the imputed values in the main analyses. All analyses were performed with SPSS statistical package version 24.0 (SPSS Inc., Chicago, IL, USA).

Results

HFrEF patients (n=8351) were on average 72.3±11.8 years old, with 13.9% less than 60 years of age, 36.0% between 60 and 74 years, and 50.2% 75 years or older; 63.9% were men. Most patients were in NYHA class II and approximately half of the patients had an ischaemic cause of their HF (Table 1).

Elderly HFrEF patients had significantly more renal insufficiency, more often atrial fibrillation, thyroid disease, chronic obstructive pulmonary disease, diabetes mellitus and hypertension and less often obstructive sleep apnoea syndrome when compared to younger patients (P<0.01, for all) (Table 1).

Table 1. Patient characteristics in HFrEF patients

	HFrEF (n=8351)‡			
	Age < 60 years (n=1206)	**Age 60-74 years (n=3105)**	**Age ≥ 75 years (n=4040)**	**p-value**
Age (years)	51.3 ± 7.1	68.0 ± 4.2	81.8 ± 4.7	<0.01
Male gender	763 (63.6)	2163 (70.0)	2388 (59.3)	<0.01
BMI, kg/m2	28.7 ± 6.1	27.9 ± 5.4	26.2 ± 4.4	<0.01
NYHA				
I	322 (26.9)	569 (18.5)	421 (10.6)	<0.01
II	667 (55.7)	1845 (60.0)	2176 (54.6)	
III	192 (16.0)	618 (20.1)	1295 (32.5)	
IV	16 (1.3)	42 (1.4)	91 (2.3)	
LVEF, %	30.4 ± 10.4	31.6 ± 10.0	34.2 ± 10.8	<0.01
Cause of HF				
Ischemic cause of HF	435 (37.1)	1630 (54.0)	2113 (54.3)	<0.01
Non-ischemic cause of HF	738 (62.9)	1390 (46.0)	1779 (45.7)	
Systolic BP, mmHg	123.1 ± 20.0	126.2 ± 20.6	126.0 ± 20.9	<0.01
Diastolic BP, mmHg	74.3 ± 11.5	72.5 ± 11.2	69.3 ± 11.1	<0.01
Heart rate, bpm	72.8 ± 13.8	71.8 ± 14.2	71.9 ± 13.6	0.09
Atrial fibrillation	87 (7.3)	678 (22.1)	1341 (33.6)	<0.01
LBBB	156 (12.9)	490 (15.8)	767 (19.0)	<0.01
QRS ≥130 ms	289 (27.8)	957 (37.2)	1525 (46.0)	<0.01
eGFR, ml/min	79.3 ± 22.8	64.8 ± 23.6	50.8 ± 21.6	<0.01
eGFR				
<30 ml/min	23 (3.0)	154 (7.1)	490 (16.5)	<0.01
30-59 ml/min	116 (15.2)	774 (35.8)	1552 (52.4)	
≥60 ml/min	622 (81.7)	1231 (57.0)	921 (31.1)	
Comorbidities				
Hypertension	306 (29.1)	1097 (39.4)	1573 (43.2)	<0.01
Diabetes Mellitus	252 (23.9)	848 (30.4)	1072 (29.4)	<0.01
COPD	118 (11.2)	546 (19.6)	717 (19.7)	<0.01
OSAS	95 (9.0)	246 (8.8)	154 (4.2)	<0.01
Thyroid disease	57 (5.4)	209 (7.5)	290 (8.0)	0.02
Renal insufficiency†	191 (20.3)	1214 (47.1)	2543 (72.9)	<0.01

HFrEF Heart Failure with reduced Ejection Fraction; BMI, Body Mass Index; NYHA, New York Heart Association classification; LVEF, Left Ventricular Ejection Fraction; HF, Heart Failure; BP, Blood Pressure; LBBB, Left-Bundle Branch Block; eGFR, estimated Glomerular Filtration Rate; COPD, Chronic Obstructive Pulmonary Disease; OSAS, Obstructive Sleep Apnea Syndrome.

† Defined as eGFR <60mL/min or a history of renal failure

‡ In nine patients data on age was missing

Pharmacological therapy in HFrEF

Elderly patients less often received beta-blockers, renin–angiotensin system (RAS) inhibitors, MRAs and ivabradine, but significantly more diuretics than younger patients (Table 2). These differences gradually increased with age.

Patients received all three of the HF medications (beta-blockers, RAS inhibitors and MRAs), if indicated, in 47.8%, 38.7% and 29.6% of the patients in the three age groups (<60 years, 60–74 years and ≥75 years, respectively), two out of three were prescribed in 39.9%, 45.4% and 47.6%, one out of three was prescribed in 10.2%, 14.0% and 19.5%, and none of these medications were prescribed in 2.1%, 1.9% and 3.3%, respectively (P<0.01). Supplementary Figure 1 shows the use of RAS inhibitors divided into ACEIs and ARBs.

The total reported contraindication or intolerance rates were 3.2% (beta-blockers), 4.6%, (RAS inhibitors), 4.7% (MRAs) and 1.7% (ivabradine) (Table 3). The reported contraindication or intolerance rates in elderly patients were significantly higher for beta-blockers, RAS inhibitors and MRAs (P<0.01). However, in a substantial number of patients the reason for not receiving RAS inhibitors or MRAs was not specified in the patients' charts.

Elderly patients less often received the recommended target dose of beta-blockers, RAS inhibitors and MRAs than the younger patient groups (P<0.01, for all) (Figure 1). Fifty per cent or greater of the target dose of all three of the HF medication groups (beta-blockers, RAS inhibitors and MRAs) was achieved in 25.4%, 17.7% and 11.0% of the patients (<60 years, 60–74 years and ≥75 years, respectively); 50% or greater of the target dose of two out of three medications in 38.6%, 40.6% and 35.7%, respectively; 50% or greater of the target dose of none out of three medication in 27.1%, 32.2% and 38.3%, respectively. Younger patients more often received 50% or greater of the target dose of all three guideline-recommended medications than elderly patients, P<0.01.

Table 2. Percentage of HF therapy use in HFrEF and HFmrEF patients

	Pharmacotherapy					Device therapy		
	Beta-blocker	**RAS inhibitor**	**MRA**	**Ivabradine***	**Diuretics**	**ICD**	**CRT**	**Pacemaker**
ESC Guideline 2012								
HFrEF								
<60 years	978 (84.2)	1042 (89.7)	692 (59.6)	112 (9.3)	843 (72.6)	417 (44.1)	158 (16.7)	13 (1.4)
60-74 years	2492 (81.5)	2627 (85.9)	1639 (53.6)	153 (4.9)	2440 (79.8)	1018 (41.2)	500 (20.2)	102 (4.1)
≥75 years	3103 (77.8)	2999 (75.2)	2017 (50.6)	119 (2.9)	3513 (88.1)	612 (18.9)	473 (14.6)	446 (13.8)
p-value	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01
ESC Guideline 2016								
HFrEF								
<60 years	834 (84.5)	888 (90.0)	630 (63.8)	101 (9.9)	746 (75.7)	385 (45.9)	145 (17.3)	9 (1.1)
60-74 years	2073 (81.5)	2209 (86.9)	1397 (55.0)	133 (5.2)	2048 (80.6)	950 (44.7)	463 (21.8)	82 (3.9)
≥75 years	2473 (78.6)	2393 (76.1)	1629 (51.8)	101 (3.2)	2783 (88.5)	565 (21.8)	428 (16.5)	335 (12.9)
p-value	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01
HFmrEF								
<60 years	144 (82.3)	154 (88.0)	62 (35.4)	11 (5.9)	97 (55.4)	32 (29.9)	13 (12.1)	4 (3.7)
60-74 years	419 (81.0)	418 (80.9)	242 (46.8)	20 (3.8)	392 (76.0)	68 (19.8)	37 (10.8)	20 (5.8)
≥75 years	630 (74.7)	606 (71.9)	388 (46.0)	18 (2.1)	730 (86.6)	47 (7.2)	45 (6.9)	111 (17.0)
p-value	p<0.01	p<0.01	p=0.02	p=0.02	p<0.01	p<0.01	p=0.05	p<0.01

CRT: cardiac resynchronisation therapy; ESC: European Society of Cardiology; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mid-range ejection fraction; ICD: implantable cardioverter defibrillator; MRAs: mineralocorticoid receptor antagonists; RAS: renin–angiotensin syndrome.
*If ivabradine is indicated (n=500), patients with HFrEF according to the 2012 ESC Guideline received 78.3%, 75.0% and 77.8% (<60, 60–74 and ≥75 years, respectively, P=0.73) ivabradine.

Table 3. Reasons for not prescribing HF medication in HFrEF patients

		Contraindicated or intolerance	No reason specified
Beta-blocker	Total population	262 (3.2)	971 (11.8)
	<60 years	21 (1.8)	109 (9.4)
	60-74 years	90 (2.9)	300 (9.8)
	≥75 years	150 (3.8)	562 (14.1)
RAS-inhibitors	Total population	380 (4.6)	1161 (14.1)
	<60 years	21 (1.8)	99 (8.5)
	60-74 years	105 (3.4)	327 (10.7)
	≥75 years	254 (6.4)	735 (18.4)
MRA	Total population	387 (4.7)	3479 (42.3)
	<60 years	25 (2.2)	445 (38.3)
	60-74 years	115 (3.8)	1305 (42.7)
	≥75 years	247 (6.2)	1724 (43.2)
Ivabradine*	Total population	143 (1.7)	7691 (93.6)
	<60 years	12 (1.0)	1038 (89.3)
	60-74 years	52 (1.7)	2854 (93.3)
	≥75 years	79 (2.0)	3790 (95.0)

HF, heart failure; HFrEF, heart failure with reduced ejection fraction

* If indicated (n=500) 22.6%, 23.5% and 22.2% (<60, 60-74 and ≥75 years, resp.) of patients did not receive ivabradine with no specified reason

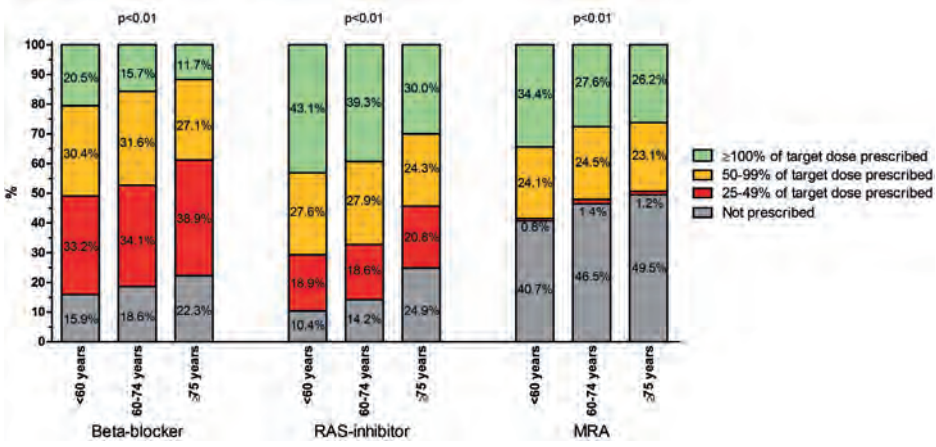

Figure 1. Percentages of target dose prescribed in heart failure with reduced ejection fraction

Table 4. Multivariable analysis: likelihood of receiving guideline recommended therapy per 10 years of age in patients with HFrEF

	Univariable		Multivariable					
			Model 1		Model 2		Model 3	
	OR	p-value	OR	p-value	OR	p-value	OR	p-value
Guideline recommended pharmacotherapy								
Beta-blocker	0.87 [0.83-0.92]	<0.01	0.87 [0.83-0.91]	<0.01	0.88 [0.83-0.92]	<0.01	0.83 [0.79-0.88]	<0.01
RAS-inhibitor	0.67 [0.64-0.71]	<0.01	0.67 [0.64-0.71]	<0.01	0.71 [0.67-0.75]	<0.01	0.75 [0.71-0.80]	<0.01
MRA	0.93 [0.89-0.96]	<0.01	0.93 [0.91-0.94]	<0.01	0.90 [0.86-0.93]	<0.01	0.86 [0.83-0.90]	<0.01
Ivabradine *	0.72 [0.67-0.78]	<0.01	0.72 [0.67-0.77]	<0.01	0.69 [0.64-0.75]	<0.01	0.69 [0.62-0.75]	<0.01
Diuretics	1.42 [1.35-1.48]	<0.01	1.41 [1.38-1.45]	<0.01	1.32 [1.26-1.39]	<0.01	1.15 [1.09-1.21]	<0.01
Guideline recommended device therapy								
ICD	0.63 [0.60-0.66]	<0.01	0.63 [0.60-0.66]	<0.01	0.61 [0.57-0.65]	<0.01	0.62 [0.57-0.67]	<0.01
CRT	0.88 [0.83-0.92]	<0.01	0.88 [0.86-0.90]	<0.01	0.83 [0.78-0.88]	<0.01	0.75 [0.71-0.80]	<0.01
Pacemaker	2.29 [2.07-2.53]	<0.01	2.29 [2.17-2.41]	<0.01	2.17 [1.94-2.41]	<0.01	2.25 [2.00-2.53]	<0.01

COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronisation therapy; eGFR: estimated glomerular filtration rate; HFrEF: heart failure with reduced ejection fraction; ICD: implantable cardioverter defibrillator; MRAs: mineralocorticoid receptor antagonists; NYHA: New York Heart Association; OR: odds ratio; OSAS: obstructive sleep apnoea syndrome; RAS: renin–angiotensin syndrome.

Model 1 included age and gender.

Model 2 included age, gender, NYHA classification, left ventricular ejection fraction (and QRS for device therapy).

Model 3 included age, gender, NYHA classification, left ventricular ejection fraction (QRS duration for device therapy), hypertension, diabetes mellitus, COPD, OSAS, thyroid disease, renal insufficiency (defined as eGFR <60 mL/min or a history of renal insufficiency) and atrial fibrillation.

*For ivabradine atrial fibrillation was not included in the model; if ivabradine was indicated (n=500) the ORs were 1.00 (0.85–1.18), 1.00 (0.92–1.09), 0.97 (0.82–1.15) and 0.97 (0.80–1.17) for univariable, model 1–3, respectively, P>0.70.

After multivariable adjustment, the probability of receiving a beta-blocker, RAS inhibitor, MRA and ivabradine decreases for each 10-year increase in age by 10% (MRAs), 12% (beta-blockers), 29% (RAS inhibitors) and 21% (ivabradine), whereas the probability of receiving diuretics increases by 32% (Table 4). Multiple imputation did not change these findings. The age differences in HF therapy, adjusted for the differences in comorbidities, are presented in Table 4.

The percentage of fluid and sodium restriction recommendations are presented in Supplementary Figure 2.

Device implantation in HFrEF

Elderly patients received significantly more pacemakers, but fewer ICD and CRT devices, compared to younger patients (Table 2). After adjustment for multiple clinical parameters, the chance of receiving an ICD and CRT device decreases by 39% and 17%, respectively, for every 10-year increase in age (Table 4). After multiple imputation, the described differences did not change.

General therapy in subgroups of HFmrEF

HFmrEF patients were on average 73.7±11.7 years old, and 58.4% were men. The differences in baseline characteristics between HFrEF and HFmrEF patients are shown in Supplementary Table 2. Beta-blockers (82.3% vs. 74.7%, P<0.01), RAS inhibitors (88.0% vs. 71.9%, P<0.01) and ivabradine (5.9% vs. 2.1%, P=0.02) were less often prescribed in patients aged 75 years and older compared to patients less than 60 years, while MRAs (35.4% vs. 46.0%, P=0.02) and diuretics (55.4% vs. 86.6%, P<0.01) were more often prescribed (Table 2). The inferences of the HFmrEF group are comparable to the findings in HFrEF.

Discussion

This large practice-based clinical registry of 8351 HF patients including a relatively large group of elderly patients demonstrates that aged HFrEF patients less often receive guideline-recommended therapy. Furthermore, the prescribed dosages as a percentage of the target dose, especially to elderly patients, are lower than recommended.

Pharmacological therapy

Previous recent large registries demonstrated an age-related decline of ESC HF guidelines recommended HF therapy, especially in patients older than 75 years.[11,14–17]

However, these registries are older and were not using the ESC HF guidelines of 2012. Our results also demonstrate an age-related decline, but in contrast to these earlier registries, the decline in our study started already in patients older than 60 years of age and seems to be continuous, indicating that the decline is not restricted to the very old.

It has been suggested that the higher rate of comorbidities or the different aetiology of HF might be an explanation for the age-associated decline in drug prescription. [16] Although we demonstrated significant differences in comorbidities between age groups, these differences were not large enough to explain the observed differences in prescription rates as shown in our multivariable analysis. In chronic HF patients, chronic obstructive pulmonary disease frequently coexists and symptoms overlap, and while getting more prevalent with increasing age, adequate treatment of underlying diseases gets even more challenging.[18]

Frailty in elderly patients is highly prevalent and is associated with a worse prognosis[19] and might explain in some part the lower prescription rate in elderly patients; however, this could not be tested in our registry as no information on frailty was available.

Although elderly patients constitute a large part of the general HF population, patients aged 75 years of age and older are underrepresented in large randomized clinical trials.[2,5,11] Thereby the positive effect of the HF medication in the elderly HF population is not yet properly investigated. This might be another explanation for the decline in prescription rates in elderly patients. However, the decline appears to be not limited to the very old, but to be a continuum, starting at a younger age than was previously assumed, indicating that the decline cannot be fully explained by lack of evidence in the elderly alone.

In contrast to the HF medication, diuretics, fluid and sodium restrictions are more often used in elderly patients. However, after adjustment in the multivariable analysis for comorbidities, the influence of age is largely reduced, in contrast to the other recommendations. This might indicate that the use of diuretics, fluid and sodium restrictions can partially be explained by worse renal function in elderly patients.

Despite the fact that elderly patients less often received guideline-recommended pharmacological therapy, we still observed an overall high prescription rate in all age groups, compared to the CHAMP–HF registry. [20] Importantly, when HF medication is

prescribed, the actual dosages are significantly lower in elderly than in younger patients, which could potentially lead to a worse outcome. As has been shown, good adherence to the guidelines, with prescription of at least 50% of the recommended dosage, is associated with better clinical outcomes.[21]

Despite relative good guideline adherence, there still seems to be room for further improvement, especially in the prescribed dosages, and in the elderly population. As previously demonstrated, the uptitration of HF medication is possible, even in elderly patients.[22] However, evidence on the effect of HF therapy in patients aged 75 years and older is very limited,[22,23] and appropriate prospective trials are urgently needed to address the important question as to whether treatment should differ depending on age.

Device therapy

Elderly patients less often received a ICD or CRT device, and more frequently received a pacemaker. These results are in line with recent publications, showing a decline of the CRT device and ICD implantation rate in older patients[11,14,16] and an increase of the pacemaker implantation rate.[11]

The age differences in implantation rates might be explained by more perceived or actual comorbidities or contraindications, including non-HF-related comorbidities such as cognitive and mobility impairments.[16] It has been shown that elderly HF patients have a higher non-cardiac mortality rate compared with younger HF patients.[24] This might negatively influence the benefits and cost-effectiveness of implanted devices in the elderly. However, after multivariable analysis, the age-related differences remained. Also, device implantation, such as ICDs, has been shown to be effective and even warranted in elderly patients if life expectancy is longer than one year.[24] Still, a recent study in patients with non-ischaemic cardiomyopathy found a strong relationship between reduced mortality by ICD and age, with only younger patients having any benefit in post-hoc analysis. [25] Furthermore, assumption of a higher risk of complications due to the implantation procedure in elderly patients might explain the lower implantation rates. However, as recently reported there are no differences in the number of complications in elderly patients compared with younger patients.[26] Finally, the perception that quality of life is seen as more important for elderly patients than a prolonged survival period might result in the lower implantation rates of a ICD. However, the preference of patients to prefer longevity over optimal quality of life was found to be surprisingly high and not individually predictable even at a high age.[27]

The use of a CRT device not only reduces morbidity and mortality, but also symptoms and improves quality of life, also in elderly patients.[28] In addition, it can lead to a rise in blood pressure and protect against bradycardia. [29] These gains may lead to a better adherence to recommended HF medication, such as beta-blockers.[29] Thus, there is no evidence that a CRT device may be less important in HFrEF patients at an older age. As elderly patients are more often in need of a pacemaker, as shown in our results, and a CRT device holds positive treatment effects for elderly patients, it might be beneficial to treat these patients with biventricular CRT pacing instead of right ventricular pacing using a pacemaker.

Limitations and strengths

Our study has some limitations. CHECK–HF has a cross-sectional design with no follow-up data on patient outcomes. In addition, for some important variables data were missing, which might influence the results. However, imputation of missing data did not influence the results. The strengths of the CHECK–HF registry include the large scale, a reflection of the true practice of outpatient HF management in The Netherlands representative of western European countries. A further strength is the availability of a large number of elderly patients with detailed information on medication prescription and dosage.

Conclusion

In this large Dutch registry of a real-world outpatient HF population, HFrEF patients in a higher age group less often received guideline-recommended HF drugs, at lower dosages and less often ICD and CRT device therapy. The differences cannot be fully explained by clinical variables, comorbidities or higher reported contraindications or intolerance. Our study indicates the need to focus especially on elderly HF patients, in order to optimise their medical therapy, and further uptitrate their dosages or reflect on policy and accept lower age-adjusted target doses in elderly patients as they do not tolerate higher dosages.

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Supplementary content

Supplementary Table 1. Target doses of guideline recommended therapy

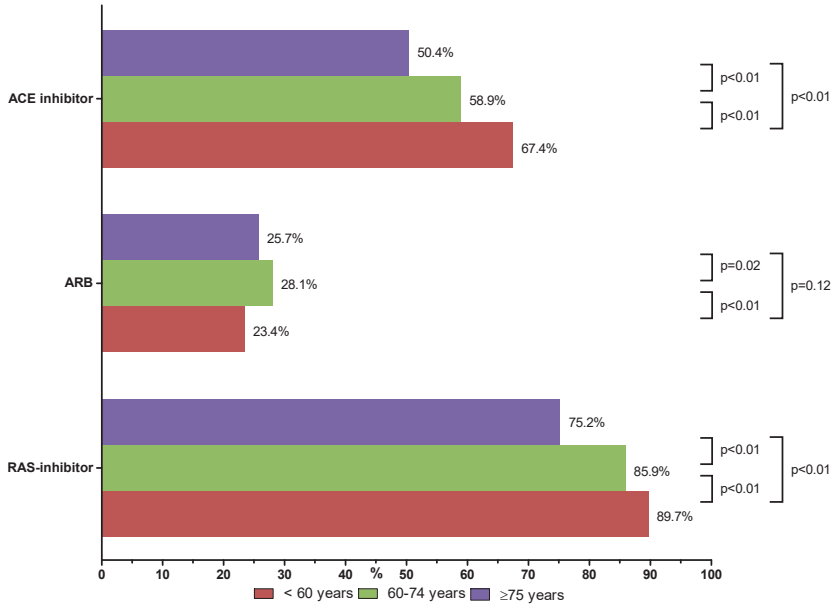
Beta-blocker	
Bisoprolol	10 mg
Carvedilol	50 mg
Metoprolol succinate	200 mg
Nebivolol	10 mg
ACE-inhibitor	
Captopril	150 mg
Enalapril	20 mg
Lisinopril	40 mg
Ramipril	10 mg
Perindopril	8 mg
ARB	
Candesartan	32 mg
Losartan	150 mg
Valsartan	320 mg
MRA	
Eplerenone	50 mg
Spironolactone	25 mg

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist

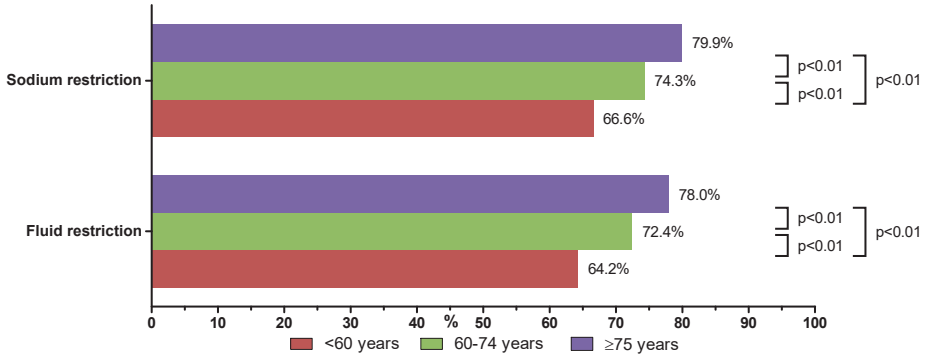
Supplementary Table 2. Patient characteristics of HF patients according to 2016 ESC HF Guideline

	HFrEF (n=6786)	HFmrEF (n=1574)	p-value
Age (years)	71.9 ± 11.8	73.7 ± 11.7	p<0.01
Male gender	4403 (65.2)	917 (58.4)	p<0.01
BMI, kg/m2	27.2 ± 5.1	27.5 ± 5.4	p<0.01
NYHA			
I	1029 (15.3)	284 (18.2)	p<0.01
II	3838 (57.2)	854 (54.8)	
III	1716 (25.6)	392 (25.2)	
IV	121 (1.8)	28 (1.8)	
LVEF, %	29.3 ± 9.0	45.0 ± 5.4	p<0.01
Cause of HF			
Ischemic cause of HF	3491 (53.1)	691 (45.4)	p<0.01
Non-ischemic cause of HF	3082 (46.9)	830 (54.6)	
Systolic BP, mmHg	124.8 ± 20.4	129.5 ± 21.6	p<0.01
Diastolic BP, mmHg	71.1 ± 11.2	71.8 ± 12.0	p<0.01
Heart rate, bpm	71.9 ± 13.8	72.5 ± 14.3	p=0.03
Atrial fibrillation	1575 (23.5)	534 (34.3)	p<0.01
LBBB	1198 (17.7)	216 (13.7)	p<0.01
QRS ≥130 ms	2358 (42.0)	416 (31.5)	p<0.01
eGFR	60.3 ± 24.7	56.2 ± 23.7	p<0.01
eGFR			
<30	534 (10.9)	133 (13.7)	p<0.01
30-59	2003 (40.8)	439 (45.1)	
≥60	2373 (48.3)	401 (41.2)	
Comorbidity			
Hypertension	2359 (38.9)	619 (43.7)	p<0.01
Diabetes Mellitus	1777 (29.3)	397 (28.0)	p=0.10
COPD	1090 (18.0)	291 (20.5)	p=0.03
OSAS	379 (6.2)	116 (8.2)	p<0.01
Thyroid disease	446 (7.3)	111 (7.8)	p=0.40
Renal insufficiency †	3205 (55.4)	745 (60.9)	p<0.01
No relevant comorbidity	757 (14.6)	98 (9.0)	p<0.01

BMI, Body Mass Index; NYHA, New York Heart Association classification; LVEF, Left Ventricular Ejection Fraction; HF, Heart Failure; BP, Blood Pressure; LBBB, Left-Bundle Branch Block; eGFR, estimated Glomerular Filtration Rate; NT-proBNP, N-terminal pro Brain Natriuretic Peptide; COPD, Chronic Obstructive Pulmonary Disease; OSAS, Obstructive Sleep Apnea Syndrome.
† Defined as eGFR <60mL/min or a history of renal failure



Supplementary Figure 1. Percentage of RAS-inhibitors prescription in heart failure with reduced ejection fraction



Supplementary Figure 2. Lifestyle therapy in heart failure with reduced ejection fraction

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Medical treatment of octogenarians with chronic heart failure: data from CHECK-HF

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Abstract

Background: Elderly heart failure (HF) patients are underrepresented in clinical trials, though are a large proportion of patients in real-world practice. We investigated practice-based, secondary care HF management in a large group of chronic HF patients aged ≥ 80 years (octogenarians).

Methods: We analyzed electronic health records of 3490 octogenarians with chronic HF at 34 Dutch outpatient clinics in the period between 2013 and 2016 , 49% women. Study patients were divided into HFpEF [LVEF ≥ 50%; n = 911 (26.1%)], HFrEF [LVEF < 40%; n = 2009 (57.6%)] and HF with mid-range EF [HFmrEF: LVEF 40–49%; n = 570 (16.3%)].

Results: Most HFrEF patients aged ≥ 80 years received a beta blocker and a renin–angiotensin system (RAS) inhibitor (angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker), i.e. 78.3% and 72.8% respectively, and a mineralocorticoid receptor antagonist (MRA) was prescribed in 52.0% of patients. All three of these guideline-recommended medications (triple therapy) were given in only 29.9% of octogenarians with HFrEF, and at least 50% of target doses of triple therapy, beta blockers, RAS inhibitor and MRA, were prescribed in 43.8%, 62.2% and 53.5% of the total group of HFrEF patients. Contraindications or intolerance for beta blockers was present in 3.5% of the patients, for RAS inhibitors and MRAs in, 7.2% and 6.1%.

Conclusions: The majority of octogenarians with HFrEF received one or more guideline-recommended HF medications. However, triple therapy or target doses of the medications were prescribed in a minority. Comorbidities and reported contraindications and tolerances did not fully explain underuse of recommended HF therapies.

Introduction

Elderly patients represent a major proportion of the heart failure (HF) population. Most of these elderly patients have multiple morbidities. [1–3] This may complicate adherence to advocated HF management.

In general, optimizing guideline-recommended HF therapies improves quality of life, morbidity and mortality significantly. [4-6] However, randomized clinical trials investigating HF therapies did not represent the real-life HF population. The patients enrolled in these trials were on average 10 years younger than in real-world practice; elderly patients were largely underrepresented and very elderly were even excluded, except for the SENIORS-study. [7–10]

As such, there are considerable gaps of knowledge in HF treatment effects in octogenarians. Practice guidelines do not provide age-specific recommendations for implementation and utilization of HF therapies, [4, 5] but several registries reported lower prescription rates of evidence-based medication in the elderly. [11–18] High age-related factors, e.g., frailty, fall risk, cognitive impairment, dementia and disability, and also polypharmacy and concerns on drug interaction may interfere with initiation and persistence of HF medication, and as such are potential barriers for optimal therapy. [5] Importantly, detailed data regarding prescribed HF medication in the very elderly are scarce.

In a large-scale real-world registry at Dutch HF outpatient clinics, we investigated medical HF therapies and determinants of prescription of individual HF drugs in a substantial group of octogenarians, [19, 20] better reflecting contemporary practice-based HF in secondary care.

Methods

The design and methods of the CHECK-HF (Chronisch Hartfalen ESC-richtlijn Cardiologische praktijk Kwaliteitsproject HartFalen) registry have been published in detail earlier. [19] Briefly, the CHECK-HF registry consists of 10,910 patients with chronic HF from a total of 34 participating Dutch centers. Between 2013 and 2016, all centers included patients diagnosed with HF based on the 2012 ESC Guidelines on HF (i.e., based on symptoms and echo parameters) who were seen at the outpatient HF clinic (96%) or general cardiology outpatient clinic (4%) if no specific HF clinic was present.

From electronic health records, baseline patient characteristics, etiology of HF, comorbidities, basic echocardiographic and electrocardiographic (ECG) parameters, laboratory markers, pacemaker, ICD and CRT treatment as well as prescription rates of medication (drug name, dosage and frequency and total daily dose) were recorded. The target doses of guideline-recommended HF medication are presented in Suppl. Table 1. Drug doses were calculated compared to the recommended dose and according to guidelines as a daily dose or percentage of actual recommended daily dose.

Furthermore, contraindications and intolerance as indicated by the treating physician were collected. No predefined rules were applied to determine absolute contraindications. CHECK-HF is a cross-sectional observational cohort study and there were no outcome data collected.

There were 3601 patients aged ≥ 80 years, comprising 33.1% of the total CHECK-HF cohort. In 111 (3.1%) patients, recording of ejection fraction or age in the database was insufficient to classify patients; so, these patients were excluded from this analysis. In the current analyses of the remaining 3490 patients, aged ≥ 80 years, we focused on the prescribed HF medication.

Based on echocardiographic results, octogenarians were divided based on LVEF or visual assessment of the function of the left ventricle (LV) according to the contemporary 2016 ESC HF Guidelines into HFpEF [LVEF ≥ 50%; n = 911 (26.1%)], HFrEF [LVEF < 40%; n = 2009 (57.6%)] and HF with mid-range EF [HFmrEF: LVEF 40–49%; n = 570 (16.3%)].

This study was approved by the medical ethics committee 2017 at Maastricht University Medical Center (Maastricht, the Netherlands). No informed consent of the participants in this registry was required.

Statistics

Continuous data are expressed as mean value ± SD or median and interquartile range, depending on the distribution of the data, and compared by applying one-way analysis of variances (ANOVA) or Mann–Whitney U-test. Categorical data are expressed as counts and percentages, and compared by the Pearson Chi-square test. A two-sided p value of 0.05 was considered statistically significant.

Multivariable predictors for the use of HF medication were sought, using multivariable logistic regression analysis, using the stepwise backward procedure. All predictors of

medication use in univariable analysis (data not shown) at a p value of < 0.10 were included in the multivariable regression analysis. Results of logistic regression are presented as odds ratio (ORs). Some missing data occurred in the variables included in the multivariable analyses, which we corrected using multiple imputation. If the missing variables showed a monotone pattern of missing values, the monotone method was used; otherwise, an iterative Markov chain Monte Carlo method was used with a number of 10 iterations. A total of 5 imputations were performed, and the pooled data were analyzed. The imputed data were only used for the multivariable analysis. For all reported data of the multivariable analysis, we compared crude and imputed p values as well as the odds ratios and confidence intervals to analyze whether imputation changed the results, and if no significant changes occurred, we present the imputed values in the main analyses.

All analyses were performed with SPSS Statistical Package version 24.0 (SPSS Inc, Chicago, Illinois).

Results

Baseline characteristics of the 3490 HF patients aged ≥ 80 years are shown in Table 1. The median [IQR] age was 84 [82.0–87.0] years and 49% were women. Most patients were in NYHA class II and approximately half of the patients had a ischemic cause of their HF. Median [IQR] LVEF was 40% [30.0–50.0], one quarter had diabetes mellitus and the majority (74%) had an eGFR < 60 ml/min/m2 (Table 1). Several baseline characteristics differed significantly between LVEF groups, also when subdividing men and women (Suppl. Table 2). HFpEF patients (n = 911) were older and more often women, had a higher body mass index, more often had a non-ischemic cause of HF, hypertension, and atrial fibrillation in comparison to HFrEF patients (n = 2009). Octogenarians with HFrEF more often had a QRS-width ≥ 130 ms and left bundle branch block (LBBB) on their ECG, when compared to those with HFpEF, in those with sinus rhythm or atrial fibrillation, and not in HF patients with paced or ectopic rhythm (Table 1 and Suppl. Table 3).

Table 1. Characteristics of octogenarians with HF according to LVEF groups (ESC Guidelines 2016)

	Total (n=3490)	HFrEF (n=2009)	HFmrEF (n=570)	HFpEF (n=911)	p-value
Age (years) (n=3490)	84.0 [82.0-87.0]	84.0 [82.0-87.0]	84.0 [82.0-87.0]	85.0 [82.0-88.0]	<0.01
Men (n=3475)	1775 (51.1)	1160 (58.0)	290 (51.1)	325 (35.8)	<0.01
Duration of HF (n=3480)					
<1 year	411 (11.8)	222 (11.1)	78 (13.7)	111 (12.2)	
1 - 2 years	737 (21.2)	407 (20.3)	126 (22.2)	204 (22.5)	0.17
≥ 2 years	2332 (67.0)	1376 (68.6)	364 (64.1)	592 (65.3)	
BMI, kg/m2 (n=3139)	25.0 [23.0-29.0]	25.0 [23.0-28.0]	26.0 [23.0-29.0]	26.0 [24.0-30.0]	<0.01
NYHA (n=3440)					
I	335 (9.7)	189 (9.5)	44 (7.8)	102 (11.4)	
II	1791 (52.1)	1036 (52.3)	310 (55.1)	445 (49.7)	0.20
III	1217 (35.4)	705 (35.6)	195 (34.6)	317 (35.4)	
IV	97 (2.8)	52 (2.6)	14 (2.5)	31 (3.5)	
LVEF, % (n=2326)	40.0 [30.0-50.0]	30.0 [25.0-35.0]	45.0 [40.0-47.0]	58.0 [52.0-60.0]	<0.01
Cause of HF (n=3369)					
Ischemic cause of HF	1518 (45.1)	1061 (54.5)	247 (45.6)	210 (23.8)	<0.01
Non-ischemic cause of HF	1851 (54.9)	885 (45.5)	295 (54.4)	671 (76.2)	
Systolic BP, mmHg (n=3455)	125.0 [111.0-140.0]	122.0 [110.0-139.0]	125.5 [114.3-140.0]	130.0 [118.0-145.0]	<0.01
Diastolic BP, mmHg (n=3461)	70.0 [60.0-76.0]	70.0 [60.0-75.0]	70.0 [60.0-76.0]	70.0 [60.0-79.0]	0.01
Heart rate, bpm (n=3446)	70.0 [63.0-80.0]	70.0 [63.0-80.0]	71.0 [62.0-82.0]	70.0 [63.0-80.0]	0.42
Atrial fibrillation (n=3445)	1371 (39.8)	666 (33.7)	268 (47.3)	437 (48.4)	<0.01
LBBB (n=3490)	594 (17.0)	432 (21.5)	79 (13.9)	83 (9.1)	<0.01
QRS ≥130 ms (n=2830)	1131 (40.0)	786 (48.5)	167 (35.8)	178 (24.0)	<0.01
eGFR (n=2459)	44.2 [32.4-60.6]	45.2 [33.1-61.2]	43.4 [31.6-58.5]	42.0 [31.2-59.6]	0.03

Table 1. *(continued)*

	Total (n=3490)	HFrEF (n=2009)	HFmrEF (n=570)	HFpEF (n=911)	p-value
eGFR (n=2459)					
<30	498 (20.3)	283 (18.9)	87 (21.6)	128 (22.8)	
30-59	1324 (53.8)	806 (53.9)	222 (55.2)	296 (52.7)	0.18
≥60	637 (25.9)	406 (27.2)	93 (23.1)	138 (24.6)	
Comorbidity (n=3158)					
Hypertension	1485 (47.0)	763 (42.2)	237 (46.1)	485 (57.9)	<0.01
Diabetes Mellitus	862 (27.3)	495 (27.4)	139 (27.0)	228 (27.2)	0.98
COPD	614 (19.4)	326 (18.1)	114 (22.2)	174 (20.8)	0.06
OSAS	93 (2.9)	51 (2.8)	8 (3.5)	24 (2.9)	0.72
Thyroid disease	259 (8.2)	153 (8.5)	31 (6.0)	75 (8.9)	0.13
No relevant comorbidity	148 (5.5)	107 (6.8)	17 (3.8)	24 (3.7)	<0.01

HF heart failure, *LVEF* left ventricular ejection fraction, *ESC* European Society of Cardiology, *HFrEF* heart failure with reduced ejection fraction, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *BMI* body mass index, *NYHA* New York Heart Association classification, *BP* blood pressure, *LBBB* left-bundle branch block, *eGFR* estimated glomerular filtration rate, *COPD* chronic obstructive pulmonary disease, *OSAS* obstructive sleep apnea syndrome

Characteristics of HFmrEF patients aged ≥ 80 years (n = 570) did not differ much from those with HFrEF except for a higher prevalence of atrial fibrillation and some other relevant comorbidities and fewer LBBB on ECG (Table 1). COPD was more prevalent in HFmrEF compared to HFrEF patients (22.2% and 18.1%, respectively, p = 0.04). HFpEF patients had more often hypertension when compared to both HFrEF and HFmrEF patients (Fig. 1).

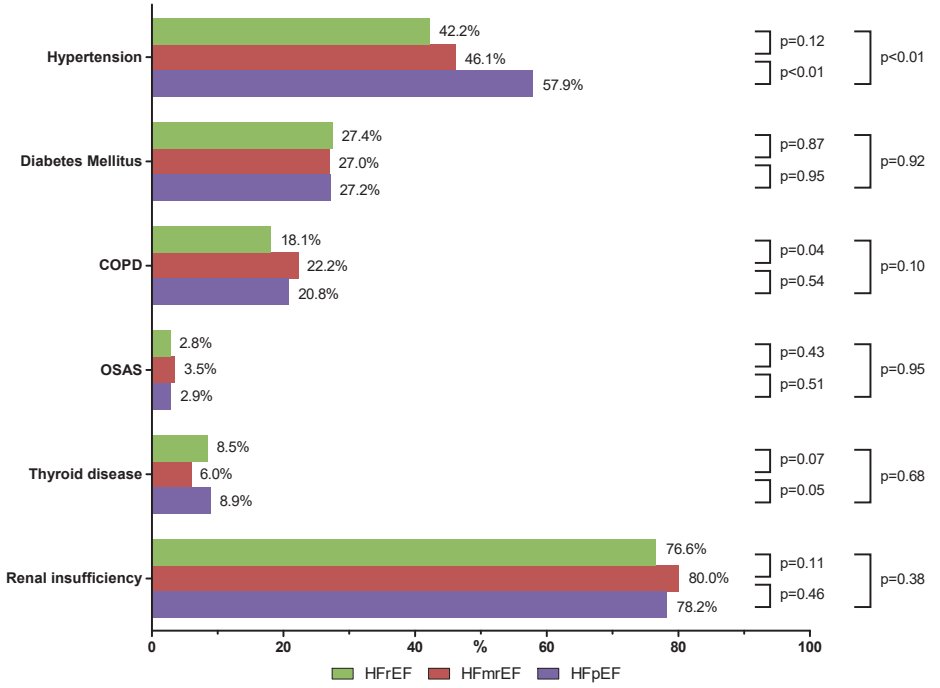

Fig. 1 Comorbidities in octogenarians with heart failure: HFrEF vs. HFmrEF vs. HFpEF (ESC Guidelines 2016). *HFrEF* heart failure with reduced ejection fraction, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *ESC* European Society of Cardiology, *COPD* chronic obstructive pulmonary disease, *OSAS* obstructive sleep apnea syndrome.
Renal insufficiency: defined as eGFR < 60 mL/min or a history of renal failure

Guideline-recommended medical therapy in HFrEF

Following the ESC guidelines 2016, a large proportion of HFrEF patients aged ≥ 80 years received a beta blocker or a RAS inhibitor [angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)], i.e., 78.3% and 72.8%, respectively. An MRA was prescribed in 52.0% of patients and diuretics in 90.4%. Women received more often a beta blocker and a thiazide diuretic, than men (Table 2).

The combination of all three HF medication (beta blocker, RAS inhibitor and MRA), were prescribed to 29.9% of HFrEF patients aged ≥ 80 years patients, two out of three HF medication in 46.5%, one out of three in 20.3%, and none of these medications were prescribed in 3.3% of octogenarians with HFrEF. In total, 55 patients (2.7%) received ivabradine, which represents 77% of those where ivabradine was indicated.

MRA was less used in patients with more than 2 years of follow-up than in those with < 1 year of HF follow-up, 49.0% and 61.5% respectively, p < 0.01 (Suppl. Table 4a).

The percentages of target dose of HF medication prescribed in the 2009 HFrEF patients (LVEF < 40%) aged ≥ 80 years are shown in Fig. 2. At least, 50% of target doses of beta blockers, RAS inhibitor and MRA were prescribed in 43.8%, 62.2% and 53.5% of HFrEF patients, respectively (Fig. 2). A ≥ 50% of target dose of all three of the HF medications groups was achieved in 9.5% of the patients; ≥ 50% of the target dose for two out of three HF medications in 35.9%; ≥ 50% of the target dose for one out of three HF medications in 39.2%; and ≥ 50% of the target dose for none of these HF medications in 15.5%.

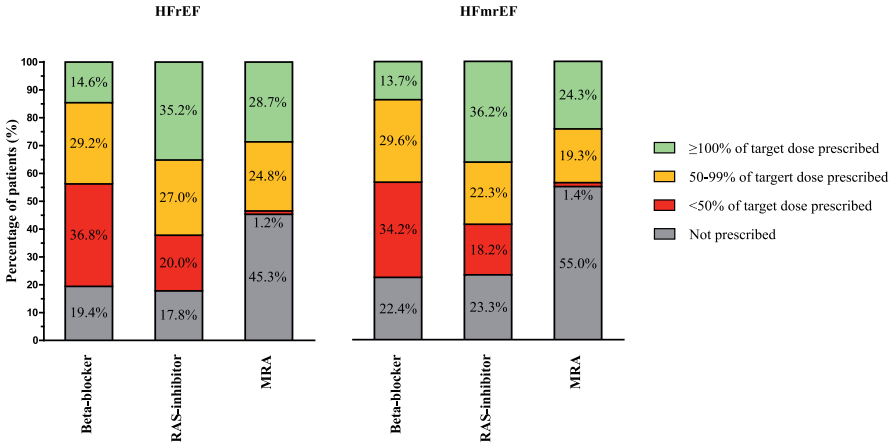

Fig. 2 Percentages of target dose of HF medication prescribed in octogenarians with HFrEF (LVEF < 40%). *HF* heart failure, *HFrEF* heart failure with reduced ejection fraction, *RAS* renin–angiotensin system, *RAS inhibitor* angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor

The reasons of non-adherence or not prescribing recommended HF medication (ESC Guidelines 2016) were reported by the centers and are depicted in Table 3. Contraindications or intolerance for beta blockers was present in 3.5% of the patients, for RAS inhibitors, MRAs and ivabradine in, respectively, 7.2%, 6.1% and 2.2%. There were no substantial differences between men and women (Suppl. Table 5). In a substantial number of patients, the reasons for not receiving recommended HF-medication were not specified.

Table 2. Percentage of HF therapy use in HFrEF, HFmrEF and HFpEF patients aged ≥ 80 years, for men and women.

		Guideline-recommended pharmacotherapy					Loop diuretics	Thiazide diuretics
		Beta-blocker	**RAS-inhibitor**	**MRA**	**Ivabradine**	**Diuretics**		
	Men	879 (76.4)	856 (74.4)	592 (51.4)	32 (2.8)	1035 (89.9)	1016 (88.3)	20 (1.7)
HFrEF	Women	672 (81.2)	585 (70.7)	438 (52.9)	23 (2.7)	754 (91.1)	731 (88.3)	31 (3.7)
	p-value	0.01	0.07	0.52	0.98	0.40	0.99	0.01
	Men	201 (70.3)	189 (66.1)	131 (45.8)	4 (1.4)	252 (88.1)	244 (85.3)	10 (3.5)
HFmrEF	Women	206 (74.6)	191 (69.2)	146 (52.9)	6 (2.2)	255 (92.4)	251 (90.9)	4 (1.4)
	p-value	0.25	0.43	0.09	0.48	0.09	0.04	0.12
	Men	226 (70.4)	195 (60.7)	144 (44.9)	4 (1.2)	293 (91.3)	277 (86.3)	16 (5.0)
HFpEF	Women	437 (76.5)	358 (62.7)	253 (44.3)	1 (0.2)	520 (91.1)	506 (88.6)	17 (3.0)
	p-value	0.04	0.57	0.87	0.06	0.92	0.31	0.13

HF heart failure, *HFrEF* heart failure with reduced ejection fraction, *HFmrEF* heart failure with mid-range ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *RAS* renin–angiotensin system, *RAS inhibitor* angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), *MRA* mineralocorticoid receptor antagonists

Table 3. Reasons for not prescribing HF medication in HFrEF patients aged ≥ 80 years

	Contraindicated or intolerance	No reason specified
Beta-blocker	69 (3.5)	287 (14.4)
RAS-inhibitors	145 (7.2)	396 (19.9)
MRA	121 (6.1)	834 (41.9)
Ivabradine[a]	43 (2.2)	1891 (95.1)

HF heart failure, *HFrEF* heart failure with reduced ejection fraction, *RAS* renin–angiotensin system, *RAS inhibitor* angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), *MRA* mineralocorticoid receptor antagonists

[a] If indicated (*n* = 19) 25.7% of patients did not receive ivabradine with no specified reason

Table 4. Multivariable predictors of the use of HF medication in HFrEF patients aged ≥ 80 years

	Beta-blocker	RAS inhibitor	MRA	Diuretics
	OR	OR	OR	OR
Female gender	1.31 [1.02-1.68]	-	-	-
Age (per 10 y)	-	0.63 [0.48-0.83]	-	-
BMI (kg/m2)	-	-	-	1.06 [1.01-1.12]
Systolic BP (per 10 mmHg)	-	1.09 [1.02-1.16]	0.80 [0.75-0.85]	-
Diastolic BP (per 10 mmHg)	-	-	-	0.77 [0.63-0.93]
NYHA-class (per class)	-	-	-	2.07 [1.49-2.88]
Heart rate (per 10 bpm)	-	-	-	-
QRS-duration (per 10 ms)	-	0.97 [0.94-1.00]	-	-
eGFR (per 10 ml/min)	-	-	-	0.85 [0.76-0.94]
Ischemic etiology	-	-	-	-
Hypertension	-	-	-	1.42 [1.04-1.94]
Diabetes mellitus type 2	-	-	-	-
COPD	-	-	-	-
Renal failure	-	0.73 [0.55-0.98]	-	1.93 [1.18-3.16]

HF heart failure, *HFrEF* heart failure with reduced ejection fraction, *RAS* renin–angiotensin system, *RAS inhibitor* angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), *MRA* mineralocorticoid receptor antagonists, *OR* odds ratio, *BMI* body mass index, *BP* blood pressure, *NYHA* New York Heart Association classification, *eGFR* estimated glomerular filtration rate, *COPD* chronic obstructive pulmonary disease, – variable not included in the model

The results of multivariable analysis on guideline-directed pharmacotherapy in octogenarians with HFrEF are presented in Table 4. Lower prescription rates of recommended RAS inhibitors were associated with higher age, NYHA class and heart rate, wider QRS, and also HFmrEF (versus HFrEF). Higher prescription rates of RAS inhibitors and diuretics were related to hypertension. Lower prescription of RAS inhibitors but higher use of beta blocker was associated with the presence of renal

failure. MRA use was not associated with these comorbidities. Prescription rates of recommended HF medication were not independently associated with ischemic etiology of HF, diabetes mellitus 2 and COPD.

Digoxin was prescribed in one fifth of elderly HFrEF patients (21.4%), amiodarone in 7.7% and statins in 69.8%. Polypharmacy including beta blocker, RAS inhibitor, MRA, ivabradine, diuretics, statin, digoxin and amiodarone, median 4 of these drugs, was only slightly related to prescription of recommended beta blocker, RAS inhibitor and MRA (Suppl. Table 6).

Medical treatment of HFmrEF patients

In the 570 patients with HFmrEF aged ≥ 80 years, beta blockers, RAS inhibitor and MRA were prescribed in 72.5%, 67.6% and 49.1% of elderly HFmrEF patients, respectively. These proportions did not differ much from those in HFrEF patients (Table 2). Also, the percentages of the combined beta blocker, RAS inhibitor and/or MRA use in HFmrEF patients, aged ≥ 80 years, were only slightly lower than in HFrEF octogenarians, for men and women (Fig. 3). Statins, digoxin and amiodarone were prescribed in 66.3%, 22.0% and 5.4% of HFmrEF patients, respectively.

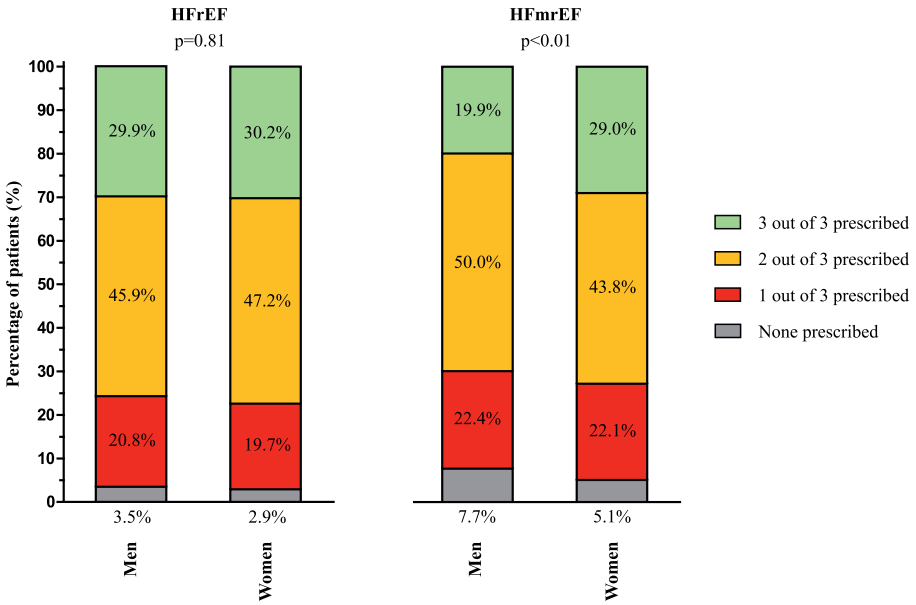

Fig. 3 Percentage of beta blocker, RAS inhibitor and/or MRA use in HFrEF and HFmrEF patients aged ≥ 80 years for men and women. *HFrEF* heart failure with reduced ejection fraction, *HFmrEF* heart failure with mid-range ejection fraction, *RAS* renin–angiotensin system, *RAS inhibitor* angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), *MRA* mineralocorticoid receptor antagonists, *ESC* European Society of Cardiology

Medical treatment of HFpEF patients

In the 911 HFpEF patients aged ≥ 80 years, diuretics were used by most frequently (91.2%), followed by beta blockers (74.3%), RAS inhibitors (62.0%) and MRAs (44.6%). Proportions of beta blockers, RAS inhibitors, MRA and diuretics did not differ much from those in HFrEF patients. Digoxin was prescribed in one fifth of elderly HFpEF patients (20.4%); and ivabradine and amiodarone in very few patients, 0.5% and 9.6%, respectively.

The subgroup of HF with supernormal LVEF (LVEF > 65%; HFsnEF) in our CHECK-HF octogenarians contained only 58 patients (1.7%), see Suppl. Table 7. This new entity compromised too small patients group to make inferences and was not further included in the analyses.

Discussion

From our Dutch outpatient registry of chronic HF patients, we demonstrated that most octogenarians received recommended HF medication, although at lower percentages of target doses than previously reported in the entire group, except for MRAs. [20] Also, all three of the HF medications (beta blocker, RAS inhibitor and MRA) were prescribed in only about one quarter of octogenarians with HFrEF. Notably, women received more often beta blockers and thiazides than men.

The guidelines do not recommend specific HF therapies in patients with HFmrEF and HF medication did not differ significantly from HFrEF patients.

In the HFpEF group aged ≥ 80 years, prescription rates of diuretics were higher than 90%. A substantial proportion received also a beta blocker, RAS inhibitor or MRA, likely to be related to the treatment of prevalent comorbidities. Due to clinical referral to out-hospital heart failure clinics, irrespective of patients' age, CHECK-HF contains a relatively high percentage of patients with HFrEF (overall 52% and in octogenarians: 58%) in comparison to the prevalence of HFpEF in Western populations. Although, the National Audit for England and Wales also reported that substantially more HFrEF than HFpEF patients (66.8% and 33.2%, respectively) were included in their registry (2016–2017), e.g., after a hospital admission for heart failure. [21]

Pharmacological therapy

Elderly patients constitute a large part of the HF population in Western countries, [1–4] but only few studies addressed HF pharmacologic management of patients aged ≥ 80 years [11–17]. In the Euro Heart Failure Survey (EHFS) II, both mortality rates of octogenarians during hospital stay and during follow-up of 12 months were significantly higher than in younger patients. [12] Notably, from the consecutive EHFS programs, a gradual improvement, though still suboptimal, of medical therapies in octogenarians hospitalized for HF was reported. The presence of comorbidities predicted mortality and the use of ACE inhibitors and beta blockers were associated with better outcome. [11, 12] The French OCTOCARDIO study found that even in the absence of comorbidity, in elderly patients with HF, ACE inhibitors and beta blockers were prescribed to only 40% and 48% of patients, respectively, probably because of their advanced age alone. [13] Data from a French national observational retrospective cohort of 1825 patients aged > 80 years who were for the first time hospitalized for HF demonstrated that only 5% of them received an optimal treatment at discharge (combination of RAS inhibitor, beta blocker and MRA). [14] During their follow-up period of 2 years, only beta-blocker prescription levels ($p = 0.02$) increased. In the CHECK-HF registry in chronic HF, about one third of patients were aged ≥ 80 years, thus resembling contemporary real-world practice in civilized countries. We found higher prescription rates of recommended HF medication than in these previous registries, which may be related to the delivery of specialist outpatient HF care in the vast majority of patients. However, in a substantial part of the HFrEF group, the actual dosages were lower than in younger patients. [20]

Many factors may play a role in suboptimal therapy in the very old HF patients. In CHECK-HF, lower rates of guideline-directed pharmacotherapy in octogenarians with HFrEF were associated with NYHA class, LVEF and comorbidities. Lower prescription rates and tolerable dosages of recommended HF medication may be attributed to several limiting factors, e.g., low blood pressure and renal failure. [27] Also, recent data from the CHAMP-HF registry of in total 3518 patients from 150 primary care and cardiology practices showed that lower medication utilization or dose was associated with older age, lower blood pressure, more severe functional class, renal insufficiency, and recent HF hospitalization. [18] Remarkably, a recent post hoc analysis of the BIOSTAT-CHF study suggested that women with HFrEF might need lower doses of RAS inhibitors and beta blockers than men, also adjusted for age. [22]

The Swedish Heart Failure Registry reported that 80% of HFrEF patients with age > 80 years used RAS inhibitors, which was associated with reduced morbidity and

mortality in this observational study. [16] Also, the use of beta blockers was associated with improved all-cause and CV survival. [17] So, suboptimal use of HF medication may lead to worse clinical outcomes. Also, only 40% patients of the total HFrEF cohort of that registry (11,215 patients, 27% women; mean age 75 ± 11 years) received a MRA. [23] Notably, the underuse of MRA was not related to hyperkalaemia, but among other factors, to impaired renal function, even in the range of a creatinine clearance 30–59.9 ml/min, which is not a contraindication for MRA use. Adherence to guideline-directed therapy of HFrEF, with prescription of at least 50% of the target dosage, is associated with better outcome; [6,24–27] although, this association has not been proven for very elderly HF patients. In the QUALIFY international registry, mainly younger patients were included and both mean age and age ≥ 74 years did not influence adherence to (ESC 2012) guideline-directed medical therapy in HFrEF patients.

In addition, other age-related factors, particularly frailty, cognitive impairment and polypharmacy may contribute to suboptimal therapy of elderly HF patients. [28]. In previous randomized clinical trials, patients aged ≥ 75 years were underrepresented. [7-10] Consequently, there is no conclusive evidence that targeting at high dosages of medical therapy is equally beneficial in octogenarians compared with younger HFrEF patients and this may be another important reason for a lower uptake of HF medication in octogenarians. Awareness and assessment of comorbidities, and adequate management of these, may improve tailored HF care of the elderly patients. [29] In addition, reflection on optimal management and accepting lower age-adjusted target, tolerable dose of HF medication in elderly, may also be advocated. Accordingly, patient preferences and caregiver perceptions may influence therapeutic decisions in older HF patients. [30]

In HFpEF, there are unmet needs for evidence-based therapies in general and in elderly patients in particular, because of the steeply increasing prevalence with age. Interestingly, in the Swedish Heart Failure Registry, the use of RAS antagonists and beta blockers in HFpEF was associated with lower all-cause mortality. [31, 32] However, observational associations in HF have limited potential to make reliable therapeutic inferences, because (residual) confounding cannot be excluded. [33]

Limitations and strengths

The CHECK-HF registry is a large-scale real-word registry of heart failure outpatient clinics in the Netherlands reflective of Western European countries. However, some limitations should be mentioned, such as the cross-sectional design and there were

no outcome data collected. In addition, some missing data exist, which might influence results. However, imputation of missing data in multivariable analyses did not influence results. The etiology of heart failure was judged by the physician of the participating centers. Our registry included only patients seen in secondary, but not in primary care, which limits the generalizability of our findings to the primary care setting. Data on high age-related factors, e.g., frailty, cognitive impairment, dementia and disability were not collected, which may limit the understanding of the reason of not following the guidelines. Hardly any information was available for the use of sacubitril/valsartan, since it was approved in the Netherlands only in June 2016. Also, the use of oral nitrates (isosorbide-dinitrate or isosorbidemononitrate) combined with hydralazine is so low in the Netherlands that data was not collected. Strengths of the study are the reflection of the true practice of nationwide out-patient HF management and the high percentages of elderly patients with detailed information on medication prescription and dosage.

Conclusion

In this Dutch real-world registry of outpatient HF population, the majority of octogenarians received evidence-based HF medication, but at lower doses than recommended and only a minority received all three of the HF medication (beta blocker, RAS inhibitor (ACE inhibitor or ARB) and MRA). Analyses of clinical variables, including higher rates of comorbidities and reported contraindications and tolerances, did not fully explain the underuse of recommended HF therapies in octogenarians with HFrEF. Thus, future research should lead to strategies to improve management of elderly HF patients. Both in the HFmrEF group and the HFpEF group, in which evidence-based therapies are lacking, prescription rates of diuretics were also high and a substantial part of them received a beta blocker, RAS inhibitor and MRA.

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Supplementary content

Suppl. Table 1. Target doses of guideline recommended therapy

Beta-blocker	
Bisoprolol	10 mg
Carvedilol	50 mg
Metoprolol succinate	200 mg
Nebivolol	10 mg
ACE-inhibitor	
Captopril	150 mg
Enalapril	20 mg
Lisinopril	40 mg
Ramipril	10 mg
Perindopril	8 mg
ARB	
Candesartan	32 mg
Losartan	150 mg
Valsartan	320 mg
MRA	
Eplerenone	50 mg
Spironolactone	25 mg

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist

Suppl. Table 2. Characteristics of octogenarians with HF according to LVEF groups (ESC Guidelines 2016) for men and women

	HFrEF			HFmrEF			HFpEF		
	Men (n=1,160)	**Women (n=839)**	**p-value**	**Men (n=290)**	**Women (n=278)**	**p-value**	**Men (n=325)**	**Women (n=583)**	**p-value**
Age (years)	84.1 ± 3.4 83.0 [81.0-86.0]	85.0 ± 3.7 85.0 [82.0-87.0]	<0.01 <0.01	84.5 ± 3.3 84.0 [82.0-87.0]	85.2 ± 3.8 85.0 [82.0-88.0]	0.01 0.04	84.8 ± 3.7 84.0 [82.0-87.0]	85.3 ± 3.8 85.0 [82.0-88.0]	0.06 0.06
BMI, kg/m2	25.7 ± 3.8 25.0 [23.0-28.0]	25.4 ± 4.4 25.0 [22.0-28.0]	0.17 0.03	25.8 ± 3.7 25.0 [23.0-28.0]	26.6 ± 4.7 26.0 [23.0-29.8]	0.04 0.10	26.8 ± 4.4 26.0 [24.0-29.0]	27.3 ± 5.3 26.0 [23.0-31.0]	0.20 0.29
NYHA									
I	109 (9.5)	80 (9.6)		32 (11.2)	12 (4.3)		37 (11.5)	65 (11.4)	
II	616 (53.9)	415 (50.0)	0.35	161 (56.3)	149 (54.0)	0.01	174 (54.2)	270 (47.2)	0.19
III	388 (34.0)	312 (37.6)		86 (30.1)	108 (39.1)		100 (31.2)	216 (37.8)	
IV	29 (2.5)	23 (2.8)		7 (2.4)	7 (2.5)		10 (3.1)	21 (3.7)	
LVEF, %	31.0 ± 9.8 30.0 [25.0-35.0]	30.9 ± 9.5 30.0 [25.0-35.0]	0.89 0.98	45.1 ± 5.5 45.0 [40.0-46.0]	45.1 ± 5.5 45.0 [40.0-47.0]	0.92 0.70	57.5 ± 5.9 57.0 [53.0-60.0]	58.2 ± 6.9 58.0 [52.0-61.0]	0.22 0.41
Cause of HF									
Ischemic cause of HF	705 (62.9)	353 (43.3)		160 (58.2)	86 (32.5)		109 (34.7)	100 (17.7)	
Non-ischemic cause of HF	416 (37.1)	462 (56.7)	<0.01	115 (41.8)	179 (67.5)	<0.01	205 (65.3)	464 (82.3)	<0.01
Systolic BP, mmHg	123.6 ± 20.3 120.0 [110.0-135.0]	127.0 ± 21.4 125.0 [110.0-140.0]	<0.01 <0.01	127.3 ± 21.6 124.0 [111.5-140.0]	128.7 ± 20.3 128.0 [115.0-140.0]	0.44 0.33	130.0 ± 22.0 130.0 [115.0-145.0]	134.3 ± 23.5 130.0 [120.0-149.0]	0.01 0.02
Diastolic BP, mmHg	68.2 ± 10.5 69.0 [60.0-75.0]	69.3 ± 11.1 70.0 [60.0-76.0]	0.03 0.02	68.2 ± 11.2 70.0 [60.0-75.0]	69.9 ± 12.0 70.0 [60.0-79.0]	0.09 0.11	69.3 ± 11.5 70.0 [60.0-76.3]	70.5 ± 12.1 70.0 [63.0-80.0]	0.14 0.26
Heart rate, bpm	71.3 ± 13.8 70.0 [61.0-80.0]	73.7 ± 13.5 72.0 [64.0-81.0]	<0.01 <0.01	71.3 ± 13.8 70.0 [60.0-80.0]	74.8 ± 14.7 72.0 [64.0-84.0]	<0.01 0.01	72.9 ± 14.7 70.0 [64.0-80.0]	73.6 ± 15.8 40.9 [30.9-58.0]	0.50 0.95
Atrial fibrillation	380 (33.2)	281 (34.1)	0.68	129 (44.8)	139 (50.4)	0.19	153 (47.4)	282 (48.9)	0.67
LBBB	235 (20.3)	196 (23.4)	0.10	32 (11.0)	47 (16.9)	0.04	24 (7.4)	59 (10.1)	0.17

Suppl. Table 2. *(continued)*

	HFrEF			HFmrEF			HFpEF		
	Men (n=1,160)	**Women (n=839)**	**p-value**	**Men (n=290)**	**Women (n=278)**	**p-value**	**Men (n=325)**	**Women (n=583)**	**p-value**
QRS ≥130 ms	487 (52.6)	295 (42.8)	<0.01	90 (37.5)	76 (33.8)	0.40	82 (30.5)	96 (20.4)	<0.01
eGFR	49.4 ± 21.1 46.4 [33.8-61.8]	47.4 ± 20.8 43.8 [32.2-59.3]	0.07 0.05	45.3 ± 20.5 42.8 [31.2-55.5]	48.0 ± 21.3 44.6 [31.6-61.0]	0.21 0.28	48.9 ± 24.6 42.6 [31.5-63.6]	45.2 ± 19.6 40.9 [30.9-58.0]	0.05 0.24
eGFR									
<30	151 (17.5)	132 (21.0)		43 (22.2)	44 (21.2)		47 (22.3)	81 (23.1)	
30-59	462 (53.4)	344 (54.6)	0.07	114 (58.8)	108 (51.9)	0.17	105 (49.8)	191 (54.4)	0.34
≥60	252 (29.1)	154 (24.4)		37 (19.1)	56 (26.9)		59 (28.0)	79 (22.5)	
Comorbidity									
Hypertension	388 (37.3)	374 (49.1)	<0.01	107 (41.0)	129 (51.2)	0.02	154 (50.8)	329 (61.8)	<0.01
Diabetes Mellitus	273 (26.3)	221 (29.0)	0.19	64 (24.5)	75 (29.8)	0.18	71 (23.4)	156 (29.3)	0.07
COPD	214 (20.6)	110 (14.5)	<0.01	67 (25.7)	47 (18.7)	0.06	79 (26.1)	94 (17.7)	<0.01
OSAS	42 (4.0)	9 (1.2)	<0.01	13 (5.0)	5 (2.0)	0.07	12 (4.0)	12 (2.3)	0.16
Thyroid disease	65 (6.3)	88 (11.6)	<0.01	5 (1.9)	26 (10.3)	<0.01	15 (5.0)	60 (11.3)	<0.01
Renal insufficiency †	754 (74.1)	581 (80.0)	<0.01	198 (80.8)	200 (79.4)	0.69	200 (77.2)	359 (79.1)	0.56
No relevant comorbidity	71 (7.8)	35 (5.3)	0.06	12 (5.4)	5 (2.2)	0.07	11 (4.6)	13 (3.2)	0.37

HF, Heart Failure; LVEF, Left Ventricular Ejection Fraction; ESC, European Society of Cardiology; HFrEF, Heart Failure with reduced Ejection Fraction; HFmrEF, Heart Failure with mid-range Ejection Fraction; HFpEF, Heart Failure with preserved Ejection Fraction; BMI, Body Mass Index; BP, Blood Pressure; NYHA New York Heart Association classification; eGFR estimated Glomerular Filtration Rate; LBBB, Left Bundle Branch Block; COPD, Chronic Obstructive Pulmonary Disease; OSAS, Obstructive Sleep Apnea Syndrome.

Suppl. Table 3. Heart rate, QRS-duration and LBBB according to heart rhythm

	Overall	HFrEF (n=2009)	HFmrEF (n=570)	HFpEF (n=911)	p-value
Sinus rhythm (n=1583)					
Heart rate	68.0 [61.0-76.0]	68.0 [61.0-76.0]	66.0 [60.0-75.0]	68.0 [60.0-76.0]	0.49
QRS ≥130 ms	468 (35.1)	359 (43.1)	51 (27.3)	58 (18.5)	<0.01
LBBB	327 (20.7)	253 (25.7)	34 (15.2)	40 (10.7)	<0.01
Atrial fibrillation (n=1371)					
Heart rate	75.0 [65.0-85.0]	75.0 [65.0-85.0]	76.0 [65.0-86.0]	75.0 [66.0-85.0]	0.92
QRS ≥130 ms	322 (30.0)	200 (38.8)	64 (29.8)	58 (16.9)	<0.01
LBBB	201 (14.7)	130 (19.5)	38 (14.2)	33 (7.6)	<0.01
Paced rhythm (n=438)					
Heart rate	70.0 [62.0-80.0]	70.0 [63.0-80.0]	72.0 [64.5-80.0]	72.0 [64.5-80.0]	0.33
QRS ≥130 ms	306 (86.2)	203 (88.6)	46 (86.8)	57 (78.1)	0.07
LBBB	53 (12.1)	39 (13.4)	5 (7.7)	9 (11.0)	0.42
Ectopic rhythm (n=53)					
Heart rate	72.0 [60.0-87.5]	74.0 [59.5-93.4]	70.0 [62.0-75.5]	71.0 [57.0-80.0]	0.72
QRS ≥130 ms	24 (46.2)	17 (53.1)	3 (33.3)	4 (36.4)	0.44
LBBB	11 (20.8)	9 (27.3)	1 (11.1)	1 (9.1)	0.32

LBBB, Left Bundle Branch Block; HFrEF, Heart Failure with reduced Ejection Fraction; HFmrEF, Heart Failure with mid-range Ejection Fraction; HFpEF, Heart Failure with preserved Ejection Fraction.

Suppl. Table 4a. Prescription rates according to duration of HF follow-up in HFrEF patients

HF-medication	< 1 year HF follow-up	1 – 2 years HF follow-up	≥2 years HF follow-up	p-value
Beta-blocker	180 (81.4)	327 (80.5)	1,047 (77.1)	0.16
RAS-inhibitor	158 (71.5)	287 (70.7)	1,001 (73.7)	0.43
MRA	136 (61.5)	230 (56.7)	665 (49.0)	<0.01
Ivabradine	7 (3.2)	12 (2.9)	36 (2.6)	0.87
Diuretics	201 (91.0)	369 (90.9)	1,225 (90.2)	0.88
Loop diuretics	198 (89.6)	359 (88.4)	1,196 (88.1)	0.81
Thiazide diuretics	3 (1.4)	12 (3.0)	36 (2.7)	0.46

Suppl. Table 4b. Prescription rates according to duration of HF follow-up in HFmrEF patients

HF-medication	< 1 year HF follow-up	1 - 2 years HF follow-up	≥2 years HF follow-up	p-value
Beta-blocker	57 (73.1)	92 (73.6)	260 (72.4)	0.97
RAS-inhibitor	50 (64.1)	88 (70.4)	242 (67.4)	0.64
MRA	46 (59.0)	71 (56.8)	160 (44.6)	0.01
Ivabradine	1 (1.3)	4 (3.2)	5 (1.4)	0.39
Diuretics	72 (92.3)	112 (89.6)	323 (90.0)	0.79
Loop diuretics	70 (89.7)	108 (86.4)	317 (88.3)	0.76
Thiazide diuretics	3 (3.8)	4 (3.2)	7 (1.9)	0.53

Suppl. Table 4c. Prescription rates according to duration of HF follow-up in HFpEF patients

HF-medication	< 1 year HF follow-up	1 – 2 years HF follow-up	≥2 years HF follow-up	p-value
Beta-blocker	83 (75.5)	153 (75.7)	426 (73.6)	0.80
RAS-inhibitor	51 (46.4)	127 (62.9)	376 (64.9)	<0.01
MRA	67 (60.9)	116 (57.4)	214 (37.0)	<0.01
Ivabradine	1 (0.9)	1 (0.5)	3 (0.5)	0.87
Diuretics	107 (97.3)	196 (97.0)	509 (87.9)	<0.01
Loop diuretics	107 (97.3)	193 (95.5)	482 (83.2)	<0.01
Thiazide diuretics	1 (0.9)	3 (1.5)	29 (5.0)	0.02

HF, Heart Failure; HFrEF, Heart Failure with reduced Ejection Fraction; HFmrEF, Heart Failure with mid-range Ejection Fraction; HFpEF, Heart Failure with preserved Ejection Fraction; RAS, Renin-Angiotensin System; RAS-inhibitor, angiotensin-converting-enzyme (ACE)-inhibitor or angiotensin-receptor-blocker (ARB); MRA, Mineralocorticoid Receptor Antagonists.

Suppl. Table 5. Reasons for not prescribing HF medication in HFrEF patients aged ≥ 80 years in men and women

		Contraindicated or intolerance	No reason specified
Beta-blocker	Men	57 (4.0)	234 (16.3)
	Women	42 (3.8)	151 (13.7)
RAS-inhibitors	Men	124 (8.6)	268 (18.6)
	Women	65 (5.9)	263 (23.8)
MRA	Men	96 (6.7)	618 (43.0)
	Women	62 (5.6)	458 (41.5)
Ivabradine	Men	28 (1.9)	1,373 (95.5)
	Women	27 (2.4)	1,048 (94.9)

HF, Heart Failure; HFrEF, Heart Failure with reduced Ejection Fraction; RAS, Renin-Angiotensin System; RAS-inhibitor, angiotensin-converting-enzyme (ACE)-inhibitor or angiotensin-receptor-blocker (ARB); MRA, Mineralocorticoid Receptor Antagonists

Suppl. Table 6. Multivariable predictors of the use of HF medication and polypharmacy in HFrEF patients aged ≥ 80 years

	Beta-blocker	RAS-inhibitor	MRA	Diuretics
	OR	OR	OR	OR
Univariable				
Polypharmacy *	1.10 [0.97-1.24]	0.98 [0.88-1.10]	1.04 [0.93-1.16]	1.39 [1.15-1.68]
Multivariable				
Polypharmacy *	1.09 [0.96-1.23]	1.07 [0.89-1.14]	1.05 [0.93-1.18]	1.40 [1.15-1.71]
Female gender	1.32 [1.03-1.69]	-	-	-
Age (per 10 y)	-	0.63 [0.48-0.84]	-	-
BMI (kg/m2)	-	-	-	1.06 [1.01-1.12]
Systolic BP (per 10 mmHg)	-	1.09 [1.02-1.16]	0.80 [0.75-0.85]	-
Diastolic BP (per 10 mmHg)	-	-	-	0.78 [0.64-0.94]
NYHA-class (per class)	-	-	-	2.11 [1.52-2.93]
Heart rate (per 10 bpm)	-	0.82 [0.76-0.89]	-	-
QRS-duration (per 10 ms)	-	0.97 [0.94-0.99]	-	-
eGFR (per 10 ml/min)	-	-	-	0.85 [0.76-0.95]
Ischemic etiology	-	-	-	-
Hypertension	-	-	-	-
Diabetes mellitus type 2	-	-	-	-
COPD	-	-	-	-
Renal failure	-	0.73 [0.55-0.98]	-	2.01 [1.22-3.32]

* is the number of drugs (beta-blockers, RAS-inhibitors, MRA, ivabradine, diuretics, statine, digoxine or amiodarone); exclusive the HF medication in the model (e.q. in the model of beta-blocker, beta-blocker is not included in the polypharmacy count.

OR of polypharmacy indicate the OR per extra drug

HF, Heart Failure; HFrEF, Heart Failure with reduced Ejection Fraction; RAS, Renin-Angiotensin System; RAS-inhibitor, angiotensin-converting-enzyme (ACE)-inhibitor or angiotensin-receptor-blocker (ARB); MRA, Mineralocorticoid Receptor Antagonists; OR, odds ratio; BMI, Body Mass Index; BP, Blood Pressure; NYHA New York Heart Association classification; eGFR estimated Glomerular Filtration Rate; COPD, Chronic Obstructive Pulmonary Disease

Suppl. Table 7. Characteristics of octogenarians with HF according to LVEF groups (ESC Guidelines 2016)

	Total (n=3490)	HFrEF (n=2009)	HFmrEF (n=570)	HFpEF (n=853)	HFsnEF (n=58)	p-value
Age (years) (n=3490)	84.0 [82.0-87.0]	84.0 [82.0-87.0]	84.0 [82.0-87.0]	85.0 [82.0-88.0]	84.0 [81.0-86.0]	<0.01
Men (n=3475)	1775 (51.1)	1160 (58.0)	290 (51.1)	307 (36.1)	18 (31.0)	<0.01
Duration of HF (n=3480)						
<1 year	411 (11.8)	222 (11.1)	78 (13.7)	107 (12.6)	4 (6.9)	
1 - 2 years	737 (21.2)	407 (20.3)	126 (22.2)	193 (22.7)	11 (19.0)	0.17
≥ 2 years	2332 (67.0)	1376 (68.6)	364 (64.1)	549 (64.7)	43 (74.1)	
BMI, kg/m2 (n=3139)	25.0 [23.0-29.0]	25.0 [23.0-28.0]	26.0 [23.0-29.0]	26.0 [24.0-30.0]	27.0 [24.0-32.0]	<0.01
NYHA (n=3440)						
I	335 (9.7)	189 (9.5)	44 (7.8)	96 (11.5)	6 (10.3)	
II	1791 (52.1)	1036 (52.3)	310 (55.1)	413 (49.3)	32 (55.2)	0.33
III	1217 (35.4)	705 (35.6)	195 (34.6)	300 (35.8)	17 (29.3)	
IV	97 (2.8)	52 (2.6)	14 (2.5)	38 (3.3)	3 (5.2	
LVEF, % (n=2326)	40.0 [30.0-50.0]	30.0 [25.0-35.0]	45.0 [40.0-47.0]	55.0 [50.0-60.0]	70.0 [67.5-76.5]	<0.01
Cause of HF (n=3369)						
Ischemic cause of HF	1518 (45.1)	1061 (54.5)	247 (45.6)	195 (23.6)	15 (27.3)	<0.01
Non-ischemic cause of HF	1851 (54.9)	885 (45.5)	295 (54.4)	631 (76.4)	40 (72.7)	
Systolic BP, mmHg (n=3455)	125.0 [111.0-140.0]	122.0 [110.0-139.0]	125.5 [114.3-140.0]	130.0 [118.0-140.0]	131.0 [110.0-157.5]	<0.01
Diastolic BP, mmHg (n=3461)	70.0 [60.0-76.0]	70.0 [60.0-75.0]	70.0 [60.0-76.0]	70.0 [60.0-76.0]	70.0 [62.0-80.0]	0.02
Heart rate, bpm (n=3446)	70.0 [63.0-80.0]	70.0 [63.0-80.0]	71.0 [62.0-82.0]	71.0 [64.0-84.0]	68.0 [60.0-76.0]	0.35
Atrial fibrillation (n=3445)	1371 (39.8)	666 (33.7)	268 (47.3)	416 (49.2)	21 (36.8)	<0.01
LBBB (n=3490)	594 (17.0)	432 (21.5)	79 (13.9)	80 (9.4)	3 (5.2)	<0.01
QRS ≥130 ms (n=2830)	1131 (40.0)	786 (48.5)	167 (35.8)	172 (24.5)	6 (15.0)	<0.01
eGFR (n=2459)	44.2 [32.4-60.6]	45.2 [33.1-61.2]	43.4 [31.6-58.5]	42.7 [31.5-64.5]	41.8 [35.9-60.9]	0.07

Suppl. Table 7. *(Continued)*

	Total (n=3490)	HFrEF (n=2009)	HFmrEF (n=570)	HFpEF (n=853)	HFsnEF (n=58)	p-value
eGFR (n=2459)						
<30	498 (20.3)	283 (18.9)	87 (21.6)	124 (23.4)	4 (12.1)	
30-59	1324 (53.8)	806 (53.9)	222 (55.2)	277 (52.4)	19 (57.6)	0.19
≥60	637 (25.9)	406 (27.2)	93 (23.1)	128 (24.2)	10 (30.3)	
Comorbidity (n=3158)						
Hypertension	1485 (47.0)	763 (42.2)	237 (46.1)	455 (57.8)	30 (58.8)	<0.01
Diabetes Mellitus	862 (27.3)	495 (27.4)	139 (27.0)	213 (27.1)	15 (29.4)	0.98
COPD	614 (19.4)	326 (18.1)	114 (22.2)	161 (20.5)	13 (25.5)	0.09
OSAS	93 (2.9)	51 (2.8)	8 (3.5)	24 (3.0)	0 (0.0)	0.53
Thyroid disease	259 (8.2)	153 (8.5)	31 (6.0)	70 (8.9)	5 (9.8)	0.25
No relevant comorbidity	148 (5.5)	107 (6.8)	17 (3.8)	24 (3.9)	0 (0.0)	0.01

HF, heart failure; ; LVEF, Left Ventricular Ejection Fraction; ESC; European Society of Cardiology; HFrEF, Heart Failure with reduced Ejection fraction; HFmrEF, Heart Failure with mid-range Ejection Fraction; HFpEF, Heart Failure with preserved Ejection Fraction; HFsnEF, Heart Failure with supernormal Ejection Fraction; BMI, Body Mass Index; NYHA, New York Heart Association classification; BP, Blood Pressure; LBBB, Left-Bundle Branch Block; eGFR, estimated Glomerular Filtration Rate; COPD, Chronic Obstructive Pulmonary Disease; OSAS, Obstructive Sleep Apnea Syndrome.

4

Impact of sex-specific target dose in chronic heart failure patients with reduced ejection fraction

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Abstract

Aims: A recent study suggested that women with heart failure and heart failure reduced ejection fraction might hypothetically need lower doses of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (= renin-angiotensin-system inhibitors) and β-blockers than men to achieve the best outcome.We assessed the current medical treatment of heart failure reduced ejection fraction in men and women in a large contemporary cohort and address the hypothetical impact of changing treatment levels in women.

Methods: This analysis is part of a large contemporary quality of heart failure care project which includes 5320 (64%) men and 3003 (36%) women with heart failure reduced ejection fraction. Detailed information on heart failure therapy prescription and dosage were collected.

Results: Women less often received renin-angiotensin-system inhibitors (79% vs 83%, p<0.01), but more often b-blockers (82% vs 79%, p<0.01) than men. Differences in guideline-recommended target doses between sexes were relatively small. Implementing a hypothetical sex-specific dosing schedule (at 50% of the current recommended dose in the European Society of Cardiology guidelines in women only) would lead to significantly higher levels of women receiving appropriate dosing (β-blocker 87% vs 54%, p<0.01; renin-angiotensin-system inhibitor 96% vs 75%, p<0.01). Most interestingly, the total number of women with >100% of the new hypothetical target dose would be 24% for b-blockers and 52% for renin-angiotensin-system inhibitors, which can be considered as relatively overdosed.

Conclusion: In this large contemporary heart failure registry, there were significant but relatively small differences in drug dose between men and women with heart failure reduced ejection fraction. Implementation of the hypothetical sex-specific target dosing schedule would lead to considerably more women adequately treated. In contrast, we identified a group of women who might have been relatively overdosed with increased risk of side-effects and intolerance.

Introduction

The overall enrolment of women in clinical trials investigating treatment and outcome in heart failure (HF) is generally low and, accordingly, women are underrepresented in these trials as compared to the real-world.[1] Studies on optimal dose in HF with reduced ejection fraction (HFrEF) are scarce and the number of included women was low.[2,3] Likewise, the European Society of Cardiology (ESC) HF guidelines provide no sex-specific recommendations.[4] Recently, the hypothesis has been suggested that women with HFrEF might need lower dose of angiotensin-converting enzyme inhibitors (ACE-is), angiotensin II receptor blockers (ARBs) and β-blockers than men, which brings into question what the true optimal level of drug therapy is for women.[5] Whereas men obtained the maximal reduction of mortality and HF hospitalization at the guideline recommended target dose of β -blockers, ACE-Is and ARBs. In male HFrEF patients, not achieving target dose is equal to not achieving maximum treatment benefit.

In contrast, in women the largest treatment benefit was already observed at 50% of recommended target dose, achieving 30% lower overall cardiovascular risk (all-cause mortality or hospitalization for HF). At higher doses, no additional benefit was observed in women, therefore the hypothesis is that maximum benefit can be achieved at 50% of target dose at no further expense of intolerance of side-effects.[5] The clinical impact of this post-hoc analysis can be considerable but should be assessed in large contemporary HFrEF cohorts.

The Chronisch Hartfalen ESC-richtlijn Cardiologische praktijk Kwaliteitsproject HartFalen (CHECK-HF) registry is a large scale (n=8323) contemporary and well defined Dutch cohort of HFrEF patients,[6,7] enabling us to assess the impact of adopting the hypothetical sex-specific dose schedule in a real-world outpatient setting.

Methods

The design and methods of the CHECK-HF registry have been published in detail earlier.[6,7] Briefly, the CHECK-HF study is a large contemporary crosssectional observational cohort, including a total of 10,910 chronic HF patients from 34 participating Dutch centres between September 2013–September 2016. All patients were diagnosed and treated according to the 2012 ESC HF guidelines,[8] and almost all were seen at a dedicated outpatient HF clinic (96%). Detailed information on patient characteristics, echocardiographic parameters and HF therapy, including HF drug prescription, dose,

contraindication and intolerance, as well as device therapy were recorded. This study was conducted according to the Helsinki Declaration, and was approved by the medical ethics committee in 2017 at the Maastricht University Medical Center (Maastricht, the Netherlands). Patients were not involved in the research process.

Left ventricular function, assessed during the most recent outpatient clinical visit, was used to categorise HF patients. Patients were categorised based on left ventricle ejection fraction (LVEF) or visual assessment of left ventricle (LV) function into HFrEF (LVEF<50% (n=8360 (76.6%)) and HF with preserved ejection fraction (HFpEF) (LVEF≥50% (n=2267 (20.8%)). In 283 patients, recording of LV function in the database was insufficient to classify patients into HF type. In addition, standard baseline demographic data was missing in 37 additional HFrEF patients, leaving 8323 HFrEF patients to be included in the analysis.

For a sub-analysis according to the newer 2016 ESC HF guidelines,[4] patients with an assessed LVEF<50% were categorised into HF with mid-range ejection fraction (HFmrEF) (LVEF 40–49% (n=1571 (18.9%)) and HFrEF (LVEF<40% (n=5677 (68.2%), only in those patients with a exactly specified LVEF or into patients with only a semi-quantitative analysis of LV function (n=1075 (12.9%)).

In order to investigate the impact of the hypothetical sex-specific dose schedule of b-blockers and reninangiotensin-system inhibitors (RAS-is) (i.e. ACE-is or ARBs), we analysed the prescribed dosages expressed as a percentage of the recommended target dose and of the hypothetical target dosage (50% of the guideline recommend target dose) in women. Target doses of guideline-recommended HF therapy are presented in Supplementary Material Table 1 and in line with the ESC HF guidelines.[4]

Statistical analysis

Continuous data are expressed as mean value±standard deviation (SD) or median and interquartile range, depending on the distribution of the data, and compared by one-way analyses of variance (ANOVAs) or Mann-Whitney U-test. Categorical data are expressed as counts and percentages, and compared by the Pearson Chi-square test. The prescribed dosages are expressed as a percentage of the recommended target dose. The differences between the recommended and newly suggested target dose were compared by the McNemar test.

Multivariable predictors of HF medication use were assessed using multivariable logistic regression analysis. All predictors of medication use in univariable analysis at

a p-value of <0.10 were included in a forward step manner in the multivariable logistic regression analysis. Results of logistic regression are presented as odds ratio (ORs) with 95% confidence intervals (CIs).

For variables with missing data in the multivariable analysis, we used multiple imputation modelling. If the missing variables showed a monotone pattern of missing values, the monotone method was used, otherwise, an iterative Markov chain Monte Carlo method was used with a number of 10 iterations. A total of five imputations was performed, and the pooled data were analysed. All analyses were performed with SPSS Statistical Package version 25.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Baseline characteristics of men and women with HFrEF are presented in Table 1.

Table 1. Patient characteristics in heart failure with reduced ejection fraction (HFrEF) patients.

	Men (n=5320)	Women (n=3003)	p-value
Age (years) (n=8314)	71.6 ± 11.4	73.4 ± 12.4	<0.01
BMI, kg/m^2 (n=7638)	27.3 ± 4.8	27.1 ± 5.8	0.32
NYHA (n=8226)			
I	913 (17.4)	395 (13.3)	<0.01
II	3000 (57.1)	1671 (56.2)	
III	1248 (23.8)	850 (28.6)	
IV	90 (1.7)	59 (2.0)	
LVEF, % (n=6154)	32.2 ± 10.4	33.5 ± 10.8	<0.01
Cause of HF (n=8058)			
Ischemic	3016 (58.5)	1149 (39.6)	<0.01
Non-ischemic	2137 (41.5)	1756 (60.4)	
Systolic BP, mmHg (n=8209)	125.3 ± 20.5	126.4 ± 21.0	0.02
Diastolic BP, mmHg (n=8215)	71.5 ± 11.3	70.7 ± 11.4	<0.01
Heart rate, bpm (n=8211)	71.2 ± 13.7	73.5 ± 14.0	<0.01
Atrial fibrillation (n=8216)	1366 (26.0)	734 (24.8)	0.25
LBBB (n=8323)	838 (15.8)	574 (19.1)	<0.01
QRS ≥130 ms (n=6908)	1877 (42.5)	887 (35.7)	<0.01
eGFR (n=5883)	61.4 ± 24.8	56.6 ± 24.0	<0.01
eGFR (n=5883)			
<30	364 (9.8)	303 (14.0)	<0.01
30-59	1510 (40.6)	932 (43.0)	
≥60	1844 (49.6)	930 (43.0)	

Table 1. *(continued)*

	Men (n=5320)	Women (n=3003)	p-value
Comorbidities (n=7459)			
Hypertension	1801 (37.9)	1168 (43.2)	<0.01
Diabetes Mellitus	1380 (29.0)	789 (29.2)	0.87
COPD	904 (19.0)	466 (17.2)	0.06
OSAS	401 (8.4)	92 (3.4)	<0.01
Thyroid disease	257 (5.4)	300 (11.1)	<0.01

BMI: body mass index; BP: blood pressure; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; HF: heart failure; LBBB: Left Bundle Branch Block; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; OSAS: obstructive sleeping apnoea syndrome.

Pharmacological therapy in HFrEF

Female HFrEF patients significantly less often received a RAS-i (78.9% vs 82.6%, p<0.01) and more often β-blockers (82.0% vs 79.1%, p<0.01), ivabradine (5.2% vs 4.2%, p¼0.04) and diuretics (85.0% vs 81.6%, p<0.01) compared to male HFrEF patients (Figure 1(a)). Of the women that received a RAS-i, a significantly lower percentage received the guideline-recommended target dose (74.8% vs 76.1%, p=0.01) as compared to men (Figure 1(b)). Triple HF therapy, consisting of β -blocker, RAS-i and mineralocorticoid receptor antagonist (MRA) (at indication), as well as triple therapy prescribed at ≥50% of the guideline-recommended target dose, were equally prescribed in women and men (Figure 1(c) and (d)). No sex-specific significant differences in the number of reported contraindications or intolerances were observed, although the numbers of contraindications and intolerances were very low in both groups (Supplementary Material Table 2).

Predictors of prescription and target dose of HF therapy

In the multivariable regression analysis, lower age and the presence of hypertension were significant predictors of prescription of β-blockers; lower age, male gender and renal insufficiency were significant predictors of prescription of a RAS-i; and lower age, higher New York Heart Association (NYHA)-classification and lower systolic blood pressure were significant predictors of prescription of MRAs (Table 2). In multivariate analysis, the chance of receiving the guideline-recommended target dose of a RAS-i was independently related to male gender, while the chance of receiving the guideline-recommended target dose of MRA was independently related to female gender (Table 3). Multiple imputations did not change the results (data not shown).

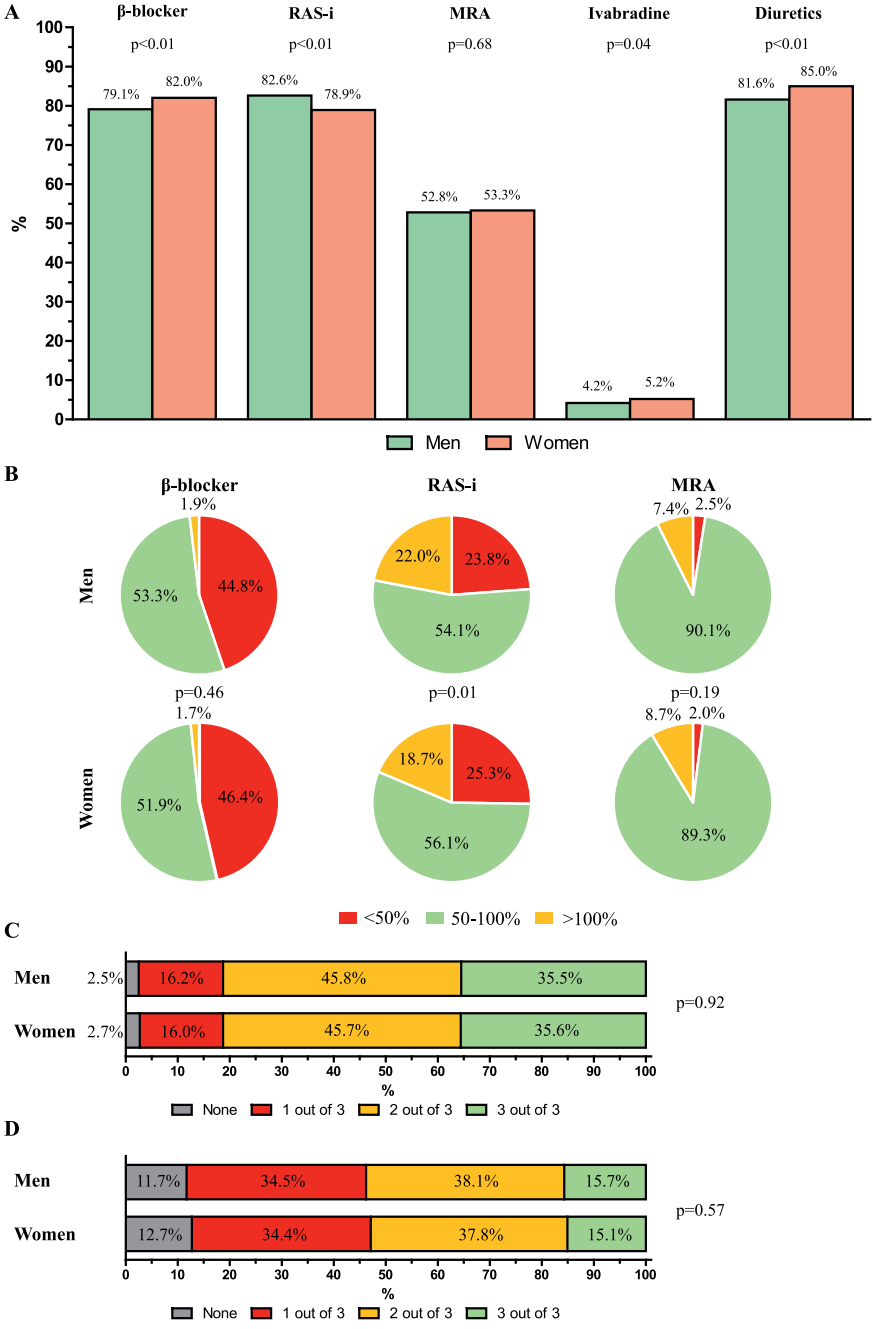

Figure 1. (a) Heart failure (HF) therapy usages; (b) prescribed dosages expressed as a percentage of recommended target dose; (c) triple therapy prescribed; and (d) triple therapy at ≥50% of the recommended target dose prescribed in men and women.
RAS-i: renin-angiotensin-system inhibitor; MRA: mineralocorticoid receptor antagonist.

Table 2. Multivariable predictors of the use of heart failure (HF) therapy in heart failure with reduced ejection fraction (HFrEF) patients in relation to gender.

		β-blocker	RAS-i	MRA	Ivabradine	Diuretics
Univariable	Gender	1.20 [1.07-1.35]	0.79 [0.70-0.88]	1.02 [0.93-1.11]	1.24 [1.01-1.53]	1.28 [1.13-1.45]
Multivariable	Gender	1.16 [0.99-1.36]	0.82 [0.70-0.97]	1.11 [0.99-1.23]	1.29 [1.04-1.60]	1.30 [1.07-1.58]
	Age (per 10 years increase)	0.84 [0.79-0.90]	0.78 [0.72-0.85]	0.91 [0.87-0.95]	0.66 [0.61-0.72]	1.22 [1.12-1.33]
	BMI	-	1.03 [1.01-1.05]	1.02 [1.01-1.03]	-	1.06 [1.04-1.08]
	LVEF	-	0.99 [0.98-0.99]	0.99 [0.99-0.99]	0.98 [0.97-0.99]	-
	NYHA classification	-	0.76 [0.67-0.86]	1.32 [1.22-1.42]	1.44 [1.23-1.69]	1.66 [1.43-1.92]
	Ischemic etiology HF	-	-	-	-	-
	Systolic blood pressure (per 10 mmHg increase)	-	-	0.83 [0.80-0.85]	-	0.92 [0.86-0.97]
	Diastolic blood pressure (per 10 mmHg increase)	-	-	-	0.80 [0.73-0.88]	0.85 [0.77-0.94]
	Heart rate (per 10 beats/min increase)	-	0.86 [0.81-0.91]	0.96 [0.93-1.00]	-	1.14 [1.06-1.22]
	QRS duration (per 10 ms increase)	-	0.96 [0.94-0.99]	1.03 [1.01-1.05]	-	1.03 [1.01-1.06]
	eGFR (per 10 ml/min increase)	-	1.08 [1.04-1.12]	-	-	0.67 [0.83-0.90]
	Hypertension	1.26 [1.08-1.46]	-	-	0.60 [0.37-0.96]	-
	Diabetes mellitus	-	-	-	1.61 [1.29-2.00]	1.37 [1.11-1.70]
	COPD	-	-	-	1.70 [1.33-2.16]	-

BMI: body mass index; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association.

This table shows the results from the univariable logistic regression analysis, demonstrating the likelihood of using HF therapy in women over men. Additionally, it demonstrates the likelihood of using HF therapy in women over men adjusted in the full multivariable model.- indicates variable not included in the model.

Table 3. Multivariable predictors of receiving guideline-recommended target dose of HF medication in HFrEF patients in relation to gender.

		β-blocker	RAS-i	MRA
Univariable	Gender	1.03 [0.90-1.17]	0.88 [0.80-0.98]	1.35 [1.19-1.52]
Multivariable	Gender	1.00 [0.83-1.22]	0.87 [0.76-0.99]	1.34 [1.01-1.11]
	Age (per 10 years increase)	0.87 [0.80-0.94]	0.86 [0.81-0.91]	-
	BMI	1.02 [1.00-1.04]	1.03 [1.02-1.04]	1.03 [1.01-1.12]
	LVEF	-	-	-
	NYHA classification	-	0.81 [0.73-0.90]	-
	Ischemic etiology HF	0.81 [0.67-0.98]	-	-
	Systolic blood pressure (per 10 mmHg increase)	-	1.24 [1.20-1.29]	0.91 [0.88-0.95]
	Diastolic blood pressure (per 10 mmHg increase)	1.19 [1.09-1.29]	-	-
	Heart rate (per 10 beats/min increase)	-	0.95 [0.91-1.00]	1.06 [1.01-1.11]
	QRS duration (per 10 ms increase)	-	-	1.03 [1.01-1.05]
	eGFR (per 10 ml/min increase)	-	-	-
	Hypertension	1.33 [1.10-1.60]	1.38 [1.21-1.58]	-
	Diabetes mellitus	1.30 [1.06-1.59]	-	1.17 [1.00-1.36]

MI: body mass index; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; HF: heart failure; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association.

This table shows the results from the univariable logistic regression analysis, demonstrating the likelihood of prescribing the guideline-recommended target dose of HF drugs in women over men. Additionally, it demonstrates the likelihood of prescribing the guideline-recommended target dose of HF drugs in women over men adjusted in the full multivariable model. - indicates variable not included in the model.

Clinical impact of new hypothetical sex-specific target dose schedule

Using the hypothetical sex-specific target doses (at 50% of the current recommended dose in the ESC guidelines in women only), leads to an considerable increase in the number of women who received the target dose for β-blockers (87.2% vs 53.6%, p<0.01) and RAS-is (96.0% vs 74.8%, p<0.01) (Figure 2(a)). A large number of women might be relatively overdosed, 23.5% of women received >100% of the hypothetical target dose for β-blockers and 52.1% for RAS-is, in our study. A significant increase in women receiving both HF drugs (with indication) at ≥50% of the new hypothetical target dose (56.3% vs 29.5%, p<0.01) was observed (Figure 2(b)).

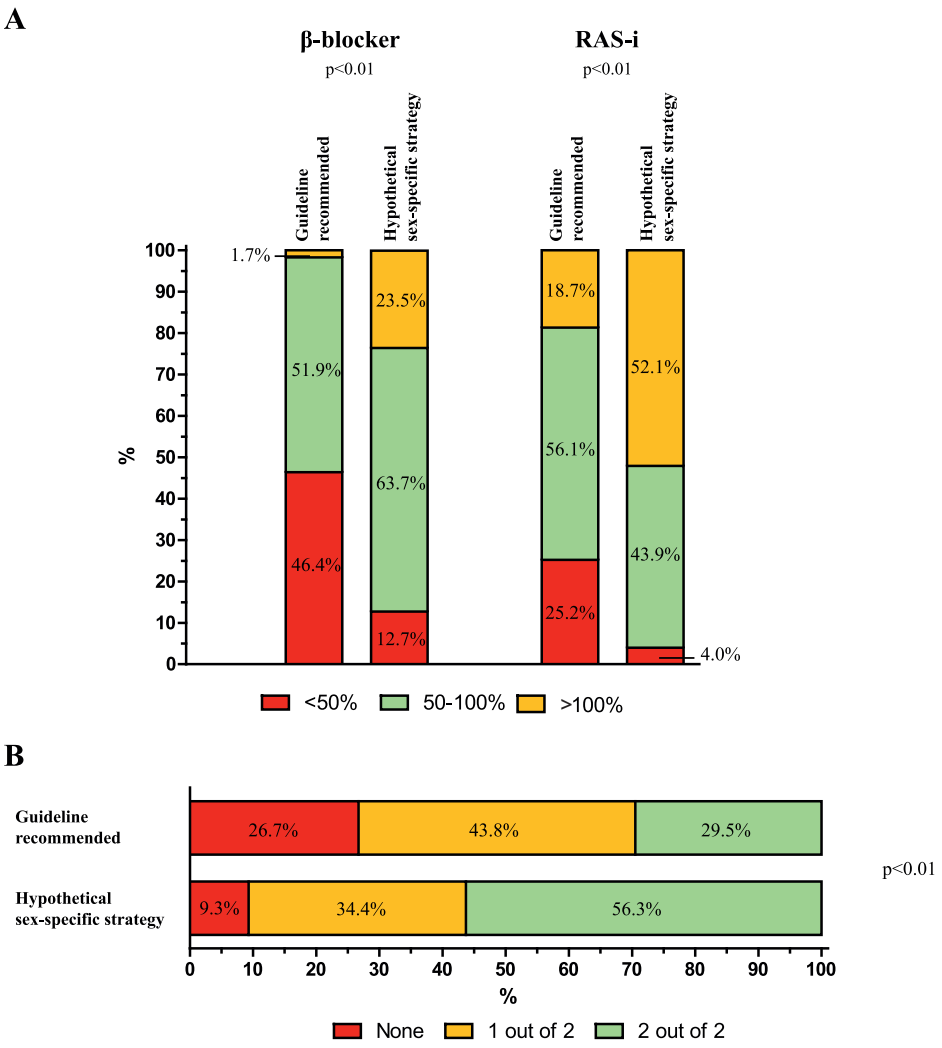

Figure 2. Impact of the newly proposed sex-specific target dose strategy (a) prescribed dosages expressed as a percentage of the guideline and newly proposed target dose of β-blockers and renin-angiotensin-system inhibitors (RAS-is), and (b) dual therapy at ≥50% of the guideline and newly proposed target dose prescribed in women.

Analysis in patients with HFmrEF according to 2016 ESC guidelines

A sub-analysis studying the different cut-off of HFmrEF and HFrEF according to the ESC 2016 guidelines does not change the inferences of this analysis (Supplementary Material Table 3, Supplementary Material Figure 1). Likewise, the subgroup of semiquantitative LV function showed similar differences (Supplementary Material Figure 1).

Discussion

The current analysis shows that HF treatment between men and women differs in this large real-world contemporary cohort of HFrEF patients. Women received lower doses of HF drugs compared to men. The level of the target dose of HF drugs or maximally tolerated levels has been frequently discussed and recently gained more attention from a study suggesting that the optimal dose level might be 50% lower in women compared with men at maximum sex-specific treatment benefit.[5] This hypothesis has major implications for HF treatments in general, and we assessed the impact of this new hypothetical dose schedule in women.

In this patient sample, doctors were urged to titrate to guideline-recommended dosages, and this was successful in some, but not all, patients.

In male patients with HFrEF, the post-hoc analysis from BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) shows that male patients only achieve maximum treatment benefit at the full recommended target dose of HF medication. In women, the maximum treatment benefit was observed at 50% of the target dose with no further gain in benefit, with only futile risk of intolerance. Naturally, if lower dosages were accepted as 'optimal' in females, a much larger proportion of the female patients would be regarded as being treated optimally when 50% of the recommended dose would be regarded as optimal. Notably, this approach identifies a potential subgroup of women who are relatively overdosed (>100% dose in females) with an increased risk of side effects and intolerance at no incremental benefit of treatment.

Guideline adherence and sex

Women with a (non-ST-segment elevation) myocardial infarction receive the guideline-recommended therapy less often.[9,10] Additionally, sex-specific treatment strategies for these conditions have been proposed previously.[10,11] Similarly, multiple registries have demonstrated sex-related differences in guideline adherence, with women less often receiving β-blockers,[12] ACE-is,[12–14] MRAs[12] and more often ARBs[15] and diuretics.[1,12] The

current results of our analysis are in line with these previous registries, although sex-specific differences particularly regarding guideline-recommended target doses were relatively small in CHECK-HF. Differences in patient characteristics could influence clinicians in their decision-making, but these differences do not fully explain the sex-related differences in HF drug usage and dosages in our dataset.

Optimal doses of HF therapies in men versus women

Women are underrepresented in clinical trials investigating the efficacy of HF drugs, as only 10–40% of the patients included in these trials were women.[16] Furthermore, only one trial investigated efficacy prospectively stratified by sex,[17] while all other studies analysed sex-related effects retrospectively and in post-hoc analyses, limiting these results. In women, the use of ACE-is leads to a non-significant reduction in all-cause mortality and hospitalizations compared to placebo.[18] The use of ARBs reduced all-cause mortality and hospitalizations in women compared to placebo.[19] Women using β-blockers had a better clinical outcome compared to women receiving placebo therapy,[20–22] and similar favourable treatment effects were seen in women using MRAs.[23,24] Studies investigating the ideal target dose in HFrEF are scarce, especially in women,[2,3] therefore a one-size-fits-all strategy is recommended in the ESC HF guidelines.[4]

Several sex-related pharmacological differences can cause differences in the efficacy of HF drugs between men and women. So differences in body weight, medication clearance rate and the effect of sex hormones contribute to higher plasma concentrations, and stronger effects of HF drugs in women.[25,26] Additionally, it has been suggested that HF drugs might have a larger effect in women compared to men, even if the plasma concentrations are similar.[27]

HF therapy dose and sex

Data on the ideal dosages in women are scarce. Two post-hoc analyses from the Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan (HEAAL) and Assessment of Treatment with Lisinopril and Survival (ATLAS) trials demonstrated that a lower RAS-is dosage in women was equally effective, or even more effective, compared to higher dosages.[2,28] In contrast, higher dosages of RAS-is were more effective in men. These results suggest that using a one-size-fits-all target dose could lead to overdosing in women. A sub-analysis from these trials investigating the potential overdosing and its effect would be of great interest, especially since a post-hoc analysis from the Digitalis Investigation Group (DIG) trial demonstrated that women had a higher serum concentration compared to men, although they used a slightly lower dose adjusted for

body-mass index.[29,30] A similar effect has been seen in the use of β-blockers, with women having a higher serum concentration while using a similar dosage.[25]

New hypothetical target dose levels in women

Recently, a post-hoc analysis from the BIOSTAT-CHF study investigated whether sex-related differences in the optimal dose of β-blockers and RAS-is for preventing all-cause mortality and HF-related hospitalization exists in HFrEF patients, and validated the results in the Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) dataset.[5] This post-hoc analysis demonstrated that in women a 30% risk reduction in all-cause mortality and HF-related hospitalizations can be obtained with approximately 50% of the recommended target dose of β-blockers and RAS-is, with no further decrease in risk at higher dose levels in BIOSTAT-CHF and ASIAN-HF validation cohorts. In contrast, in men the largest reduction was observed if 100% of the recommended target dose was reached. These results suggest that women with HFrEF might have similar clinical outcomes with lower doses of β-blockers and RAS-is than recommended in the ESC HF guidelines.[4] Naturally, if lower target doses were accepted as optimal in women, a larger proportion of women would be regarded as treated optimally, in our registry. Additionally, we identified a large group of women who were potentially overdosed, possibly without an incremental benefit. It is generally believed that women are more often affected by drug-related adverse effects[31–33] and differences in target doses could be an explanation for this. Unfortunately, we do not have adequate data on side-effects to support this statement from our study. In these women, the doses might be lowered, improving patient compliance and lowering intolerance rates.

Similar to these findings, specific guideline recommendations or target dosages might be warranted for different subgroups as well, for example specific guidelines for races or body mass index (BMI) category. However, these should be evaluated by additional research.

Limitations and strengths

Our study has some limitations. CHECK-HF has a cross-sectional design with no follow-up data on patient outcomes. Other prospective studies integrating dose findings of HF therapy in women and outcome are needed. Still, our analysis shows the potentially large impact of the newly proposed target levels. In addition, for some variables a limited number of data were missing, however, after using multiple imputation this did not impact the results. Additionally, with changing HF categories based on LVEF in

the newer guidelines,[4] our analysis was limited by a small number of patients where LV function was semi-quantitatively analysed with echocardiography. Strengths of the CHECK-HF registry include the large scale, contemporary (2016), and a reflection of the real-world practice of outpatient HF management in the Netherlands, representative of Western European countries. Furthermore, the availability of a large number of women with detailed information on medication prescription and dosage is important due to the lack of data in this subgroup, as previously noted.

Conclusion

In this large contemporary registry, drug dose significantly differed between men and women with HFrEF, although the differences where relatively small. As the first large HF study, we demonstrate the clinical impact of a hypothetical adjustment to a lower target dose schedule in women, by which more women would be considered adequately treated. On top of better adherence, this identifies a considerable large subgroup of women who are relatively overdosed in HF medication at no further reduction in CV risk but, rather, at higher risk of intolerance when the dose could have been further reduced.

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Supplementary material

Appendix Table 1. Target doses of guideline-recommended therapy

β-blocker	
Bisoprolol	10 mg
Carvedilol	50 mg
Metoprolol succinate	200 mg
Nebivolol	10 mg
ACE-inhibitor	
Captopril	150 mg
Enalapril	20 mg
Lisinopril	40 mg
Ramipril	10 mg
Perindopril	8 mg
ARB	
Candesartan	32 mg
Losartan	150 mg
Valsartan	320 mg
MRA	
Eplerenone	50 mg
Spironolactone	25 mg

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist

Appendix Table 2. Patient characteristics of HF patients according to 2016 ESC HF Guidelines

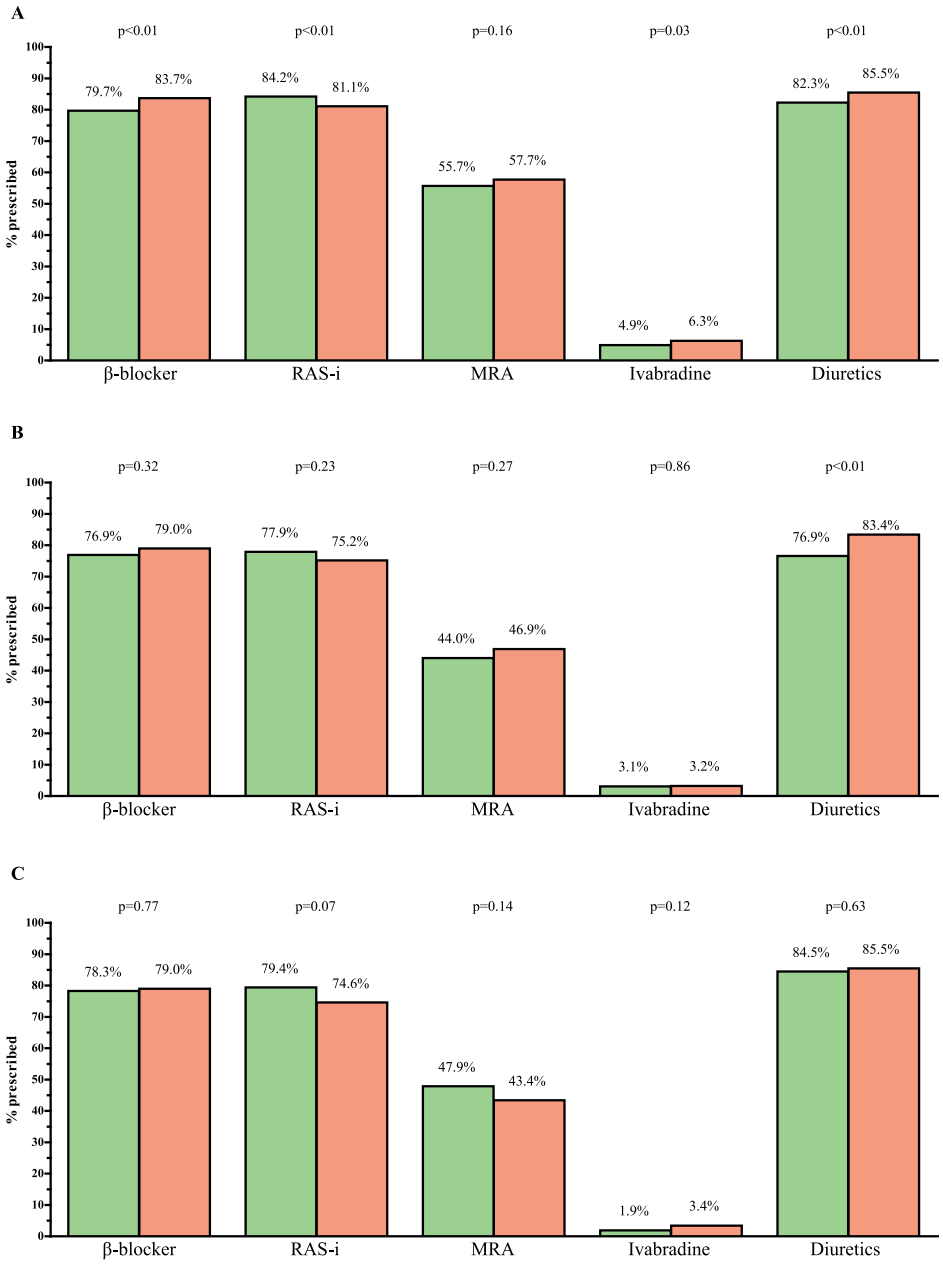
	HFrEF (n=5677)			HFmrEF (n=1571)			Semi-quantitative (n=1075)		
	Men (n=3767)	**Women (n=1910)**	**p-value**	**Men (n=917)**	**Women (n=654)**	**p-value**	**Men (n=636)**	**Women (n=439)**	**p-value**
Age (years)	71.0 ± 11.3	72.1 ± 12.7	<0.01	72.6 ± 11.5	75.2 ± 11.8	<0.01	73.6 ± 11.1	76.7 ± 11.1	<0.01
BMI, kg/m2	27.3 ± 4.8	27.2 ± 5.7	0.46	27.5 ± 5.3	27.5 ± 5.8	0.93	26.9 ± 4.8	26.6 ± 5.8	0.36
NYHA									
I	595 (16.0)	239 (12.6)		196 (21.6)	88 (13.6)		122 (19.7)	68 (15.7)	
II	2178 (58.5)	1055 (55.7)	<0.01	486 (53.6)	367 (56.5)	<0.01	336 (54.3)	249 (57.6)	0.19
III	888 (23.8)	553 (29.2)		207 (22.8)	184 (28.4)		153 (24.7)	113 (26.2)	
IV	64 (1.7)	47 (2.5)		18 (2.0)	10 (1.5)		8 (1.3)	2 (0.5)	
LVEF, %	29.2 ± 8.9	29.6 ± 9.1	0.14	44.9 ± 5.3	45.2 ± 5.4	0.37	-	-	-
Cause of HF									
Ischemic	2166 (59.5)	767 (41.6)	<0.01	476 (53.7)	213 (33.7)	<0.01	374 (59.6)	169 (39.3)	<0.01
Non-ischemic	1473 (40.5)	1076 (58.4)		410 (46.3)	419 (66.3)		254 (40.4)	261 (60.7)	
Systolic BP, mmHg	124.1 ± 19.9	125.1 ± 20.8	0.06	129.7 ± 21.8	129.4 ± 21.1	0.77	125.9 ± 20.8	127.5 ± 21.4	0.23
Diastolic BP, mmHg	71.2 ± 11.3	70.6 ± 11.2	<0.01	71.9 ± 11.9	71.7 ± 12.1	0.82	70.6 ± 10.6	69.9 ± 11.4	0.30
Heart rate, bpm	71.2 ± 13.8	73.3 ± 13.9	<0.01	71.0 ± 13.5	74.6 ± 15.3	<0.01	71.1 ± 13.5	72.7 ± 12.9	0.05
Atrial fibrillation	871 (23.4)	383 (20.4)	<0.01	298 (32.7)	236 (36.5)	0.12	197 (31.4)	115 (26.6)	0.09
QRS ≥130 ms	1435 (45.1)	638 (39.4)	<0.01	264 (33.9)	150 (27.9)	0.02	178 (38.7)	99 (30.2)	0.01
eGFR, mL/min	62.8 ± 24.9	58.2 ± 24.6	<0.01	57.7 ± 24.4	54.2 ± 22.7	0.03	56.8 ± 23.4	52.3 ± 22.0	0.01
eGFR									
<30	242 (8.8)	188 (13.1)		68 (12.4)	65 (15.3)		54 (12.6)	50 (16.6)	
30-59	1075 (39.2)	601 (41.8)	<0.01	246 (44.9)	193 (45.4)	0.34	189 (44.0)	138 (45.7)	0.17
≥60	1423 (51.9)	649 (45.1)		234 (42.7)	167 (39.3)		187 (43.5)	114 (37.7)	

Appendix Table 2. *(continued)*

	HFrEF (n=5677)			HFmrEF (n=1571)			Semi-quantitative (n=1075)		
	Men (n=3767)	Women (n=1910)	p-value	Men (n=917)	Women (n=654)	p-value	Men (n=636)	Women (n=439)	p-value
Comorbidity									
Hypertension	1237 (37.0)	703 (41.2)	<0.01	344 (41.8)	274 (46.3)	0.09	220 (37.5)	191 (47.4)	<0.01
Diabetes Mellitus	978 (29.1)	500 (29.3)	0.97	234 (28.4)	163 (27.5)	0.71	168 (28.6)	126 (31.3)	0.37
COPD	607 (18.1)	285 (16.7)	0.20	185 (22.5)	105 (17.7)	0.03	112 (19.1)	76 (18.9)	0.93
OSAS	258 (7.7)	61 (3.6)	<0.01	91 (11.1)	25 (4.2)	<0.01	52 (8.9)	6 (1.5)	<0.01
Thyroid disease	187 (5.6)	181 (10.6)	<0.01	41 (5.0)	70 (11.8)	<0.01	29 (4.9)	49 (12.2)	<0.01
Renal insufficiency †	1710 (52.3)	1023 (59.8)	<0.01	401 (58.1)	342 (64.4)	0.03	262 (57.3)	199 (62.4)	0.16
No relevant comorbidity	442 (15.2)	222 (14.4)	0.52	56 (9.2)	42 (8.8)	0.82	57 (13.7)	28 (9.6)	0.10

HFrEF; Heart Failure with reduced Ejection Fraction; HFmrEF, Heart Failure with mid-range Ejection Fraction; BMI, Body Mass Index; NYHA, New York Heart Association classification; LVEF, Left Ventricular Ejection Fraction; HF, Heart Failure; BP, Blood Pressure; eGFR, estimated Glomerular Filtration Rate; COPD, Chronic Obstructive Pulmonary Disease; OSAS, Obstructive Sleep Apnea Syndrome.

† Defined as eGFR <60mL/min or a history of renal failure



Supplementary Figure 1. HF therapy usages in **A** HFrEF patients (LVEF <40%) (n=5677), **B** HFmrEF (LVEF 40-49%) (n=1571) and **C** semi-quantitative patients (n=1075) according to the 2016 ESC HF Guidelines in men and women

5

Treatment differences in chronic heart failure patients with reduced ejection fraction according to blood pressure

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Abstract

Background: Prescribed dosages of heart failure (HF) therapy in patients with a reduced left ventricular ejection fraction remain lower than guideline recommended. It remains unclear whether systolic blood pressure (BP) influences prescription of HF drugs to HF patients with a reduced left ventricular ejection fraction in a European setting. This study aimed to investigate the role of systolic BP on the prescription rate and actual dose of guideline-recommended HF therapy.

Methods: A total of 8246 patients with chronic HF with a reduced left ventricular ejection fraction from 34 Dutch outpatient HF clinics were included. Detailed information on prescription rates and dosages of HF drugs were assessed according to systolic BP categories (<95, 95–109, 110–129, and ≥130 mm Hg).

Results: Patients with systolic BP <95 mm Hg receive more often triple therapy (β-blocker, renin-angiotensin system inhibitor, and mineralocorticoid receptor antagonist; 40.3% versus 30.4% respectively, P<0.001) compared with ≥130 mm Hg. Patients with systolic BP <95 mm Hg received significantly more often mineralocorticoid receptor antagonists (64.5% versus 43.8%), ivabradine (8.3% versus 3.6%), and diuretics (94.2% versus 78.6%) and less often renin-angiotensin system inhibitors (75.4% versus 82.8%) compared with ≥130 mm Hg (P for all trends, <0.001). The prescribed dosages of β-blockers and renin-angiotensin system inhibitors were significantly lower in patients with systolic BP <95 mm Hg compared with ≥130 mm Hg (P for all trends, <0.001).

Conclusions: In this large cross-sectional cohort of patients with reduced left ventricular ejection fraction, patients with lower systolic BP receive more HF drugs but at lower dose relative to the target dose recommended in HF guidelines. Discussion is warranted regarding what target BP is acceptable and what should be limiting factors in uptitration to adequate levels of HF medication.

Introduction

The question as to whether treatment should be targeted based on blood pressure (BP) levels in chronic heart failure (HF) patients is still open for debate. Both hypotension and hypertension are associated with an increased risk of all-cause mortality and HF-related hospitalizations in chronic HF patients.[1,2] Furthermore, symptomatic hypotension occurs more often in chronic HF patients treated with BP-lowering drugs, especially in those with initially lower BP.[2,3] These results might influence the decision-making of clinicians to initiate additional guideline-recommended HF therapy or titrate HF drugs in chronic HF patients. Adequate control of BP and inducing minor orthostasis can be a marker of achieving the maximally tolerated dose of HF medication, which is recommended by the guidelines. However, symptomatic hypotension and side effects may lower compliance but might also affect prognosis, beyond identifying a group of patients with more advanced HF.

Recently the Change the Management of Patients With Heart Failure (CHAMP-HF) investigators demonstrated in a large American registry that <20% of HF patients received the guideline-recommended target doses of both β-blockers and renin-angiotensin system (RAS) inhibitors, even in patients with higher systolic BP.[4] Accordingly, this may imply that low systolic BP hardly influences the prescription behavior in a real-world setting, but conformationally data and similar information in Europe are lacking. Therefore, it is important to compare the CHAMP-HF data with its counterpart in Europe, the Chronisch Hartfalen ESC-richtlijn Cardiologische praktijk Kwaliteitsproject HartFalen (CHECK-HF) registry with also large numbers of HF patients with reduced ejection fraction (HFrEF) with extensive detailed information on prescription rates and dosage of HF medication. The aim of this substudy of CHECK-HF was to validate and extend the discussion on the role of BP in achieving optimal HF medication prescription and dosages.

Methods

The authors declare that all supporting data are available within the article and in the Data Supplement. The design and methods of the CHECK-HF registry have been published in detail elsewhere.[5] Briefly, a total of 10 910 chronic HF patients from 34 participating Dutch centers between 2013 and 2016 were included in this cross-sectional observational cohort. All included patients were diagnosed with HF and treated according to the 2012 European Society of Cardiology (ESC) HF Guideline[6] (Table

I in the Data Supplement) and were seen at an outpatient HF clinic (96%). Detailed information on patient characteristics, echocardiographic values, and guideline-recommended HF drug prescription and dosages was recorded. The BP was assessed at the arteria brachialis of the upper arm, using an automated, cuffed BP machine during the outpatient clinic visit that was used for data entry in the study. The Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score was calculated and used as an indicator of the severity of HF.[7] The study was conducted according to the Declaration of Helsinki. Ethical approval was provided for anonymously analyzing existing patient data by the Ethical Committee of the Maastricht University Medical Center, the Netherlands.

Patients were divided based on left ventricular ejection fraction (LVEF) or visual assessment of the left ventricle into HF with reduced LVEF (LVEF <50% [n=8360, 76.6%]) and treated according to the 2012 ESC HF guidelines. Two thousand two hundred sixty-seven patients were diagnosed with HF with preserved ejection fraction (LVEF ≥50% [20.8%]) and not included in this analysis. In 283 (2.6%) patients, recording of the left ventricular function in the database was insufficient to classify patients into HF type or standard baseline demographic data were missing, and they were excluded from this analysis. A total of 8246 patients with reduced LVEF were included in this analysis. For a subanalysis according to the newer 2016 ESC HF guidelines,[8] patients with an assessed reduced LVEF <50% according to the 2012 ESC HF guidelines were categorized into HF with mid-range ejection fraction (HFmrEF; LVEF, 40%–49% [n=1556, 18.9%]) and HFrEF (LVEF <40% [n=5613, 68.1%]), only in those patients with an exactly specified LVEF. Those patients with no exact ejection fraction, we present separately as a semiquantitative patient group (n=1077 [13.1%]).

We subdivided systolic BP into 4 categories to have more insight in its relationship with HF drugs. Patients were divided into those with systolic BP <95 mm Hg (n=313 [3.8%]), 95 to 109 mm Hg (n=1255 [15.2%]), 110 to 129 mm Hg (n=3252 [39.4%]), and ≥130 mm Hg (n=3426 [41.5%]). Additionally, we studied systolic BP in categories of <110 (n=1568 [19.0%]) and ≥110 mm Hg (6678 [81.0%]) as performed in the CHAMP-HF analysis.[4]

Statistical Analysis

Continuous data are expressed as mean value±SD or median and interquartile range, depending on the distribution of the data and compared by the 1-way ANOVA or Mann-Whitney U test. Categorical data are expressed as counts and percentages and compared by the Pearson χ^2 test.

To investigate whether the observed differences between BP groups were independent of potential clinical predictors, univariable and multivariable logistic regression analyses were used, with systolic BP <95 mm Hg set as a reference. The results of these regression analyses are expressed as odds ratios with 95% CIs. A 2-sided P of 0.05 was considered statistically significant. In model 1, we adjusted for age and sex only. In model 2, we further adjusted for New York Heart Association classification and LVEF. In model 3, we further included all comorbidities using the forward step method in binary logistic regression with a P threshold of <0.10. Missing data occurred in the variables included in the multivariable analysis, which were imputed using multiple imputation as has been described previously.[9] All analyses were performed with SPSS Statistical Package, version 25.0 (SPSS, Inc, Chicago, IL).

Results

The baseline characteristics of the 8246 patients with reduced LVEF are shown in Table 1. The prescription rates of RAS inhibitors were lower in patients with systolic BP <95 mm Hg (75.4% versus 82.8% respectively, P=0.001), while mineralocorticoid receptor antagonist (MRA; 64.5% versus 43.8% respectively, P<0.001), ivabradine (8.3% versus 3.6% respectively, P<0.001), and diuretics (94.2% versus 78.6% respectively, P<0.001) were more often prescribed compared with ≥130 mm Hg (Figure 1A). Patients with systolic BP <95 mm Hg less often received the guideline-recommended target dose (in those prescribed) of β-blockers (8.3% versus 15.4% respectively, P<0.001) and RAS inhibitors (21.2% versus 44.6% respectively, P<0.001) and more often of MRA (39.6% versus 21.2% respectively, P<0.001) compared with ≥130 mm Hg (Figure 1B). Triple therapy, consisting of β-blocker, RAS inhibitor, and MRA, was prescribed in less than half of the overall population. Patients with systolic BP <95 mm Hg received more often triple therapy (40.3% versus 30.4% respectively, P<0.001; Figure 1C) but less often triple therapy at least at ≥50% of the target dose (9.6% versus 14.7% respectively, P=0.002; Figure 1D) compared with ≥130 mm Hg.

An analysis of the number of guideline-recommended HF therapy and the prescribed dosage according to combinations of mono, dual, and triple HF therapy in the different BP categories is shown in Table 2. In patients with systolic BP <110 mm Hg, patients with reduced LVEF more often receive triple therapy but also at lower overall target dose levels of β-blockers and RAS inhibitors.

Table 1. Patient characteristics

	Systolic BP <95 mmHg (n=313)	Systolic BP 95-109 mmHg (n=1255)	Systolic BP 110-129 mmHg (n=3252)	Systolic BP ≥130 mmHg (n=3426)	P-value
Age, y (n=8238)	72.3 ± 13.5	71.1 ± 12.5	72.3 ± 11.7	72.7 ± 11.4	0.001
Male gender (n=8209)	205 (65.7)	815 (65.4)	2081 (64.2)	2142 (62.8)	0.32
BMI, kg/m^2 (n=7361)	25.8 ± 4.7	26.4 ± 4.8	27.1 ± 4.9	27.7 ± 5.5	<0.001
NYHA (n=8152)					
I	22 (7.1)	160 (12.9)	459 (14.3)	653 (19.3)	<0.001
II	138 (44.5)	687 (55.3)	1854 (57.7)	1956 (57.8)	
III	121 (39.0)	368 (29.6)	847 (26.4)	741 (21.9)	
IV	29 (9.4)	28 (2.3)	52 (1.6)	37 (1.1)	
LVEF, % (n=6077)	31.2 ± 12.2	31.0 ± 10.5	31.9 ± 10.5	34.1 ± 10.3	<0.001
Cause of HF (n=7994)					
Ischemic	150 (49.7)	650 (53.9)	1642 (51.9)	1683 (50.6)	0.21
Non-ischemic	152 (50.3)	555 (46.1)	1520 (48.1)	1642 (49.4)	
Systolic BP, mmHg (n=8246)	88.3 ± 4.7	101.9 ± 3.8	117.9 ± 5.6	145.1 ± 15.0	<0.001
Diastolic BP, mmHg (n=8241)	56.5 ± 7.2	62.8 ± 7.3	69.1 ± 8.5	77.6 ± 11.3	<0.001
Heart rate, bpm (n=8155)	73.9 ± 15.3	72.2 ± 14.4	71.8 ± 13.3	72.0 ± 14.0	0.08
Atrial fibrillation (n=8159)	93 (29.9)	336 (27.0)	839 (26.1)	825 (24.3)	0.05
QRS ≥130ms (n=6884)	118 (46.8)	426 (42.3)	1,089 (40.5)	1,115 (38.0)	0.006
eGFR, ml/min/1.73m^2 (n=5835)					
<30	44 (18.7)	115 (12.3)	254 (10.5)	245 (10.9)	<0.001
30-59	108 (46.0)	373 (39.9)	1024 (42.2)	910 (40.7)	
≥60	83 (35.3)	447 (47.8)	1149 (47.3)	1083 (48.4)	
Comorbidities (n=7413)					
Hypertension	84 (29.4)	332 (30.2)	1022 (35.4)	1513 (48.2)	<0.001
Diabetes Mellitus	75 (26.2)	287 (26.1)	866 (30.0)	921 (29.3)	0.07
COPD	63 (22.0)	228 (20.8)	534 (18.5)	542 (17.3)	0.025
OSAS	23 (8.0)	72 (6.6)	188 (6.5)	207 (6.6)	0.80
Thyroid disease	21 (7.3)	76 (6.9)	217 (7.5)	236 (7.5)	0.92
Kidney insufficiency	200 (67.8)	651 (57.0)	1595 (56.1)	1464 (55.1)	0.001
MAGGIC score	28.6 ± 7.4	25.7 ± 7.2	24.4 ± 7.1	22.9 ± 6.8	<0.001

BMI indicates body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; NYHA, New York Heart Association; and OSAS, obstructive sleep apnea syndrome.

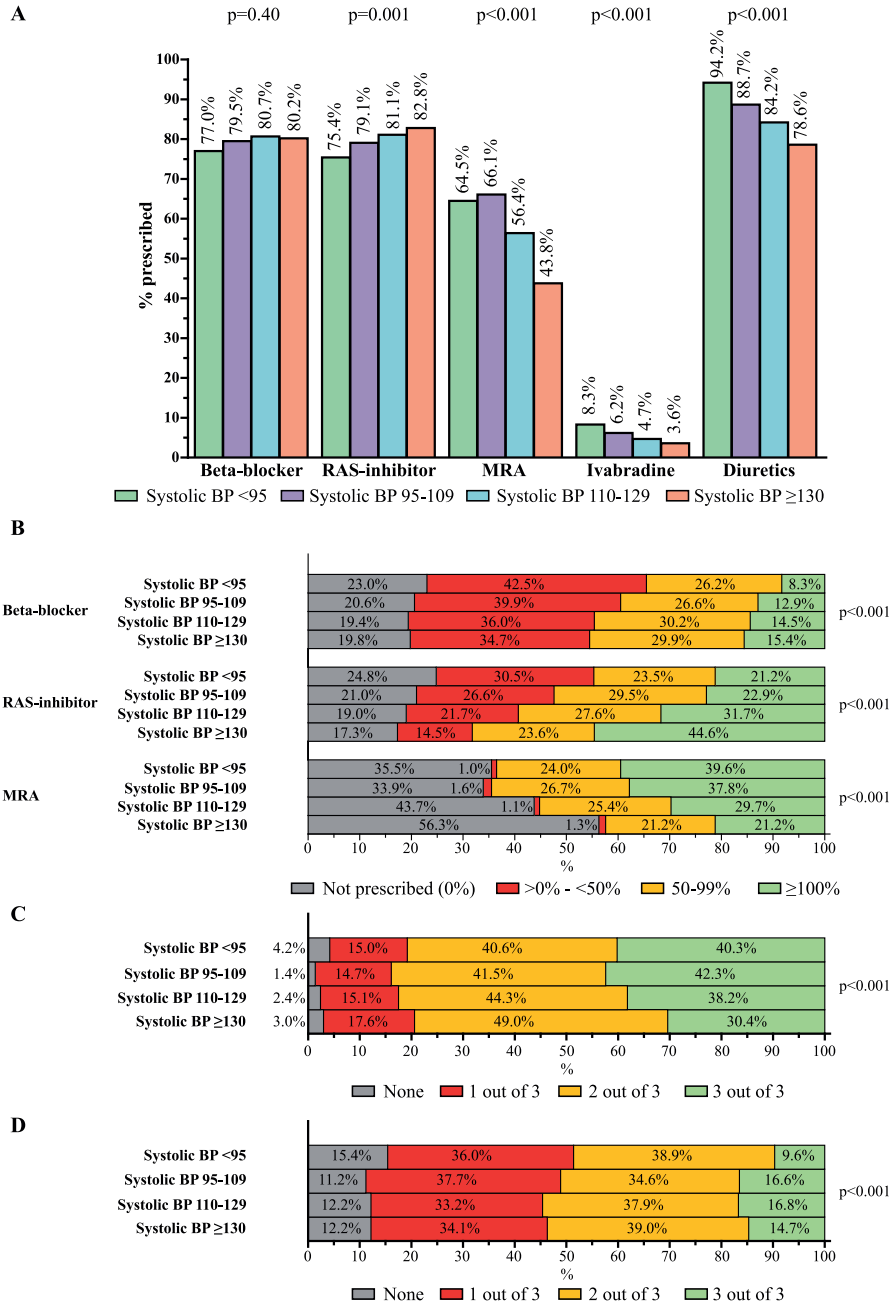

Figure 1. Guideline recommended heart failure (HF) therapy according to systolic blood pressure. **A**, Prescription rates of guideline-recommended HF therapy. **B**, Prescribed dosages expressed as a percentage of recommended target dose. **C**, HF combination therapy (β-blocker, renin-angiotensin system [RAS] inhibitor, or mineralocorticoid receptor antagonist [MRA]). **D**, HF combination therapy of at least ≥50% of the recommended target therapy according to systolic blood pressure (BP).

Table 2. Guideline-recommended HF therapy in patients with reduced systolic function stratified according to number of guideline-recommended therapy used and systolic blood pressure

	Prescribed HF medication			% of target dose prescribed		
Total population (n=7905)*	**Beta-blockers, n (%)**	**RAS-inhibitors, n (%)**	**MRA, n (%)**	**Beta-blocker**	**RAS-inhibitor**	**MRA**
Single HF therapy (n=1305, 16.5%)						
SBP<95 (n=47, 0.6%)	15 (0.2)	22 (0.3)	10 (0.1)	36.3±28.2	53.5±40.9	150.0±105.4
SBP 95-109 (n=183, 2.3%)	57 (0.7)	82 (1.0)	44 (0.6)	41.2±31.8	76.1±49.8	112.5±66.6
SBP 110-129 (n=487, 6.2%)	201 (2.5)	212 (2.7)	74 (0.9)	41.0±26.4	80.1±62.1	94.8±47.5
SBP≥130 (n=588, 7.4%)	232 (2.9)	288 (3.6)	68 (0.8)	42.2±30.5	93.7±59.2	98.5±58.6
P-value	0.08	0.34	<0.001	0.88	0.001	0.031
Dual HF therapy (n=3705, 46.9%)†						
SBP<95 (n=127, 1.6%)	100 (1.3)	88 (1.1)	66 (0.8)	42.8±29.3	68.3±46.7	119.7±85.9
SBP 95-109 (n=516, 6.5%)	405 (5.1)	375 (4.7)	252 (3.2)	43.7±30.9	70.0±56.0	97.4±61.8
SBP 110-129 (n=1425, 18.0%)	1168 (14.8)	1169 (14.8)	513 (6.5)	49.0±34.9	83.1±58.8	88.3±49.1
SBP≥130 (n=1637, 20.7%)	1431 (18.1)	1462 (18.5)	381 (4.8)	50.9±34.2	102.3±66.2	84.2±45.6
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Triple HF therapy (n=2895, 36.6%)						
SBP<95 (n=126, 1.6%)	126 (1.6)	126 (1.6)	126 (1.6)	40.8±29.0	65.7±47.3	84.5±41.7
SBP 95-109 (n=526, 6.7%)	526 (6.7)	526 (6.7)	526 (6.7)	48.4±32.2	72.4±51.7	85.6±48.5
SBP 110-129 (n=1228, 15.5%)	1228 (15.5)	1228 (15.5)	1228 (15.5)	50.1±32.9	81.6±52.0	81.2±44.6
SBP≥130 (n=1015, 12.8%)	1015 (12.8)	1015 (12.8)	1015 (12.8)	51.7±33.6	100.4±59.8	76.2±39.0
P-value	-	-	-	0.002	<0.001	<0.001

Target dose levels are demonstrated in Table I in the Data Supplement. The percentages represent the percentage of the entire population. HF indicates heart failure; MRA, mineralocorticoid receptor antagonist; RAS, renin-angiotensin system; and SBP, systolic blood pressure.

*Two hundred eight patients received no medication; in 133 patients, no data on medication use were available.

†Various combinations possible.

Patients with systolic BP <95 mm Hg had higher reported contraindication or intolerance rates for RAS inhibitors (41.6% versus 23.0% respectively, P=0.002) and MRA (12.6% versus 8.5% respectively, P=0.019) compared with ≥130 mm Hg (Table 3).

Table 3. Reasons for not prescribing HF medication according to systolic blood pressure

	Contraindicated or intolerance	No reason specified	P-value
Beta-blocker			
Total population	259 (16.1)	1350 (83.9)	
Systolic BP <95	13 (18.1)	59 (81.9)	
Systolic BP 95-109	40 (15.7)	215 (84.3)	0.73
Systolic BP 110-129	93 (15.0)	528 (85.0)	
Systolic BP ≥130	113 (17.1)	548 (82.9)	
RAS-inhibitors			
Total population	376 (24.7)	1144 (75.3)	
Systolic BP <95	32 (41.6)	45 (58.4)	
Systolic BP 95-109	71 (27.3)	189 (72.7)	0.002
Systolic BP 110-129	141 (23.2)	468 (76.8)	
Systolic BP ≥130	132 (23.0)	442 (77.0)	
MRA			
Total population	383 (10.1)	3,427 (89.9)	
Systolic BP <95	14 (12.6)	97 (87.4)	
Systolic BP 95-109	45 (10.7)	376 (89.3)	0.019
Systolic BP 110-129	164 (11.7)	1239 (88.3)	
Systolic BP ≥130	160 (8.5)	1715 (91.5)	

BP indicates blood pressure; HF, heart failure; MRA, mineralocorticoid receptor antagonist; and RAS, renin-angiotensin system.

After multivariable adjustments, only patients with systolic BP ≥130 mm Hg had a lower likelihood to receive an MRA compared with <95 mm Hg (Table II in the Data Supplement). Patients with a systolic BP between 110 and 129 and ≥130 mm Hg had a significantly lower likelihood of receiving ivabradine. Furthermore, all systolic BP groups had a lower likelihood of receiving diuretics, compared with patients with systolic BP <95 mm Hg. After multivariable adjustment, the observed difference in prescription rates of RAS inhibitors attenuated.

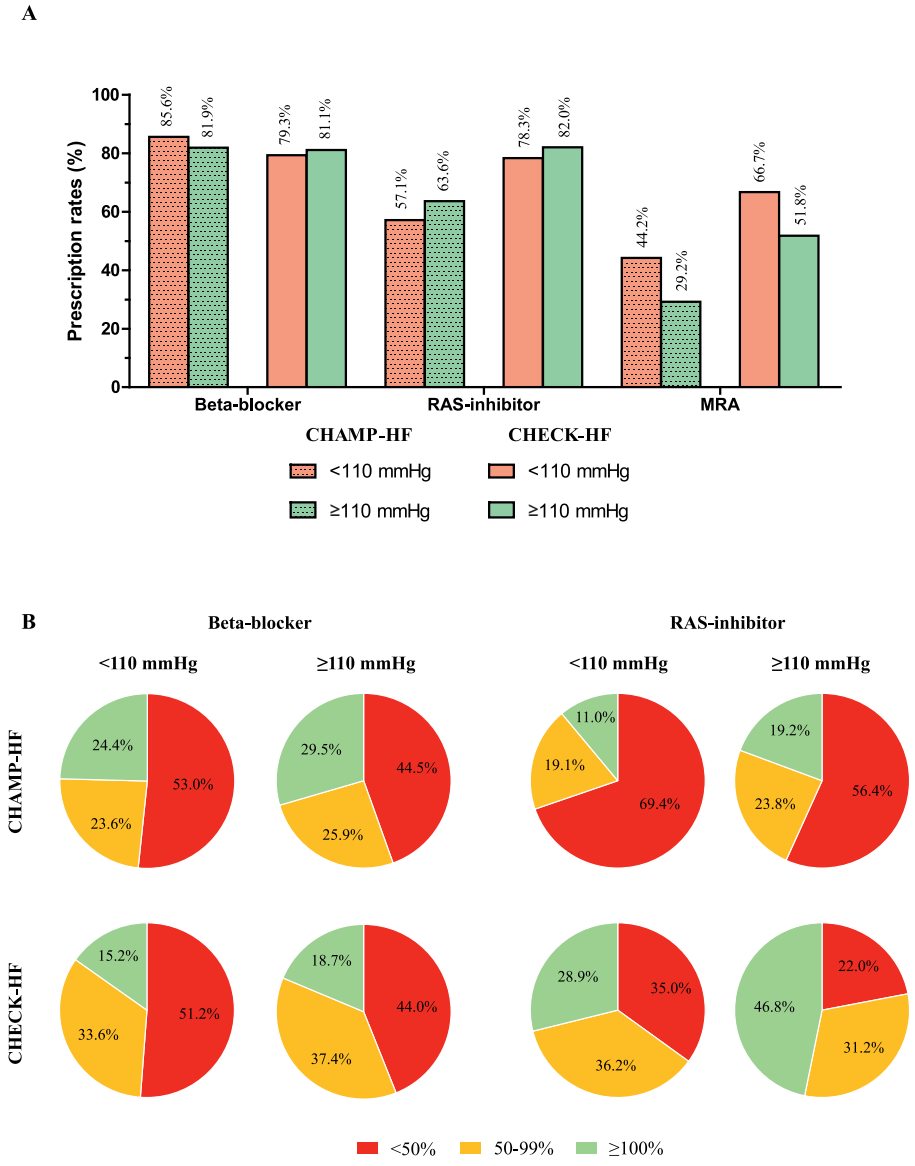

Figure 2. Guideline recommended heart failure (HF) therapy in the Change the Management of Patients With Heart Failure (CHAMP-HF) and Chronisch Hartfalen ESC-richtlijn Cardiologische praktijk Kwaliteitsproject HartFalen (CHECK-HF) registries according to systolic blood pressure.
A, Prescription rates of guideline-recommended HF therapy. **B**, Prescribed dosages expressed as a percentage of recommended target dose. MRA indicates mineralocorticoid receptor antagonist; and RAS, renin-angiotensin system.

CHAMP-HF Versus CHECK-HF

In Figure 2A, we compare the prescription rates of β- blockers, RAS, and MRA in the American CHAMP-HF registry and CHECK-HF registry according to the BP categories <110 and >110 systolic BP as used in that subanalysis. The prescription rates and prescribed dose of HF drugs in HFrEF were slightly higher in the CHECK-HF registry as compared with CHAMP-HF.[4] Both registries demonstrated a higher prescription rate for all HF drugs in patients with systolic BP <110 mm Hg compared with ≥110 mm Hg, although the absolute difference was bigger in the CHECK-HF registry. The prescribed dosages of MRA in both BP groups were much higher in the CHECK-HF registry compared with the CHAMP-HF registry (Figure 2B). In both registries, a higher prescribed dosage was observed in patients with systolic BP ≥110 mm Hg; however, the difference in the CHECK-HF registry was larger.

Medical Therapy in Subgroups of HFmrEF According to 2016 ESC Guidelines

Treatment did not differ between HFmrEF (LVEF, 49%–50%) and HFrEF (LVEF, <40%) in our data set. A subanalysis of only HFmrEF (LVEF, 40%–49%) showed a comparable distribution of prescription rates according to BP in HFmrEF patients (mean age, 73.7±11.7 years; 58.3% were men) and HFrEF patients (Figure I in the Data Supplement). Only RAS inhibitors were overall less often prescribed in HFmrEF patients, compared with HFrEF patients. Likewise, the subgroup of semiquantitative left ventricular function showed similar differences (Figure I in the Data Supplement). There was no significant interaction between ejection fraction (HFrEF versus HFmrEF) and systolic BP categories (all P=nonsignificant).

Discussion

In this large, cross-sectional Western European registry of patients with a reduced LVEF, the prescription rates and dosages of guideline-recommended HF drugs differed between categories of systolic BP levels. Most interestingly, the patients with the lowest BP received the highest number of triple therapy (β-blocker, RAS inhibitor, and MRA) but at lower overall prescribed dosages as compared with higher BP categories. This may argue that patients with lower BP have better guidelinerecommended treatment, which may have caused lower BP levels. Additionally, this group of patients had more advanced HF, indicated by a higher MAGGIC score, with more attention to optimize therapy. The number of side effects and intolerance was also reported to be higher. Another important finding of this study is that in patients with relatively high BP (≥130 mm Hg), the prescription of HF drugs is not optimal and also the dose of HF drugs is

not at target despite the additional room for uptitration with these levels of BP. It is generally assumed that low BP limits the uptitration of HF medication. Therefore, in patients with BP >130 mm Hg, other factors seem to play a role in the relatively low uptake of HF medication, such as less HF symptoms (more New York Heart Association class II) or lower MAGGIC score. The discussion becomes even more difficult as it is hard to judge on the quality of HF care based on BP alone, as we do not know whether the BP is low due to medication or due to the severity of the disease. Still, New York Heart Association class II or low MAGGIC score should not be a reason for stopping uptitration of HF drugs nor should HF be seen as stable in those patients, one can argue.

CHECK-HF Versus CHAMP-HF

The general conclusion of the comparison of the CHAMP-HF and CHECK-HF registries is that with lower BP, patients have a higher percentage of triple therapy as indicated, but the actual dose of treatment is higher in the higher BP categories. Although both registries showed similar findings, there were some essential differences between them. Notable differences of the included populations were a higher percentage of women and patients with renal insufficiency in the CHECK-HF registry. As has been demonstrated previously, patient characteristics and the presence of comorbidities influence the HF drug prescription behavior of clinicians.[10,11] Furthermore, the HF care systems differ between the 2 countries of the registries. Almost all patients in the CHECK-HF registry were treated at specialized HF outpatient clinics, consisting of specialized HF nurses and cardiologists. It has been shown that monitoring HF patients in a specialized setting, with a coordinating role for HF nurses, leads to better guideline adherence and uptitration in chronic HF patients,[12,13] which could explain some differences between the 2 registries. Additionally, healthcare insurance was available for all CHECK-HF patients, and all patients had access to a basic level of health care, including reimbursement and unrestricted access to medications prescribed including dedicated HF outpatient clinics and nurses. In contrast, patients in the CHAMP-HF might have experienced several challenges such as the access to HF therapy, different structure and organization of HF care, and high costs for HF therapy, which are very relevant public health issues in comparing CHECK-HF and CHAMP-HF in general.[14]

A dose-dependent positive effect has been described for most guideline-recommended HF drugs.[15–17] Furthermore, it has been demonstrated that β-blockers,[18,19] angiotensin-receptor blocker,[20] angiotensin repector neprilysin inhibitor,[2,21] and ivabradine[22] reduce mortality and HF-related hospitalization rates independent of baseline systolic BP. This indicates the importance of drug uptitration. Recently, the propensity-matched

Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) study demonstrated that HFrEF patients discharged with a systolic BP <130 mm Hg were at a greater risk of mortality compared with patients with a systolic BP ≥130 mm Hg.[23] These findings are in line with earlier reports from observational cohorts and post hoc analysis from randomized controlled trials, indicating that patients with lower systolic BP are at a greater risk of all-cause mortality and HF-related hospitalization,[1,2,19,20,22–25] and could also be sicker patients as reflected in the MAGGIC score. However, the HFrEF medication that lower systolic BP, are also associated with a lower mortality and hospitalization rates, and are an indicator of the level of quality of HF care.[8] So, these contradictions cause that it still remains unclear what the ideal systolic BP target in HFrEF patients should be and whether low BP is a marker of successful HF treatment with drugs at target level or a marker of elevated risk with likewise sicker patients. Therefore, new studies investigating the ideal systolic BP targets are needed. Additionally, the best uptitration strategy has not yet been properly studied and is, therefore, still under debate. In particular, it is largely unknown whether the BP response to therapy should influence the uptitration scheme to improve outcomes. A predefined BP level may be targeted during uptitration, making sure the BP does not drop too low. Another strategy may be to uptitrate HF medication close to orthostatic hypotension allowing to achieve the maximal dose. However, clinicians might be reluctant to adopt this latter strategy in fear of inducing symptomatic hypotension and significant side effects. Still, uptitrating HF medication in patients with low systolic BP is possible in most patients by using a slow and closely monitored titration strategy.[3] However, implementing these kinds of strategies into a real-world practice can be challenging, which may result in patients with low systolic BP levels receiving less often HF drugs at the recommended dose, as shown in our registry. Furthermore, only a minority of patients received triple HF therapy at the recommended dose, even in patients with higher systolic BP. In addition, other factors, often unclear, influence the uptitration decision as well. Further understanding of the decision-making process in uptitration is urgently needed to optimize this process.

Recently, the use of dapagliflozin has been investigated in HFrEF patients. In these patients, most likely the natriuretic effect of dapagliflozin influenced BP significantly.[26] We believe that dapagliflozin will be a very useful addition in the treatment of HFrEF patients; however, the exact place of these new drugs in relation to BP levels in adequately treated HFrEF patients or undertreated patients with still elevated BP is still to be determined.

Limitations and Strengths

Strengths of this registry are the large sample size, the contemporary recent data, and real-world practice-based HF registry, with detailed information on HF medication prescription and dosages. This registry has some limitations. Most importantly, due to its cross-sectional design, there are no data on clinical events and longitudinal patient outcomes. Additionally, with changing HF categories based on LVEF in the newer guidelines, our analysis was limited by a small number of patients where left ventricle function was semiquantitatively analyzed with echocardiography— a practice not following guidelines. The registry is a quality of HF care project to study the determinants of guideline-recommended HF therapy in the Netherlands; however, the systolic blood pressure could be lowered due to HFrEF medication, which has been associated with a lower mortality and hospitalization rates, and are an indicator of the level of quality of HF care.

Conclusions

In this large study of patients with reduced LVEF, we observe that the highest level of HF drug triple therapy (β-blocker, RAS inhibitor, and MRA) is prescribed in those patients with the lowest systolic BP, but this is limited by lower levels of prescribed dose as compared with higher BP levels and higher levels of intolerance. Systolic BP appears to be one of the limiting factors in the uptitration of the dose of guideline-recommended HF therapy. Debate is warranted whether the optimal level of HF drugs should be based on the level of the BP, the severity of the disease, the tolerated level by the patient, or the guideline-recommended dose as advocated.

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Supplementary content

Supplementary Table 1 – Target doses of guideline-recommended therapy

Beta-blocker	
Bisoprolol	10 mg
Carvedilol	50 mg
Metoprolol succinate	200 mg
Nebivolol	10 mg
ACE-inhibitor	
Captopril	150 mg
Enalapril	20 mg
Lisinopril	40 mg
Ramipril	10 mg
Perindopril	8 mg
ARB	
Candesartan	32 mg
Losartan	150 mg
Valsartan	320 mg
MRA	
Eplerenone	50 mg
Spironolactone	25 mg

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist

Supplementary Table 2. Multivariable analysis: the likelihood of receiving guideline-recommended therapy according to systolic blood pressure

	Univariable		Multivariable					
			Model 1		Model 2		Model 3	
Guideline-recommended pharmacotherapy	**OR**	**p-value**	**OR**	**p-value**	**OR**	**p-value**	**OR**	**p-value**
Beta-blocker								
SBP <95 mmHg	ref		ref		ref		ref	
SBP 95-109 mmHg	1.16 [0.86-1.56]	0.33	1.13 [0.97-1.32]	0.41	1.16 [0.79-1.69]	0.45	1.16 [0.86-1.56]	0.33
SBP 110-129 mmHg	1.25 [0.95-1.65]	0.12	1.24 [0.94-1.64]	0.13	1.39 [0.98-1.97]	0.07	1.28 [0.96-1.69]	0.09
SBP ≥130 mmHg	1.21 [0.92-1.60]	0.18	1.21 [0.92-1.60]	0.18	1.27 [0.90-1.81]	0.18	1.22 [0.92-1.62]	0.16
RAS-inhibitor								
SBP <95 mmHg	ref		ref		ref		ref	
SBP 95-109 mmHg	1.23 [0.92-1.65]	0.16	1.17 [0.87-1.58]	0.29	1.08 [0.80-1.46]	0.60	1.05 [0.78-1.43]	0.74
SBP 110-129 mmHg	1.40 [1.07-1.84]	0.016	1.40 [1.06-1.85]	0.018	1.27 [0.96-1.68]	0.10	1.21 [0.91-1.61]	0.19
SBP ≥130 mmHg	1.57 [1.20-2.06]	0.001	1.61 [1.22-2.13]	0.001	1.44 [1.08-1.91]	0.012	1.32 [0.99-1.76]	0.06
MRA								
SBP <95 mmHg	ref		ref		ref		ref	
SBP 95-109 mmHg	1.07 [0.83-1.39]	0.60	1.07 [0.93-1.22]	0.64	1.15 [0.89-1.50]	0.29	1.16 [0.90-1.51]	0.26
SBP 110-129 mmHg	0.71 [0.56-0.91]	0.006	0.71 [0.63-0.81]	0.007	0.79 [0.62-1.00]	0.05	0.80 [0.63-1.02]	0.07
SBP ≥130 mmHg	0.43 [0.34-0.55]	<0.001	0.43 [0.38-0.55]	<0.001	0.49 [0.39-0.63]	<0.001	0.50 [0.39-0.64]	<0.001

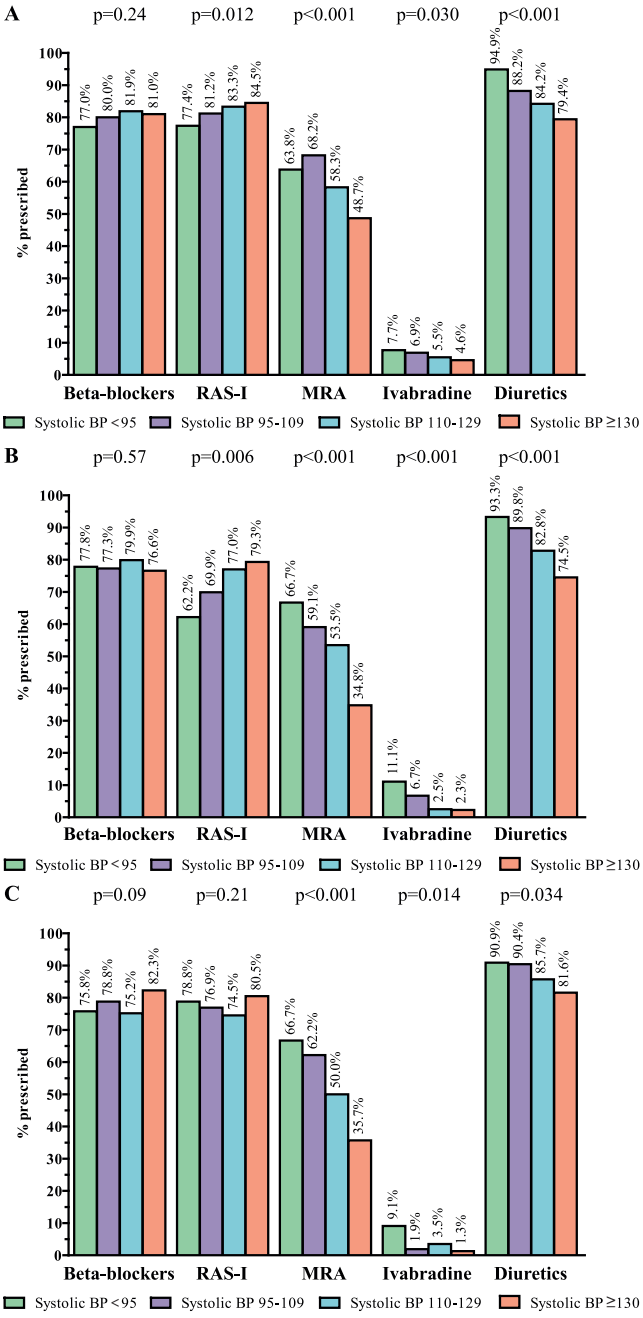
Supplementary Table 2. *(continued)*

	Univariable		Multivariable					
			Model 1		Model 2		Model 3	
Guideline-recommended pharmacotherapy	**OR**	**p-value**	**OR**	**p-value**	**OR**	**p-value**	**OR**	**p-value**
Ivabradine								
SBP <95 mmHg	ref		ref		ref		ref	
SBP 95-109 mmHg	0.73 [0.46-1.16]	0.19	0.71 [0.45-1.14]	0.16	0.81 [0.51-1.31]	0.39	0.76 [0.47-1.23]	0.27
SBP 110-129 mmHg	0.55 [0.35-0.84]	0.006	0.56 [0.36-0.87]	0.009	0.66 [0.42-1.03]	0.07	0.60 [0.38-0.95]	0.028
SBP ≥130 mmHg	0.42 [0.27-0.65]	<0.001	0.44 [0.28-0.68]	<0.001	0.55 [0.35-0.87]	0.011	0.49 [0.31-0.78]	0.003
Diuretics								
SBP <95 mmHg	ref		ref		ref		ref	
SBP 95-109 mmHg	0.48 [0.29-0.80]	0.005	0.48 [0.37-0.63]	0.006	0.56 [0.33-0.94]	0.029	0.58 [0.34-0.97]	0.039
SBP 110-129 mmHg	0.33 [0.20-0.53]	<0.001	0.30 [0.24-0.39]	<0.001	0.37 [0.22-0.60]	<0.001	0.38 [0.23-0.63]	<0.001
SBP ≥130 mmHg	0.22 [0.14-0.36]	<0.001	0.20 [0.16-0.26]	<0.001	0.26 [0.16-0.42]	<0.001	0.26 [0.16-0.42]	<0.001

Model 1 included age and gender

Model 2 included age, gender, NYHA classification, left ventricular ejection fraction

Model 3 included age, gender, NYHA classification, left ventricular ejection fraction, diabetes mellitus, COPD, OSAS, thyroid disease, renal insufficiency (defined as eGFR <60mL/min or a history of renal insufficiency), and atrial fibrillation



Supplementary Figure 1 – Prescription rates of guideline-recommended HF therapy in **A** HFrEF patient (EF <40%) (n=5,613), **B** HFmrEF patient (EF 40-49%) (n=1,556) and **C** semi-quantitative patients (n=1,077) according to ESC 2016 guidelines according to systolic blood pressure

6

Atrial fibrillation in chronic heart failure patients with reduced ejection fraction: the CHECK-HF registry

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Abstract

Background: Atrial fibrillation (AF) is common in chronic heart failure (HF) patients and influences the choice and effects of drug and device therapy. In this large real-world HF registry, we studied whether the presence of AF affects the prescription of guideline-recommended HF therapy.

Methods: We analyzed 8253 patients with chronic HF with reduced ejection fraction (HFrEF) from 34 Dutch out-patient clinics included in the period between 2013 and 2016 treated according to the 2012 ESC guidelines.

Results: 2109 (25.6%) of these patients were in AF (mean age 76.8 ± 9.2 years, 65.0% were men) and 6.144 (74.4%) had no AF (mean age 70.7 ± 12.2 years, 63.6% were men). Patients with AF more often received beta-blockers (81.7% vs. 79.7%, p = 0.04), MRAs (57.1% vs. 51.7%, p < 0.01), diuretics (89.7% vs. 80.6%, pb0.01) and digoxin (40.1% vs. 9.3%, p < 0.01) compared to patients without AF, whereas they less often receive renin-angiotensin-system (RAS)-inhibitors (76.1% vs. 83.1%, p < 0.01). The number of patients who received beta-blockers, RAS-inhibitor and MRA at ≥ 50% of the recommended target dose was comparable between those with and without AF (16.6% vs. 15.2%, p = 0.07).

Conclusion: In this large cohort of chronic HFrEF patients, the prevalence of AF was high and we observed significant differences in prescription of both guideline-recommended HF between patients with and without AF.

Introduction

Atrial fibrillation (AF) is a common comorbidity in chronic heart failure (HF) patients,with a prevalence that has been reported from 10% up to 50–60%, depending on age and severity of HF [1–3]. Pathophysiological changes in HF can lead to AF and vice versa [2,4]. HF induces elevated filling pressures in the atria, leading to interstitial fibrosis of the left atrium, eventually leading to AF. Furthermore, calcium handling is altered in HF patients, and due to alterations in the electric properties of the atrial tissue in HF patients, AF can be induced. Otherwise, AF affects the left ventricular function due to loss of atrial contraction, irregular ventricular heart rhythm, and often rapid ventricular response, leading to and sustaining HF.

Multiple studies have shown that incident AF in chronic HF patients is associatedwith an increased risk of all-causemortality, cardiovascular mortality, stroke and transient ischemic attack [1,5]. Moreover, concomitant AF may influence the choice of HF therapy, as the effects of therapies may differ in HF patients with AF [6]. There are European Society of Cardiology (ESC) guidelines for both HF and AF, providing clear recommendations for the treatment of both conditions [7,8]. Information on the ESC HF guideline adherence in patients with and without AF is relatively scarce.

Therefore, the aimof this studywas to (1) investigate the adherence to the HF ESC guidelines in HF patients with reduced ejection fraction (HFrEF) depending on the existence of underlying AF as well as to (2) provide insight in the prescription of antiarrhythmic drugs and anticoagulation therapy in HFrEF patients with AF in a practice-based registry.

Methods

The design and methods of the CHECK-HF (Chronisch Hartfalen ESCrichtlijn Cardiologische praktijk Kwaliteitsproject HartFalen) registry have been reported in detail earlier [9]. Briefly, the CHECK-HF registry consists of 10,910 patientswith chronic HF froma total of 34 participating Dutch centers, participating in the inclusion of this cross-sectional observational cohort. Between 2013 and 2016, all centers included patients diagnosed with HF-based on symptoms, signs, ECG, biomarkers and echocardiography according to the 2012 ESC Guideline on HF [10],whowere seen at the outpatient HF clinic (96%) or general cardiology outpatient clinic (4%) if no specific HF clinic was present. No NTproBNP threshold levels were used as inclusion criteria in this registry. The study was

conducted according to the Declaration of Helsinki. Ethical approval was provided for anonymously analyzing existing patient data by the Ethical Committee of theMaastricht UniversityMedical Center, the Netherlands.

A dedicated database was used to register all available records of the included patients, including baseline characteristics, laboratorymarkers, device implantation rates, aswell as prescription and dosages ofmedication. Furthermore, information on contraindications and drug intolerance were collected. For HF medical therapy, sotalol was analyzed separately from other beta-blockers. Target doses of guideline recommended HF therapy are presented in Supplementary Table 1.

Patients were classified based on left ventricular ejection fraction (LVEF) or visual assessment of the left ventricle (LV) function into HFrEF (LVEF b50% (n= 8360 (76.6%)) and HF with preserved ejection fraction (HFpEF) (LVEF≥50% (n = 2267 (20.8%) according to 2012 ESC HF guidelines [10]. In 283 (2.6%) patients data on LV functionwas insufficient to classify patients, these patients, and all HFpEF patients, were excluded from this analysis. Based on a 12-lead ECG, performed during the most recent out-patient clinic visit, HFrEF patients were divided into those with documented AF (or a documented history of AF), sinus rhythmor other cardiac rhythms, in 107 (1.3%) patients data on cardiac rhythm wasmissing, and these patients were excluded fromthis analysis. Thus, a total of 8253 HFrEF patientswith AF orwithout AF (including sinus, pacemaker, and ectopic rhythm) was included.

Statistical analysis

Continuous data are expressed as mean value ± standard deviation (SD) or median and interquartile range, depending on the distribution of the data, and compared by the unpaired t-test or Mann-Whitney U test when appropriate. Categorical data are expressed as counts and percentages, and compared by the Pearson Chi-square test. In order to investigate whether the observed differences according to AF were independent of potential confounders, such as age and sex, univariable and multivariable logistic regression were used. The results of these regression analyses are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). A two-sided p-value of 0.05 was considered statistically significant.

In model 1, we adjusted for heart rate (per 10 beats/min). In model 2,we further adjusted for age, sex, New York Heart Association (NYHA) classification, and LVEF. In model 3, we further included all comorbidities which were significantly related to the

outcome variable at statistical level p-value <0.05 using the enter method in a binary logistic regression model.

For some of these potential confounders, data were missing and were imputed using multiple imputation. If the missing variables showed a monotone pattern of missing values, the monotone method was used. Otherwise, an iterative Markov chain Monte Carlo method was used with a number of 10 iterations. A total of 5 imputations were performed, and the pooled data were analyzed. The imputed data was only used for the multivariable analysis. For all reported data of the multivariable analysis, we compared crude and imputed p-values as well as the ORs and CIs in order to analyze whether imputation changed the results, and if no significant changes occurred,we only presented the imputed values in the main analyses.

A sensitivity analysis was conducted for patients with documented AF (n= 2109) and documented sinus rhythm (n= 4901).

For a sub-analysis according to the newer 2016 ESC HF guidelines, patients with an assessed LVEF <50% were categorized into HF with mid-range ejection fraction (HFmrEF) (LVEF 40–49% (n = 1559 (18.9%)) and HFrEF (LVEF<40% (n = 5625 (68.2%), only in those patients with a exactly specified LVEF or into patients with only a semiquantitative analysis of the LV function (n= 1069 (13.0%)). For a subanalysis according to type of AF, patients diagnosed with AF were categorized into those with paroxysmal, persistent, permanent AF or AF of unknown type. All analyses were performed with SPSS Statistical Package version 25.0 (SPSS Inc., Chicago, Illinois).

Results

Baseline characteristics

Of all HFrEF patients, 2109 (25.6%) patients had AF on the entry-ECG at themost recent out-patient clinic visit or had a documented history of AF, 4901 (59.4%) had sinus rhythm, 1141 (13.8%) had pacemaker rhythm and 102 (1.2) had an ectopic rhythm (in total 6144 (74.4%) had no AF). The prevalence of AF increased in higher NYHA-classifications (NYHA I 18.0%, NYHA II 24.8%, NYHA III 31.2% and NYHA IV 30.8%, p b 0.01). Patients with AF were significantly older compared to patients without AF (76.8 ± 9.2 vs. 70.7 ± 12.2 years resp., p < 0.01), were more often in NYHA III/IV (33.4% vs. 25.2% resp., p < 0.01), and had more comorbidities compared to patients without AF as shown in Table 1.

Table 1. Patient characteristics of HFrEF patients according to AF

	Overall population (n=8253)	Patients with AF (n=2109)	Patients without AF (n=6144)	p-value
Age (years) (n=8244)	72.3±11.8	76.8±9.2	70.7±12.2	<0.01
Male gender (n=8216)	5258 (64.0)	1366 (65.0)	3892 (63.6)	0.25
BMI, kg/m2 (n=7599)	27.2±5.2	27.1±5.1	27.2±5.2	0.48
NYHA (n=8160)				
I	1291 (15.8)	232 (11.1)	1059 (17.4)	<0.01
II	4644 (56.9)	1154 (55.5)	3490 (57.4)	
III	2079 (25.5)	648 (31.2)	1431 (23.5)	
IV	146 (1.8)	45 (2.2)	101 (1.7)	
LVEF, % (n=6097)	32.7±10.6	35.3±10.9	31.8±10.3	<0.01
Cause of HF (n=7998)				
Ischemic cause of HF	4122 (51.5)	850 (41.6)	3272 (54.9)	<0.01
Non-ischemic cause of HF	3876 (48.5)	1192 (58.4)	2684 (45.1)	
Systolic BP, mmHg (n=8159)	125.7±20.7	124.4±20.2	126.1±20.8	<0.01
Diastolic BP, mmHg (n=8164)	71.2±11.4	71.6±12.0	71.0±11.1	0.04
Heart rate, bpm (n=8199)	72.0±13.9	77.0±16.7	70.3±12.3	<0.01
LBBB (n=8253)	1411 (17.1)	324 (15.4)	1087 (17.7)	0.01
QRS ≥130 ms (n=6899)	2757 (40.0)	549 (32.4)	2208 (42.4)	<0.01
eGFR (n=5813)	59.7±24.6	57.6±24.2	60.4±24.7	<0.01
eGFR (n=5813)				
<30	655 (11.3)	180 (12.1)	475 (11.0)	<0.01
30-59	2410 (41.5)	671 (45.2)	1739 (40.2)	
≥60	2748 (47.3)	632 (42.6)	2116 (48.9)	
Comorbidity (n=7399)				
Hypertension	2949 (39.9)	843 (44.3)	2106 (38.3)	<0.01
Diabetes Mellitus	2148 (29.0)	589 (31.0)	1559 (28.4)	0.03
COPD	1372 (18.5)	358 (18.8)	1014 (18.4)	0.72
OSAS	491 (6.6)	120 (6.3)	371 (6.7)	0.51
Thyroid disease	551 (7.4)	160 (8.4)	391 (7.1)	0.06
Renal insufficiency [a]	3901 (56.3)	1156 (63.3)	2745 (53.8)	<0.01
No relevant comorbidity	840 (13.6)	158 (9.6)	682 (15.0)	<0.01
Previous interventions (n=6529)				
PCI	1658 (25.4)	310 (18.6)	1348 (27.7)	<0.01
CABG	1450 (22.2)	363 (21.8)	1087 (22.4)	0.63
Valve intervention	523 (8.0)	173 (10.4)	350 (7.2)	<0.01

Table 1. *(continued)*

	Overall population (n=8253)	Patients with AF (n=2109)	Patients without AF (n=6144)	p-value
Cardiac rhythm				
Sinus rhythm	4901 (59.4)	-	4901 (79.8)	
Ectopic rhythm	102 (1.2)	-	102 (1.7)	
Pacemaker rhythm	1141 (13.8)	-	1141 (18.6)	
Paroxysmal AF	305 (3.7)	305 (14.5)	-	-
Persisted AF	370 (4.5)	370 (17.5)	-	
Permanent AF	1116 (13.5)	1116 (52.9)	-	
AF of unknown type	318 (3.9)	318 (15.1)	-	

AF, Atrial Fibrillation; BMI, Body Mass Index; NYHA, New York Heart Association classification; LVEF, Left Ventricular Ejection Fraction; HF, Heart Failure; BP, Blood Pressure; LBBB, Left-Bundle Branch Block; eGFR, estimated Glomerular Filtration Rate; COPD, Chronic Obstructive Pulmonary Disease; OSAS, Obstructive Sleep Apnea Syndrome; PCI, Percutaneous Coronary Intervention; CABG, Coronary Artery Bypass Graft.

[a] Defined as eGFR <60mL/min or a history of renal failure

Pharmacological therapy

Patients with AF significantly more often received beta-blockers (81.7% vs. 79.7%, $p = 0.04$), mineralocorticoid receptor antagonists (MRAs) (57.1% vs. 51.7%, $p < 0.01$), diuretics (89.7% vs. 80.6%, $p < 0.01$), digoxin (40.1% vs. 9.3%, $p < 0.01$), oral anticoagulation (OACs) (82.4% vs. 41.7%, $p < 0.01$) and non-vitamin K antagonist oral anticoagulant (NOACs) (7.3% vs. 3.6%, $p < 0.01$), and less often RAS-inhibitors (76.1% vs. 83.1%, $p < 0.01$), amiodarone (12.9% vs. 15.2%, $p = 0.04$), and sotalol (2.7% vs. 5.6%, $p < 0.01$) compared to patients without AF, as shown in Fig. 1A. 89.7% of the patients with AF receive (N)OAC therapy as compared to 45.4% of those without AF ($p < 0.01$). Reasons for prescription of anticoagulation in patients without AF were artificial valves, severe LV dysfunction or LV thrombus. As shown in Fig. 1C, there were no significant differences in the number of patients who received triple HF therapy, consisting of beta-blocker, RAS-inhibitor, and MRA. Additionally, patients with sinus rhythm had more often an implantable cardioverter defibrillator (29.0% vs. 15.4%, $p < 0.01$) or a cardiac resynchronization therapy device (9.9% vs. 7.3, $p < 0.01$) compared to patients with AF.

The prescribed dosages of beta-blocker, RAS-inhibitors, and MRA are presented in Fig. 1B. Patients with AF significantly more often received beta-blocker at target dose as compared to patients without AF, and there were no significant differences in the prescribed dosages of RAS-inhibitors and MRAs. As shown in Fig. 1D, there was no significant difference in the number of patients who received triple HF therapy at ≥50% at the target dose.

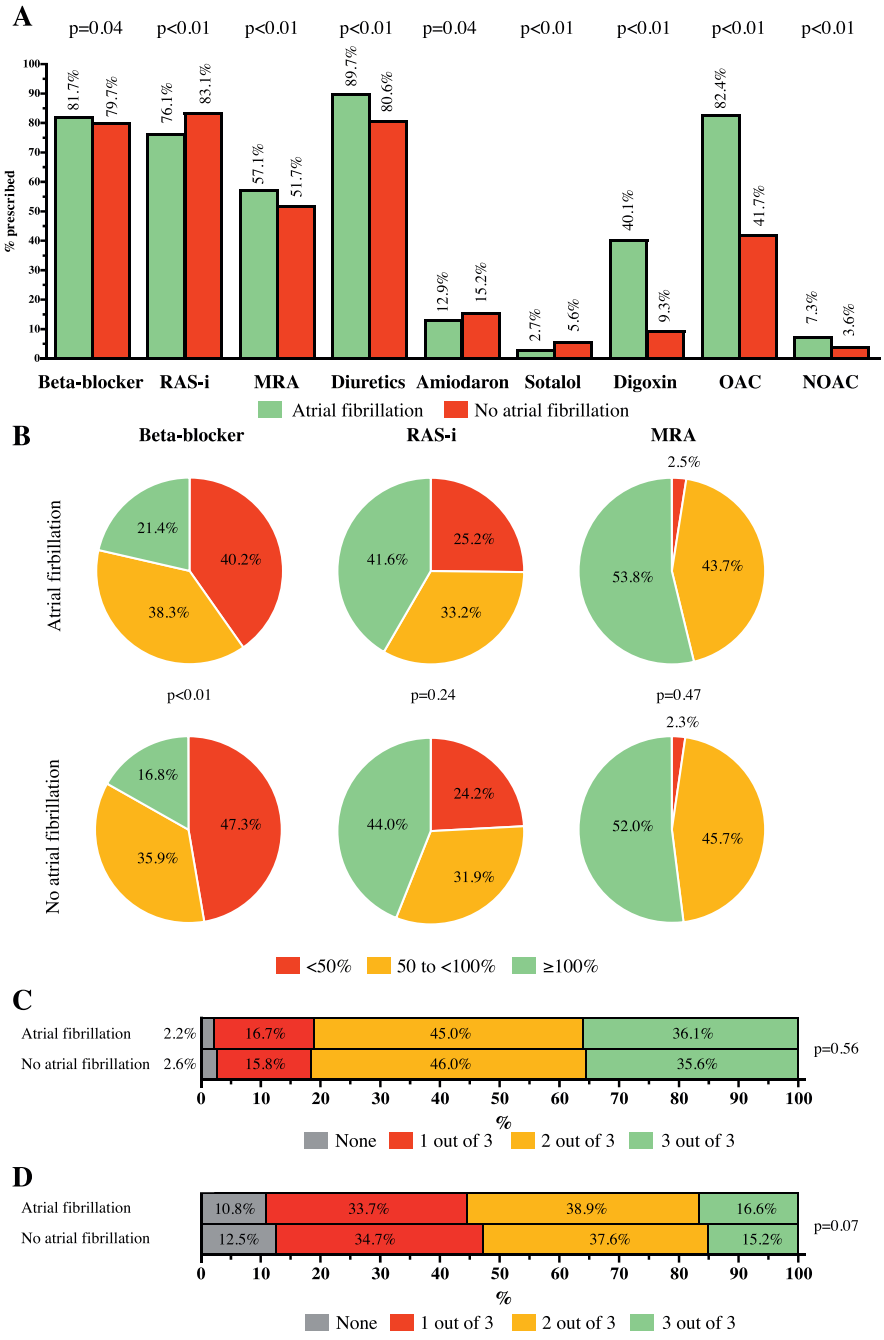

Fig. 1. A Prescription rates of HF therapy, antiarrhythmic drugs and anticoagulation therapy, **B** prescribed dosages of HF therapy expressed as percentage of recommended target dose, **C** combination of beta-blocker, RAS-inhibitor and MRA, **D** and combination of beta-blocker, RAS-inhibitor and MRA at least ≥50% of target dose prescribed, between patients with and without atrial fibrillation.

A sensitivity analysis excluding patients with pacemaker rhythm and ectopic rhythm produced qualitatively similar results with the exception of beta-blockers, which difference was no longer significant (Supplementary Fig. 1).

As shown in Table 2, after adjusting for heart rate, patients with AF had still higher odds of receiving beta-blockers, MRAs, diuretics, digoxin, OACs and NOACs, and lower odds of receiving RAS-inhibitors and sotalol. After additional adjustment for other potential confounders, patients with AF had higher odds of receiving beta-blockers, MRAs, diuretics, digoxin, OACs and NOACs and lower odds of receiving sotalol compared to patients without AF. Multiple imputation did not change the results.

Medical therapy in patients with HFmrEF according to 2016 ESC guidelines

Medical therapy did not differ between patients with HF with mid-range ejection fraction (HFmrEF) and HFrEF in this registry according to the latest HF guidelines. Baseline parameters are shown in Supplementary Table 2. A sub-analysis of only HFmrEF patients showed a similar medical therapy pattern between patients with and without AF as in HFrEF patients (Supplementary Fig. 2).

Baseline characteristics and medical therapy according AF type

Several significant differences in baseline characteristic were observed between the different AF type cohorts, as shown in Supplementary Table 3. Additionally, patients diagnosed with paroxysmal AF and HF received less often HF medical therapy compared to the other AF types, while sotalol and amiodarone were more often prescribed (Supplementary Table 3).

Table 2. Multivariable analysis: the likelihood of receiving HF therapy in patients with AF compared with patients without AF

	Univariable		Multivariable					
	OR	p-value	Model 1		Model 2		Model 3	
			OR	p-value	OR	p-value	OR	p-value
Beta-blocker	1.14 [1.01-1.30]	0.04	1.18 [1.04-1.35]	0.01	1.34 [1.17-1.53]	<0.01	1.34 [1.17-1.54]	<0.01
RAS-inhibitor	0.65 [0.57-0.73]	<0.01	0.72 [0.64-0.82]	<0.01	0.93 [0.82-1.06]	0.28	0.92 [0.80-1.05]	0.19
MRA	1.25 [1.13-1.38]	<0.01	1.28 [1.16-1.42]	<0.01	1.40 [1.26-1.56]	<0.01	1.41 [1.26-1.57]	<0.01
Diuretics	2.09 [1.79-2.44]	<0.01	2.00 [1.71-2.34]	<0.01	1.61 [1.36-1.89]	<0.01	1.63 [1.38-1.92]	<0.01
Amiodarone	0.82 [0.68-0.99]	0.04	0.93 [0.77-1.13]	0.47	0.93 [0.76-1.13]	0.45	0.93 [0.76-1.14]	0.48
Sotalol	0.47 [0.36-0.63]	<0.01	0.53 [0.39-0.70]	<0.01	0.54 [0.40-0.73]	<0.01	0.54 [0.40-0.72]	<0.01
Digoxin	6.53 [5.77-7.38]	<0.01	6.17 [5.44-7.00]	<0.01	6.13 [5.37-6.99]	<0.01	6.16 [5.40-7.03]	<0.01
OAC	6.53 [5.75-7.41]	<0.01	6.60 [5.80-7.51]	<0.01	6.12 [5.36-6.98]	<0.01	6.22 [5.45-7.11]	<0.01
NOAC	2.10 [1.69-2.62]	<0.01	2.09 [1.66-2.62]	<0.01	2.28 [1.80-2.89]	<0.01	2.26 [1.80-2.87]	<0.01

Model 1 included heart rate (per 10 beats/min)

Model 2 included heart rate (per 10 beats/min), age, gender, NYHA classification, left ventricular ejection fraction

Model 3 included heart rate (per 10 beats/min), age, gender, NYHA classification, left ventricular ejection fraction, hypertension, diabetes mellitus, COPD, OSAS, thyroid disease, renal insufficiency (defined as eGFR <60mL/min or a history of renal insufficiency), and atrial fibrillation

AF, Atrial Fibrillation; RAS, Renin-Angiotensin System; MRA, Mineralocorticoid Receptor Antagonists

Discussion

In this large practice-based outpatient registry, one-quarter of the HFrEF patients had documented AF. Patients with AF were significantly older and had more symptomatic HF. The differences in the prescription rates of antiarrhythmic drugs, anticoagulation and guideline-recommended HF therapy according to AF, could not be fully explained by heart rate, age or other patient characteristics. These results provide more insight into the clinical profile of HF patients with AF and the guideline adherence in these patients.

Pharmacological therapy

The efficacy of beta-blockers in chronic HF patients in sinus rhythm has clearly been demonstrated [8], and is reflected in high prescription rates in recent large HF registries [11–13], as well as in this registry. However, the efficacy of beta-blockers in HF patients with AF remains unclear. Several explanations for a different efficacy of beta-blockers in HF patients with AF have been proposed. Studies investigating the relationship between heart rate and mortality outcomes in HF patients reported inconsistent results. Sub-analysis from randomized controlled trials did not show an association between mortality and heart rate [14], while observational cohorts did, although these cohorts are at risk for selection bias [15]. A recent meta-analysis demonstrated that a higher heart rate was not associated with a higher mortality rate in HF patients having AF [16]. Furthermore, differences in structural or cellular function in patients with AF could lead to a difference in the efficacy of beta-blockers in these patients [17]. A higher heart rate could compensate for the loss of the atrial kick in AF patients, and thus reducing the effect of beta-blockers [18]. Moreover, irregularity might be less with a higher heart rate.

In a meta-analysis based on individual patient data of basically all major randomized controlled trials, Rienstra et al. demonstrated that the beta-blockers did not reduce the risk of mortality in HF patients with AF, in contrast to HF patients with sinus rhythm [19]. However, this analysis was published after 2016 and could, therefore, not influence the prescription pattern in CHECK-HF. Additional registries are required to see if this individual patient data basedmeta-analysis influenced the prescription pattern of beta-blockers in HFrEF patients with AF. Multiple other meta-analyses have investigated this relationship with mixed results [6,20]. Several important factors might contribute to the observed differences. Importantly, studies demonstrating a reduction in all-cause mortality in HF patients with AF using beta-blockers were all cohort studies [6]. The risk of inclusion and prescription bias limited the results of these studies.

Furthermore, patients included in the randomized controlled trials were on average more symptomatic patients compared with patients included in the cohort studies. It could be that these less symptomatic patients could tolerate beta-blockers better, and in a higher dose, and therefore benefit more from beta-blockers, although this clearly is not the case in patients with sinus rhythm. In a non-randomized cohort study, a dose-dependent effect of beta-blockers in HF patients with AF has been demonstrated, with the largest reduction of events in patients up titrated to the recommended dosage [21].

RAS-inhibitors are a cornerstone in chronic HF treatment [8], and could be used to prevent the occurrence of new paroxysmal AF episodes in HF patients [22,23]. As shown in our registry, the prescription rate of RAS-inhibitors in both HF patients with and without AF was high, and the observed difference between the groups was explained by significant confounders.

Two studies have compared the efficacy of MRAs in chronic HF patients with and without AF, demonstrating similar effects in the prevention of cardiovascular deaths and HF-related hospitalizations [24,25]. Moreover, MRAs reduced the risk of any future AF event in HF patients, although this was only investigated in a post-hoc analysis [25]. We found that patientswith AFmore often receive MRAs, even after adjustment for several significant confounders. However, prescription rates were relatively low in both groups. Recent registries, investigating the guideline adherence o fMRA in chronic HF patients without AF, showed similar prescription rates between 40 and 60% [13,26]. HF patients with AF might be considered to be sicker and were more often symptomatic, indicated by the higher prevalence of AF in more symptomatic HF patients.

Antiarrhythmic drugs

In chronic HF patients, rhythm control for AF has not been shown to be superior over rate control [27], and adequate rate control prevented unfavorable ventricular remodeling in HF patients [28]. Moreover, in the ESC AF guidelines, it is recommended (Class IA indication) that rate control should be the initial approach in elderly patients with minor AF-related symptoms [7]. Additionally, the ESC HF guidelines recommend reserving rhythm control for HF patients with a reversible cause of AF, or those who do not tolerate AF [8]. This could explain the relatively low prescription rates of amiodarone and sotalol in our registry. Sotalol is considered to be contraindicated in HFrEF, explaining the low prescription rate. However, a substantial portion of HF patients without AF did receive amiodarone and sotalol. These drugs might be prescribed due to ventricular

tachycardia and premature ventricular complexes in patients without AF. Unfortunately, we cannot determine the prescription indication of these medications from our data.

In low dosages, digoxin exerts mainly neurohormonal effects, which could be beneficial primarily for reducing hospitalizations in chronic HF patients without AF [29]. The effect of digoxin in HF patients without AF has been investigated in only one randomized controlled trial [30], and showed a neutral effect on mortality, but a beneficial effect on hospitalizations. Since then, post-hoc analyses fromobservational cohorts demonstrated higher mortality in HF patients without AF treated with digoxin. However, these results are at great risk for prescription bias, with sicker HF patients receiving more often digoxin. Additionally, the use of digoxin in patients with AF without HF is controversial as well, as a meta-analysis demonstrated an association between digoxin use in AF patients and an increased risk of all-cause and cardiovascular mortality [31]. However, these results are based on post-hoc analyses from observational cohorts which are at great risk for prescription bias, with sicker patients more likely to receive digoxin. Therefore, it remains unclear whether it is safe to use digoxin in patientswith both AF and HF. The upcoming DECISION trial (NCT03783429), a multicenter randomized controlled trial, will provide more insight into the effect of digoxin in HF patients with AF.

Anticoagulation therapy

The importance of adequate anticoagulation therapy, in order to prevent stroke, systemic embolism but also excess of bleedings in HF patients with AF, is well known [32]. However, the PINNACLE-AF registry and the EuroHeart survey demonstrated that only approximately 60–70% of HFrEF patients received anticoagulation therapy [33,34]. In contrast, the prescription rates in CHECK-HF were higher, which might be explained by the close monitoring of the Dutch thrombosis service, reducing the risk of potential bleedings. Recently, two meta-analyses showed the efficacy and safety of NOACs in chronic HF patients with AF [35,36]. The prescription rates of NOACs in our registry were very low, reflecting the period of 2013 up to 2016, in which NOACs were just introduced in Dutch clinical practice.We expect that the prescription rates also in HF patients have risen significantly since then. In contrast, the prescription rates of oral anticoagulation therapy were very high in patients with AF.

Limitations and strengths

This practice-based registry has some limitations that should be noted. Due to the cross-sectional design of the registry, no follow-up data on patient outcomes is

available. Also, some data was missing in our study,which could have caused some bias, althoughmultiple imputation did not influence the results. Furthermore, patients were divided based on a 12-lead ECG, performed during the most recent out-patient clinic visit, or a documented history of AF. The history of AF might have been incomplete, and paroxysmal AF patients could have been missed. Additionally, no details on the indication for OAC/NOAC or anti-arrhythmic therapy, such as a history of ventricular arrhythmias, was available. Furthermore, in the newer guidelines [8], HF categories based on LVEF have been changes, our analysis was limited by a small number of patients where LV function was semi-quantitatively analyzed with echocardiography, and some newer treatment strategies, such as the uptake sacubitril/valsartan (substitution for ACE-i/ARB) or NOACs were only in small numbers used in this time period. Still, NOACs improbably influences the already high us of anticoagulation in AF and the use of RAS-inhibitors was high in both patients with and without AF. Therefore, it is unlikely that the conclusions from CHECK-HF are influenced by the focus on the period between 2012 and 2016. The major strengths of this study are the large sample size and the reflection of true clinical practice of the nationwide outpatient HF management, with detailed information on HF medication prescription rate and prescribed dosages.

Conclusion

In this national registry, consisting of 8253 chronic HFrEF patients, significant differences exist in prescription rates of guideline-recommended HF therapy between patients with and without AF. These results show the need for a better understanding of the efficacy and adherence of guideline-recommended HF therapy in patients with AF.

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Supplementary content

Supplementary Table 1 – Target doses of guideline-recommended therapy

Beta-blocker	
Bisoprolol	10 mg
Carvedilol	50 mg
Metoprolol succinate	200 mg
Nebivolol	10 mg
ACE-inhibitor	
Captopril	150 mg
Enalapril	20 mg
Lisinopril	40 mg
Ramipril	10 mg
Perindopril	8 mg
ARB	
Candesartan	32 mg
Losartan	150 mg
Valsartan	320 mg
MRA	
Eplerenone	50 mg
Spironolactone	25 mg

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist

Supplementary Table 2. Patient characteristics of HFrEF, HFmrEF and semi-quantitative patients with and sinus rhythm according to 2016 ESC HF guidelines

	HFrEF (n=5,625)			HFmrEF (n=1,559)			Semi-quantitative (n=1,069)		
	Patients with AF (n=1,258)	Patients without AF (n=4,367)	p-value	Patients with AF (n=534)	Patients without AF (n=1,025)	p-value	Patients with AF (n=317)	Patients without AF (n=752)	p-value
Age (years)	75.9 ± 9.3	70.1 ± 12.1	<0.01	78.2 ± 8.5	71.4 ± 12.3	<0.01	78.6 ± 9.4	73.3 ± 11.6	<0.01
Male gender	871 (69.5)	2,850 (65.6)	0.01	298 (55.8)	612 (59.9)	0.12	197 (63.1)	430 (57.6)	0.09
BMI, kg/m2	27.1 ± 5.0	27.1 ± 5.0	0.34	27.5 ± 5.4	27.5 ± 5.4	0.90	26.7 ± 5.0	26.8 ± 5.2	0.74
NYHA									
I	139 (11.2)	682 (15.8)		50 (9.5)	231 (22.8)		43 (13.8)	146 (19.8)	
II	673 (54.3)	2,538 (58.7)	<0.01	307 (58.1)	538 (53.0)	<0.01	174 (55.9)	414 (56.0)	0.06
III	394 (31.8)	1,032 (23.9)		164 (31.1)	226 (22.3)		90 (28.9)	173 (23.4)	
IV	34 (2.7)	75 (1.7)		7 (1.3)	20 (2.0)		4 (1.3)	6 (0.8)	
LVEF, %	31.2 ± 9.8	28.8 ± 8.7	<0.01	45.4 ± 5.8	44.9 ± 5.1	0.10	-	-	-
Cause of HF									
Ischemic	667 (55.8)	2,363 (56.0)	<0.01	183 (35.6)	501 (50.5)	<0.01	131 (41.6)	408 (55.1)	<0.01
Non-ischemic	536 (44.2)	1,860 (44.0)		331 (64.4)	492 (49.5)		184 (58.4)	332 (44.9)	
Systolic BP, mmHg	123.3 ± 20.0	124.7 ± 20.3	0.03	126.3 ± 20.5	131.1 ± 21.9	<0.01	125.4 ± 20.6	127.1 ± 21.4	0.22
Diastolic BP, mmHg	71.8 ± 12.0	71.0 ± 11.0	0.04	71.7 ± 12.6	71.8 ± 11.7	0.84	70.9 ± 11.3	70.0 ± 10.8	0.24
Heart rate, bpm	77.2 ± 16.8	70.4 ± 12.3	<0.01	77.4 ± 16.5	69.9 ± 12.3	<0.01	75.8 ± 15.6	70.2 ± 11.9	<0.01
QRS ≥130 ms	379 (36.3)	1,690 (45.0)	<0.01	113 (26.4)	300 (33.9)	0.01	57 (25.4)	218 (38.9)	0.01
eGFR	60.1 ± 25.0	61.7 ± 24.9	0.08	53.8 ± 22.2	57.6 ± 24.3	0.01	53.2 ± 22.5	55.7 ± 23.1	0.18
eGFR									

Supplementary Table 2. *(continued)*

	HFrEF (n=5,625)			HFmrEF (n=1,559)			Semi-quantitative (n=1,069)		
	Patients with AF (n=1,258)	**Patients without AF (n=4,367)**	**p-value**	**Patients with AF (n=534)**	**Patients without AF (n=1,025)**	**p-value**	**Patients with AF (n=317)**	**Patients without AF (n=752)**	**p-value**
<30	98 (10.7)	325 (10.1)		47 (13.0)	83 (13.8)		35 (16.7)	67 (13.0)	
30-59	390 (42.8)	1,260 (39.2)	0.08	186 (51.5)	250 (41.5)	0.01	95 (45.2)	229 (44.6)	0.35
≥60	424 (46.5)	1,629 (50.7)		128 (35.5)	269 (44.7)		80 (38.1)	218 (42.4)	
Comorbidity									
Hypertension	493 (43.4)	1,432 (37.0)	<0.01	222 (46.3)	393 (42.5)	0.17	128 (44.8)	281 (40.2)	0.19
Diabetes Mellitus	352 (31.0)	1,107 (28.6)	0.12	145 (30.3)	250 (27.1)	0.20	92 (32.2)	202 (28.9)	0.31
COPD	203 (17.9)	690 (17.8)	0.97	100 (20.9)	189 (20.5)	0.85	55 (19.2)	135 (19.3)	0.98
OSAS	71 (6.2)	246 (6.4)	0.90	33 (6.9)	83 (9.0)	0.18	16 (5.6)	42 (6.0)	0.80
Thyroid disease	92 (8.1)	273 (7.0)	0.23	40 (8.4)	70 (7.6)	0.61	28 (9.8)	48 (6.9)	0.12
Renal insufficiency †	701 (61.8)	2,002 (52.6)	<0.01	310 (67.4)	429 (57.1)	<0.01	145 (62.8)	314 (57.6)	0.18
No relevant comorbidity	118 (11.5)	541 (16.0)	<0.01	21 (5.1)	74 (11.2)	<0.01	19 (9.0)	67 (13.5)	0.10
Previous interventions									

Supplementary Table 2. *(continued)*

	HFrEF (n=5,625)			HFmrEF (n=1,559)			Semi-quantitative (n=1,069)		
	Patients with AF (n=1,258)	**Patients without AF (n=4,367)**	**p-value**	**Patients with AF (n=534)**	**Patients without AF (n=1,025)**	**p-value**	**Patients with AF (n=317)**	**Patients without AF (n=752)**	**p-value**
PCI	202 (19.3)	966 (27.0)	<0.01	63 (15.7)	210 (28.4)	<0.01	45 (20.5)	172 (31.4)	<0.01
CABG	230 (22.0)	761 (21.3)	0.60	82 (20.4)	175 (23.7)	0.21	51 (23.2)	151 (27.6)	0.21
Valve intervention	112 (10.7)	228 (6.4)	<0.01	42 (10.4)	68 (9.2)	0.50	19 (8.6)	54 (9.9)	0.60
Cardiac rhythm									
Sinus rhythm	3,432 (78.6)	-		857 (83.6)	-		612 (81.4)	-	
Ectopic rhythm	85 (1.9)	-		13 (1.3)	-		4 (0.5)	-	
Pacemaker rhythm	850 (19.5)	-		155 (15.1)	-		136 (18.1)	-	
Paroxysmal AF	-	204 (16.2)	-	-	66 (12.4)	-	-	35 (11.0)	-
Persisted AF	-	245 (19.5)		-	103 (19.3)		-	22 (6.9)	
Permanent AF	-	669 (53.2)		-	277 (51.9)		-	170 (53.6)	
AF of unknown type	-	140 (11.1)		-	88 (16.5)		-	90 (28.4)	

HFrEF, Heart Failure with reduced Ejection Fraction; HFmrEF, Heart Failure with mid-range Ejection Fraction; AF, Atrial Fibrillation; BMI, Body Mass Index; NYHA, New York Heart Association classification; LVEF, Left Ventricular Ejection Fraction; HF, Heart Failure; BP, Blood Pressure; LBBB, eGFR, estimated Glomerular Filtration Rate; COPD, Chronic Obstructive Pulmonary Disease; OSAS, Obstructive Sleep Apnea Syndrome; PCI, Percutaneous Coronary Intervention; CABG, Coronary Artery Bypass Graft.
† Defined as eGFR <60mL/min or a history of renal failure

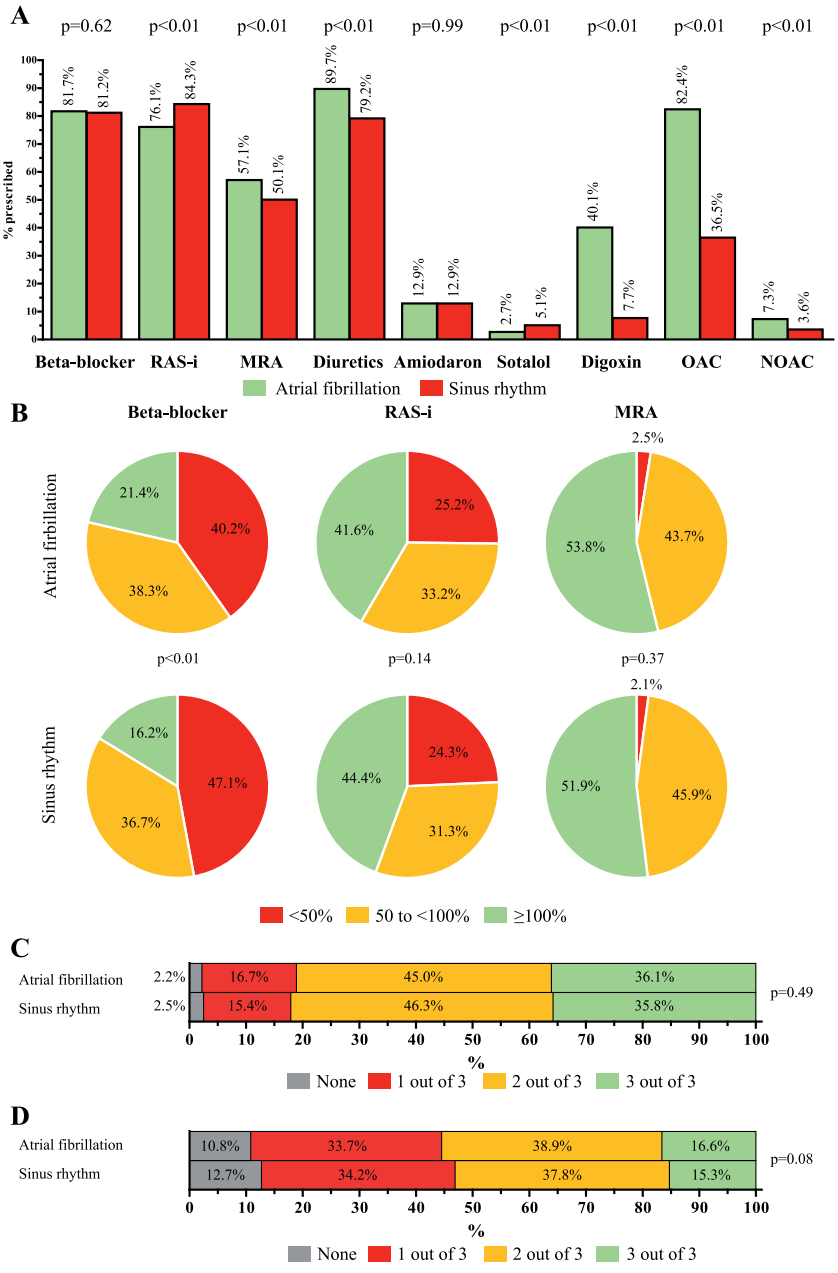
Supplementary Table 3. Patient characteristics of patients with, paroxysmal, persistent, permanent AF or AF of unknown type.

	Paroxysmal AF (n=305)	Persistent AF (n=370)	Permanent AF (n=1,116)	AF of unknown type (n=318)	p-value
Age (years)	76.0±9.6	76.7±8.9	77.6±8.7	75.1±10.2	<0.01
Male gender	200 (65.8)	242 (65.6)	704 (63.5)	220 (69.2)	0.30
BMI, kg/m2	26.9±5.5	57.5±5.1	27.1±5.0	26.9±5.1	0.34
NYHA					
I	35 (11.6)	20 (5.6)	74 (6.7)	103 (32.5)	<0.01
II	164 (54.3)	223 (61.9)	631 (57.4)	136 (42.9)	
III	90 (29.8)	111 (30.8)	374 (34.0)	73 (23.0)	
IV	13 (4.3)	6 (1.7)	21 (1.9)	5 (1.6)	
LVEF, %	32.7±10.7	33.2±8.1	36.0±11.3	35.9±10.1	<0.01
Cause of HF					
Ischemic	162 (54.4)	149 (41.6)	410 (38.4)	129 (40.6)	<0.01
Non-ischemic	136 (45.6)	209 (58.4)	658 (61.6)	189 (59.4)	
Systolic BP, mmHg	125.5±20.5	125.2±21.9	121.4±18.5	133.0±21.1	<0.01
Diastolic BP, mmHg	71.2±11.8	71.5±12.9	70.2±10.3	77.2±15.0	<0.01
Heart rate, bpm	73.2±16.1	76.3±17.7	77.1±15.7	81.4±18.6	<0.01
QRS ≥130 ms	80 (33.5)	109 (31.7)	270 (33.8)	90 (28.7)	0.41
eGFR	61.9±27.2	55.2±21.5	57.4±24.2	51.8±17.3	<0.01
eGFR					
<30	31 (12.2)	28 (12.1)	114 (12.3)	7 (10.1)	0.06
30-59	99 (38.8)	109 (47.0)	421 (45.4)	42 (60.9)	
≥60	125 (49.0)	95 (40.9)	392 (42.3)	20 (29.0)	
Comorbidity					
Hypertension	115 (40.1)	150 (43.4)	459 (47.4)	119 (39.7)	0.04
Diabetes Mellitus	88 (30.7)	109 (31.5)	319 (32.9)	73 (24.3)	0.05
COPD	46 (16.0)	66 (19.1)	202 (20.8)	44 (14.7)	0.06
OSAS	15 (5.2)	26 (7.5)	57 (5.9)	22 (7.3)	0.52
Thyroid disease	29 (10.1)	9 (2.6)	83 (8.6)	39 (13.0)	<0.01
Renal insufficiency †	192 (63.2)	217 (59.5)	698 (64.2)	49 (70.0)	0.25
No relevant comorbidity	26 (9.1)	46 (13.3)	86 (8.9)	0 (0.0)	0.01
Previous interventions					
PCI	66 (24.7)	40 (11.4)	151 (16.2)	53 (45.3)	<0.01
CABG	69 (25.8)	64 (18.2)	171 (18.4)	59 (50.4)	<0.01

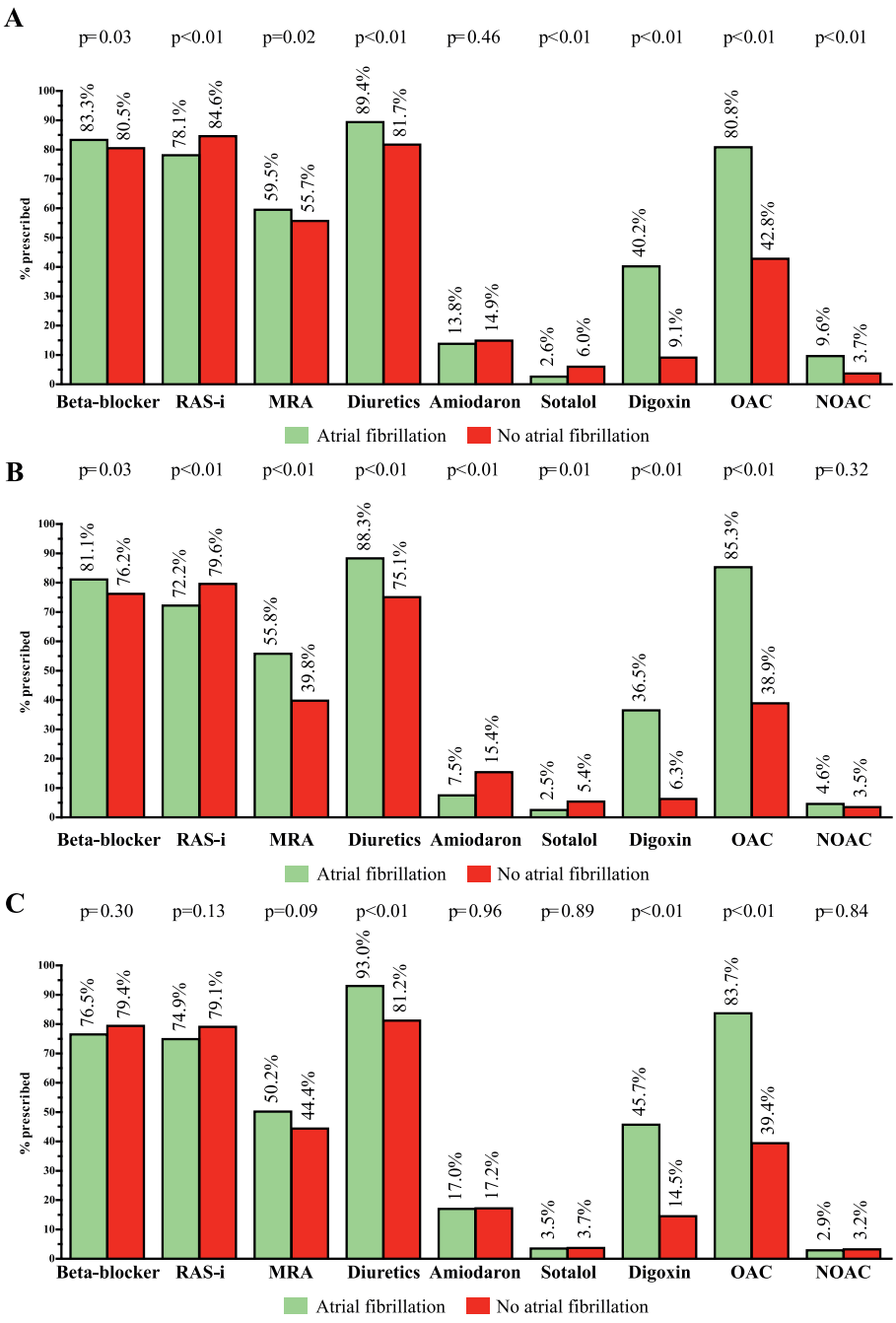
Supplementary Table 3. *(continued)*

	Paroxysmal AF (n=305)	Persistent AF (n=370)	Permanent AF (n=1,116)	AF of unknown type (n=318)	p-value
Valve intervention	27 (10.1)	23 (6.6)	90 (9.7)	33 (28.2)	<0.01
Therapy					
Beta-blocker	233 (76.6)	316 (85.4)	904 (81.1)	255 (84.7)	0.01
RAS-inhibitor	223 (73.4)	291 (78.6)	834 (74.8)	243 (80.7)	0.07
MRA	164 (53.9)	250 (67.6)	686 (61.5)	94 (31.2)	<0.01
Diuretics	265 (87.5)	334 (90.3)	1,025 (92.0)	248 (82.4)	<0.01
Amiodarone	49 (20.8)	18 (18.6)	72 (7.7)	28 (100.0)	<0.01
Digoxin	79 (26.0)	157 (42.4)	464 (41.6)	138 (45.8)	<0.01
Sotalol	21 (6.9)	4 (1.1)	28 (2.5)	4 (1.3)	<0.01
OAC	207 (71.4)	317 (92.4)	924 (83.4)	217 (77.5)	<0.01
NOAC	36 (12.4)	14 (4.1)	92 (8.3)	6 (2.1)	<0.01
ICD	54 (20.2)	29 (8.3)	116 (12.2)	56 (67.5)	<0.01
CRT	25 (9.4)	9 (2.6)	47 (4.9)	39 (47.0)	<0.01

HFrEF, Heart Failure with reduced Ejection Fraction; HFmrEF, Heart Failure with mid-range Ejection Fraction; AF, Atrial Fibrillation; BMI, Body Mass Index; NYHA, New York Heart Association classification; LVEF, Left Ventricular Ejection Fraction; HF, Heart Failure; BP, Blood Pressure; LBBB, eGFR, estimated Glomerular Filtration Rate; COPD, Chronic Obstructive Pulmonary Disease; OSAS, Obstructive Sleep Apnea Syndrome; PCI, Percutaneous Coronary Intervention; CABG, Coronary Artery Bypass Graft.
† Defined as eGFR <60mL/min or a history of renal failure



Supplementary Figure 1 – **A** Prescription rates of HF therapy, antiarrhythmic drugs and anticoagulation therapy, **B** prescribed dosages of HF therapy expressed as percentage of recommended target dose, **C** combination of beta-blocker, RAS-inhibitor and MRA, **D** and combination of beta-blocker, RAS-inhibitor and MRA at least ≥50% of target dose prescribed, between patients with atrial fibrillation (n=2,109) and sinus rhythm (n=4,901)



Supplementary Figure 2 – **A** Prescription rates of HF therapy, antiarrhythmic drug and anticoagulation therapy in HFrEF (LVEF<40%) (n=5,625), **B** HFmrEF (LVEF 40-49%) (n=1,559) and **C** semi-quantitative patients (n=1,069) according to the 2016 ESC guidelines

7

Diabetes and contemporary treatment for chronic heart failure in a large real-world heart failure population

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Under embargo

Submitted

8

Differences in guideline-recommended heart failure medication between Dutch heart failure clinics: an analysis of the CHECK-HF registry

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* Equal contributions

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Abstract

Background: Heart failure (HF) is associated with poor prognosis, high morbidity and mortality. The prognosis can be optimised by guideline adherence, which also can be used as a benchmark of quality of care. The purpose of this study was to evaluate differences in use of HF medication between Dutch HF clinics.

Methods: The current analysis was part of a crosssectional registry of 10,910 chronic HF patients at 34 Dutch outpatient clinics in the period of 2013 until 2016 (CHECK-HF), and focused on the differences in prescription rates between the participating clinics in patients with heart failure with reduced ejection fraction (HFrEF).

Results: A total of 8,360 HFrEF patients were included with a mean age of 72.3± 11.8 years (ranging between 69.1± 11.9 and 76.6± 10.0 between the clinics), 63.9% were men (ranging between 54.3 and 78.1%), 27.3% were in New York Heart Association (NYHA) class III/IV (ranging between 8.8 and 62.1%) and the average estimated glomerular filtration rate (eGFR) was 59.6± 24.6ml/min (ranging between 45.7± 23.5 and 97.1± 16.5). The prescription rates ranged from 58.9–97.4% for beta blockers ($p< 0.01$), 61.9–97.1% for renin-angiotensin system(RAS) inhibitors ($p< 0.01$), 29.9–86.8% for mineralocorticoid receptor antagonists (MRAs) ($p< 0.01$), 0.0–31.3% for ivabradine ($p< 0.01$) and 64.9–100.0% for diuretics ($p< 0.01$). Also, the percentage of patients who received the target dose differed significantly, 5.9–29.1% for beta blockers ($p< 0.01$), 18.4–56.1% for RAS inhibitors ($p< 0.01$) and 13.2–60.6% for MRAs ($p< 0.01$).

Conclusions: The prescription rates and prescribed dosages of guideline-recommended medication differed significantly between HF outpatient clinics in the Netherlands, not fully explained by differences in patient profiles.

Introduction

Heart failure (HF) is associated with a high symptom burden, morbidity and mortality [1–3]. Optimising guideline-recommended HF therapies improve health-related quality of life and prognosis [4–6]. However, in real-world practice, implementation and adherence to recommended treatment, a benchmark of quality of care, are suboptimal. A recent analysis of medication profiles of 22,476 unselected patients with a diagnosis of HF at hospital discharge between 2001 and 2015 derived from the Dutch PHARMO Database Network showed only partial improvement of prescribed HF medication over time [7]. The percentage of patients prescribed the combination of a beta blocker and an angiotensin-converting-enzyme (ACE) inhibitor or angiotensin receptor blocker increased from 24 to approximately 45% within this 15-year period. The percentage of patients who also used a mineralocorticoid receptor antagonist (MRA) reached approximately 20%. Notably, the probability of being prescribed these combinations decreased with increasing age and there was no significant increase in MRA prescriptions. Moreover, recent real-world registries demonstrated underuse of HF therapies despite clear evidence-based recommendations [8–10].

In fact, randomised clinical trials and surveys did not represent real-life HF populations [11–13]. Moreover, the distribution of recommended HF treatment and considerable practice variation between regions and hospitals are largely unexplained, but also unexplored.

In a large-scale real-world registry at Dutch HF outpatient clinics, we therefore investigated the differences in medical HF therapies and determinants of prescription of individual, recommended HF drugs in HFrEF patients [14, 15] among 34 HF clinics in the Netherlands.

Methods

The design and methods of the CHECK-HF (Chronic Heart failure ESC guideline-based Cardiology practice Quality project) registry have been published in detail earlier [14]. Briefly, the CHECK-HF registry consists of 10,910 patients with chronic HF froma total of 34 participating centres (40% of the 86 centres in the Netherlands of which 60 have an outpatient HF unit) (Fig. 1). Patients were included cross-sectionally based on the available records of these patients. Between 2013 and 2016, all participating centres included patients diagnosed with HF based on the 2012 ESC guidelines on HF (i.e. based

on symptoms and echo parameters) who were seen at the outpatient HF clinic (96%) or general cardiology outpatient clinic (4%) if no specific HF clinic was present.

Fig. 1 Geographical distribution of the 34 participating clinics of the CHECK-HF registry in the Netherlands

Baseline patient characteristics, aetiology of HF, comorbidities, basic echocardiographic and electrocardiographic (ECG) parameters, laboratory markers, pacemaker, implantable cardioverter-defibrillator treatment and cardiac resynchronisation therapy as well as prescription rates of medication (drug name, dosage and frequency and total daily dose) were recorded. The target doses of guideline-recommended HF medication are presented in Suppl. Table 1. Drug doses were calculated compared with

the recommended dose and according to guidelines as a daily dose or %, percentage of actual recommended daily dose.

Furthermore, contraindications and intolerance as indicated by the treating physician were collected. No predefined rules were applied to determine absolute contraindications.

In 283 (2.6%) patients, recording of ejection fraction in the database was insufficient to classify patients, so these patients were excluded from this analysis.

Based on echocardiographic results, the remaining 10,627 patients were divided based on left ventricular ejection fraction (LVEF) or visual assessment of the function of the left ventricle into HF with preserved ejection fraction (HFpEF) (LVEF ≥50%, n= 2,267 (21%)) and HF with reduced ejection fraction (HFrEF: LVEF <50%, n= 8,360 (79%)), according to the 2012 ESC HF guidelines [4].

For a sub-analysis according to the newer 2016 ESC HF guidelines, patients with an assessed LVEF <50% were categorised into HF with mid-range ejection fraction (HFmrEF) (LVEF 40–49%, n= 1,574 (19%)), HFrEF (LVEF <40%, n= 5,701 (68%)), and into HF with a semi-quantitative analysis of the systolic left ventricular function only (n= 1,085 (13%)). In the current analyses, we focused on the prescribed HF medication in HFrEF patients (LVEF <50%).

The Medical Research Ethics Committee of the Maastricht University Medical Center, the Netherlands, provided ethical approval for anonymously analysing existing patient data. No informed consent of the participants in this registry was required.

Statistics

Continuous data are expressed as mean value± standard deviation (SD) or median and interquartile range, depending on the distribution of the data, and compared by applying one-way analysis of variances (ANOVA) or Mann-Whitney U test as appropriate. Categorical data are expressed as counts and percentages, and compared by the Pearson chi-squared test. A two-sided p-value of 0.05 was considered statistically significant. Multivariable predictors for the use of HF medication associated with the hospital-ranked prescription of HF medication (beta blocker, renin-angiotensin system [RAS] inhibitor, MRA, ivabradine and diuretics, respectively) were sought, using multivariable logistic regression analysis, using the stepwise forward procedure. All predictors of medication use in univariable analysis at a p-value of <0.10 were included

in the multivariable regression analysis. Results of logistic regression are presented as odds ratios (ORs) and confidence intervals (CIs).

All analyses were performed with SPSS Statistical Package version 25.0 (SPSS Inc, Chicago, Illinois).

Results

Baseline characteristics of the total group of 8,360 HFrEF patients are shown in Table 1. Mean age was 72.3± 11.8 years (ranging between 69.1± 11.9 and 76.6± 10.0 between the clinics), 63.9% were men (ranging between 54.3 and 78.1%), 27.3% were in New York Heart Association (NYHA) class III/IV (ranging between 8.8 and 62.1%) and the average estimated glomerular filtration rate (eGFR) was 59.6± 24.6ml/min (ranging between 45.7± 23.5 and 97.1± 16.5). Between centres, a wide range of prevalence rates with regard to ischaemic aetiology of HF, atrial fibrillation and comorbidities were found, as presented in Table 1. When subdividing HF patients in LVEF groups according to ESC guidelines 2016, HFmrEF patients (n= 1,574) were more often female, had less often ischaemic aetiology, less wide QRS complex and more often atrial fibrillation, hypertension and chronic obstructive pulmonary disease (COPD), all compared with HFrEF patients (n= 5,701). However, in both groups, there was a wide variation of all baseline characteristics between centres (Suppl. Tables 2 and 3).

Table 1. Baseline characteristics of HFrEF patients (LVEF<50%) and range between centers

	Overall population	**Range**
Number of patients	8,360	32; 1,549
Age (years) (n=8,351)	72.27±11.8	69.1±11.9; 76.6±10.0
Male gender (n=8,323)	5,320 (63.9)	54.3; 78.1
BMI, kg/m2 (n=7,671)	27.2±5.2	26.2±4.7; 28.4±5.1
NYHA (n=8,262)		
I	1,313 (15.9)	0.0; 45.5
II	4,692 (56.8)	35.0; 88.1
III	2,108 (25.5)	8.8; 60.0
IV	149 (1.8)	0.0; 9.6
LVEF, % (n=6,179)	32.6±10.5	28.4±10.5; 44.2±16.0
Cause of HF (n=8,094)		
Ischemic cause of HF	4,182 (51.7)	34.9; 63.4
Non-ischemic cause of HF	3,912 (48.3)	36.6; 65.1

Table 1. *(continued)*

	Overall population	Range
Systolic BP, mmHg (n=8,246)	125.7±20.7	113.8±19.6; 135.4±22.7
Diastolic BP, mmHg (n=8,252)	71.2±11.4	64.9±10.4; 75.1±12.9
Heart rate, bpm (n=8,248)	72.0±13.9	64.7±8.0; 76.7±17.1
Atrial fibrillation (n=8,253)	2,109 (25.6)	12.2; 50.0
LBBB (n=8,360)	1,414 (16.9)	0.0; 30.2
QRS ≥130 ms (n=6,936)	2,774 (40.0)	0.0; 53.5
eGFR (n=5,883)	59.6±24.6	45.7±23.5; 97.1±16.5
eGFR (n=5,883)		
<30	667 (11.3)	0.0; 27.3
30-59	2,442 (41.5)	0.0; 54.5
≥60	2,774 (47.2)	18.2; 100.0
Comorbidity (n=7,488)		
Hypertension	2,978 (39.8)	7.8; 75.5
Diabetes Mellitus	2,174 (29.0)	16.7; 51.0
COPD	1,381 (18.4)	9.5; 29.9
OSAS	495 (6.6)	0.0; 14.1
Thyroid disease	557 (7.4)	0.6; 11.8
Renal insufficiency [a]	3,950 (56.3)	30.5; 78.9
No relevant comorbidity	855 (13.6)	0.0; 28.3

[a] Defined as eGFR <60ml/min or a history of renal failure

BMI body mass index, *NYHA* New York Heart Association classification, *LVEF* left ventricular ejection fraction, HF heart failure, *HFrEF* HF with reduced ejection fraction, *HFmrEF* HF with mid-range ejection fraction, *HFpEF* HF with preserved ejection fraction, *BP* blood pressure, *LBBB* left bundle branch block, *eGFR* estimated glomerular filtration rate, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *COPD* chronic obstructive pulmonary disease, *OSAS* obstructive sleep apnoea syndrome

Guideline-recommended medical therapy in HFrEF

The prescription rates ranged between centres from 58.9–97.4% for beta blocker according to ESC guidelines 2012 (p< 0.01), 61.9–97.1% for renin-angiotensin system (RAS) inhibitors (p< 0.01), 29.9–86.8% for MRA (p< 0.01), 0.0–31.3% for ivabradine (p< 0.01) and 64.9–100.0% for diuretics (p< 0.01), see Table 2 and Fig. 2. In symptomatic HF patients (NYHA class II–IV), guideline-recommended medication only slightly differed from the total HFrEF group (Suppl. Table 4).

Table 2. Prescription rates of HF medication according to ESC Guidelines 2012 versus 2016 per participating clinic (n=34)

		Guideline-recommended pharmacotherapy (average % (min.-max.))				
		Beta-blocker	**RAS-inhibitor**	**MRA**	**Ivabradine**	**Diuretics**
ESC Guidelines 2012	HFrEF	80.1 (58.9-97.4)	81.2 (61.9- 97.1)	53.0 (29.9-86.8)	4.6 (0.0-31.3)	82.8(64.9-100.0)
ESC Guidelines 2016	HFrEF	81.0 (63.6-96.0)	83.2 (65.3-97.4)	56.4 (34.1-88.0)	5.4 (0.0-31.0)	83.4 (65.4-100.0)
	HFmrEF	77.7 (30.8-100.0)	76.8 (33.3-100.0)	45.1 (22.2-100.0)	3.1 (0.0-33.3)	79.5 (58.3-100.0)
	HFsemiq	78.6 (0.0-100.0)	77.6 (0.0-100.0)	46.3(0.0-100.0)	2.5 (0.0-30.8)	84.8 (0.0-100.0)

HF heart failure, *HFrEF* HF with reduced ejection fraction, *HFmrEF* HF with mid-range ejection fraction, *HFsemiq* HF with semiquantitatively estimated left ventricular ejection fraction—though <50%, *ESC* European Society of Cardiology, *RAS* renin-angiotensin system, *MRA* mineralocorticoid receptor antagonists

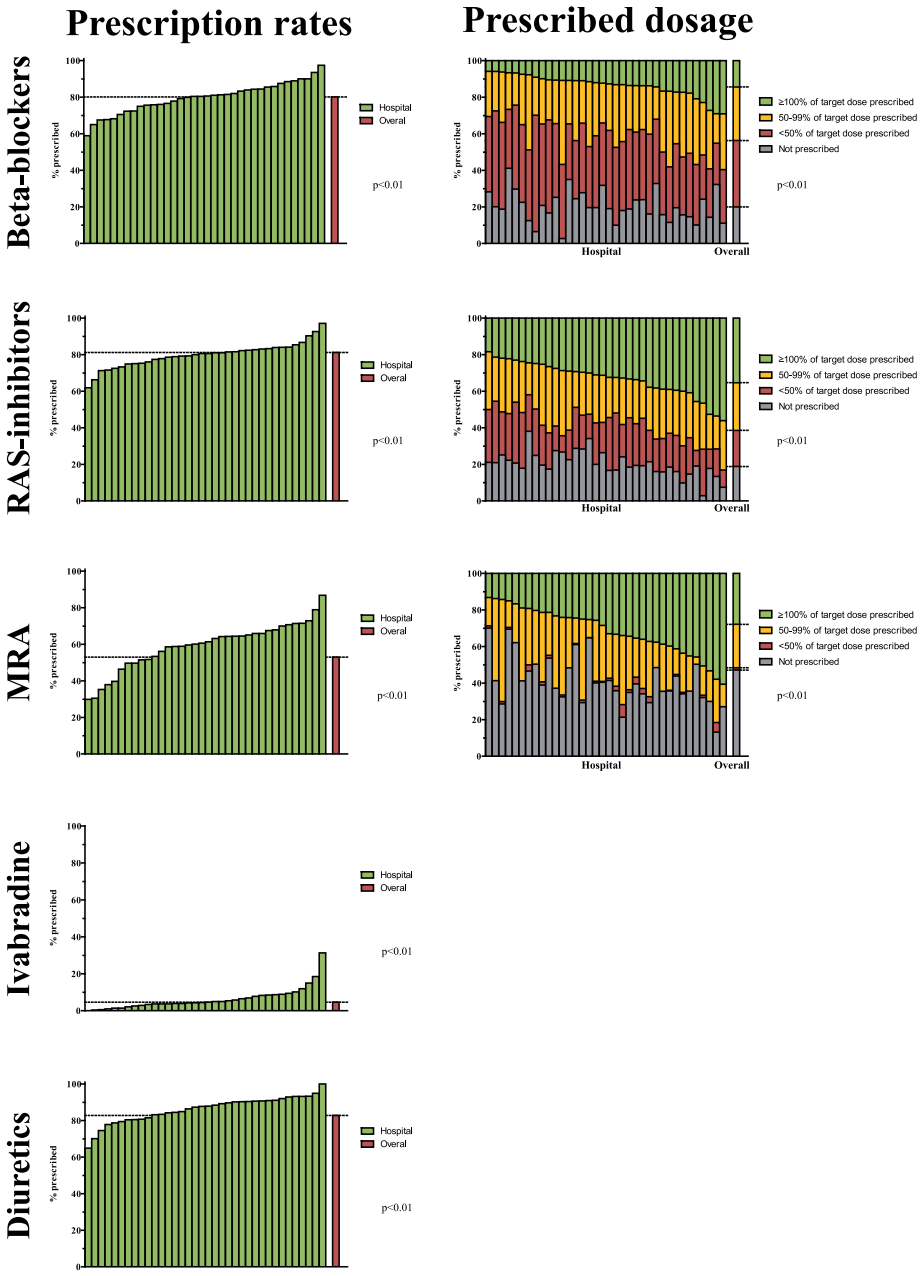

Fig. 2 Prescription rates and prescribed dosages of HFmedication in HFrEF patients (LVEF <50%) per participating clinic (n= 34) (The left panels show the order of hospitals on the x-axis based on the percentage of prescription rate of each drug. The red bar is the overall presciption rate (%) and the green bars are the prescription rates (%) in each clinic. The same order is shown in the panels on the right.) (*HF* heart failure, *HFrEF* heart failure with reduced ejection fraction, *LVEF* left ventricular ejection fraction, *RAS* renin-angiotensin system, *MRA* mineralocorticoid receptor antagonists)

Dual therapy (beta blocker and RAS inhibitor) was prescribed in average 66.3% (min. 47.7 to max. 80.5) of HFrEF patients, one out of two in 28.7% (15.6–43.7) and none in 5.0% (0.9–13.5) respectively. Triple therapy (beta blocker, RAS inhibitor and MRA) was prescribed in average 35.6% (16.1–68.4) of HFrEF patients, two out of three in 45.7% (28.9–58.9), one out of three in 16.1% (0.0–24.7) and none in 2.6% (0.0–6.9) respectively. Also, the percentage of patients who received the target dose differed significantly, 5.9–29.1% for beta blocker ($p< 0.01$), 18.4–56.1% for RAS inhibitor ($p< 0.01$) and 13.2–60.6% for MRA ($p< 0.01$).

HFrEF patients seen at HF clinics received more often beta blockers, MRA, ivabradine and diuretics in comparison with those seen in general cardiology outpatient clinics, although rates of prescribed of RAS inhibitors were similar (Suppl. Table 5). Women with HFrEF less often received RAS inhibitors (79% vs 83%), but more often beta blockers (82% vs 79%) as compared with men. MRA were given in 53% of patients, both men and women (Suppl. Table 6).

Multivariable analysis of hospitals showed that the differences in prescribed HF medication between centres cannot be explained by clinical variables (Table 3, see Suppl. Table 7 for univariable analysis).

According to ESC guidelines 2016, the prescription rates inHF patients with LVEF <40%, both overall and ranges between centres of prescription rates of HF medication, were not different in a clinically meaningful way from HF with LVEF <50%.

Medical treatment of HFmrEF and semi-quantitative patients

The distribution of beta blockers, RAS inhibitors and MRA in HFmrEF and semi-quantitative patients are shown in Table 2. Both overall prescription rates and ranges between centres did not differ in a clinically meaningful way from those in HFrEF patients. Also, in all LVEF groups, there was a wide range of prescribed dosages of HF medication percentages between centres (Suppl. Fig. 1, 2 and 3).

Table 3 Multivariable analysis of hospital differences in medical treatment of HFrEF patients (LVEF <50%)

		Beta-blocker OR [95% CI]	RAS-inhibitor OR [95% CI]	MRA OR [95% CI]	Ivabradine OR [95% CI]	Diuretics OR [95% CI]
Univariable	Hospital	1.05 [1.04-1.05]	1.04 [1.04-1.04]	1.06 [1.06-1.06]	1.09 [1.08-1.10]	1.06 [1.06-1.06]
Multivariable	Hospital	1.05 [1.04-1.06]	1.05 [1.04-1.06]	1.06 [1.05-1.07]	1.09 [1.07-1.10]	1.04 [1.03-1.05]
	Gender	1.20 [1.02-1.40]	-	-	-	1.31 [1.06-1.61]
	Age (per 10 years)	0.83 [0.78-0.89]	0.79 [0.72-0.87]	0.87 [0.83-0.91]	0.61 [0.56-0.67]	1.14 [1.04-1.25]
	BMI	-	1.04 [1.02-1.06]	1.02 [1.01-1.03]	-	1.06 [1.04-1.08]
	Systolic BP (per 10 mmHg)	-	-	0.84 [0.82-0.87]	-	0.93 [0.87-1.00]
	Diastolic BP (per 10 mmHg)	-	-	-	0.88 [0.79-0.98]	0.89 [0.80-1.00]
	NYHA classification	-	0.72 [0.63-0.82]	1.17 [1.08-1.27]	1.26 [1.05-1.50]	1.53 [1.30-1.80]
	Heart rate (per 10 beats/min)	-	0.84 [0.79-0.89]	-	-	1.12 [1.04-1.21]
	QRS duration (per 10 ms)	-	0.97 [0.95-0.99]	1.04 [1.02-1.05]	-	1.32 [1.01-1.72]
	eGFR (per 10 ml/min)	-	1.06 [1.01-1.11]	-	-	
	Ischemic etiology	-	0.76 [0.60-0.97]	-	-	
	Hypertension	1.22 [1.05-1.42]	-	-	-	
	Diabetes mellitus II	-	-	-	1.58 [1.21-2.08]	1.42 [1.11-1.81]
	COPD	-	-	-	1.58 [1.21-2.08]	1.32 [1.01-1.72]
	Renal insufficiency [a]	-	-	-	-	2.50 [2.03-3.09]

– variable not included in the model

LVEF left ventricular ejection fraction, *HF* heart failure, *HFrEF* HF with reduced ejection fraction, *OR* odds ratio, *CI* confidence interval, *RAS* renin-angiotensin system, *MRA* mineralocorticoid receptor antagonists, *BMI* body mass index, *NYHA* New York Heart Association, *BP* blood pressure, *eGFR* estimated glomerular filtration rate, *COPD* chronic obstructive pulmonary disease

[a] Defined as eGFR <60ml/min or a history of renal failure

Discussion

From our outpatient HF registry in a representative number of centres in the Netherlands, we demonstrated that demography, HF characteristics and comorbidities in HFrEF patients widely varied between those centres. Also, the prescription rates and prescribed dosages of guideline-recommended HF medication varied significantly, both for HFrEF and HFmrEF patients. Those variations between hospitals could not be explained by differences in baseline characteristics of participating HF patients.

Overall, we found higher prescription rates of recommended HF medication than in previous registries, which may be related to the delivery of specialist outpatient HF care in the vast majority of patients [10].

Variation in prescribed heart failure medication

Remarkably, a wide distribution of prescribed medication between centres was observed. Many factors may play a role both in suboptimal therapy in the HF patients and in substantial variations between centres. Previously we reported from CHECK-HF that lower rates of guideline-directed pharmacotherapy in HFrEF patients were associated with increasing age, but much less influenced by comorbidities [10]. Recorded contraindications and intolerabilities did not explain the underuse of RAS inhibitors, beta blockers and MRA. Further analyses demonstrated that elderly heart failure patients with reduced ejection fraction (≥75 years) were prescribed significantly fewer beta blockers (77.8% vs 84.2%), RAS inhibitors (75.2% vs 89.7%), MRAs (50.6% vs 59.6%) and ivabradine (2.9% vs 9.3%), but significantly more diuretics (88.1% vs 72.6%) compared with patients aged less than 60 (P for all trends <0.01) [16]. In addition, the prescribed target dosages were significantly lower in elderly patients. Notably, patients with HFmrEF showed a similar trend in use of medication as in patients with HFrEF.

Also, recently reported data from the CHAMP-HF registry with 3,518 participating patients from 150 primary care and cardiology practices, demonstrated that lower medication utilisation or dose, was associated with older age, lower blood pressure, more severe functional class, renal insufficiency, and recent HF hospitalisation [9].

Notably, only 40% of the total HFrEF cohort of the Swedish Heart Failure Registry (11,215 patients, 27% women; mean age 75± 11 years) received an MRA [17]. Underuse of MRA was not related to hyperkalaemia, but it was, among other factors, related to impaired renal function (even moderately impaired), which is not a contraindication for MRA

use. An explanation for the underuse ofMRA might be the reluctance of prescribing an MRA to a vulnerable group of HF patients, already treated with an RAS inhibitor, beta blocker and in the majority of cases also a diuretic [18, 19]. Remarkably, age of patients in the present analysis had no impact on the differences in prescription of HF medication between centres.

Therefore, perceived polypharmacy, presence of comorbidities and overestimation of side-effects may influence use and dosing of evidence-based medication. In addition, patient preferences and family caregiver perceptions may influence therapeutic decisions [20]. Furthermore, an analysis by the BIOSTAT-CHF study group suggested that women with HFrEF might need lower doses of RAS inhibitors and beta blockers than men, also adjusted for age [21].

However, it is unclear why not only new medication, e.g. ivabradine and more recently sacubitril/valsartan, but also long-standing, established, disease-modifying therapies are not widely adopted nor fully prescribed. Therefore, it is important to gain detailed insights in reasons for not adopting recommended therapies both at a hospital level and at an individual patient level. Assessing information on real motivation of medical decisions and perceived barriers would contribute to effective improvement of HF care.

Importantly, suboptimal use of HF medication may have detrimental effects on clinical outcomes. Adherence to guideline-directed therapy of HFrEF, with prescription of at least 50% of the target dosage is associated with better outcome [6, 22], at least in younger patients with little comorbidities [23].

Optimising heart failure management

Although nonadherence to guideline-directed HF therapies is not fully understood, several practical recommendations to improve HF management can be made (Suppl. Table 8).

Obviously, being informed on performance of health care professionals involved in HF management, will contribute to improving delivery of care. Therefore, the CHECK-HF centres received individual feedback and in national meetings possible solutions to optimise HF care were shared. Furthermore, a nationwide, structured HF registry is being launched.

Acknowledging that HF care should be delivered seamless to patients, the Netherlands Society of Cardiology, started the CONNECT Heart Failure programme, in which concepts of integrated collaboration were translated towards detailed protocols by joint health care professionals in geographic regions [24]. These collaborations also provide strategies for optimising diagnostic pathways and HF therapies, accompanied by educational activities for professional teams. The initiated national registry will provide information on the effectiveness of incorporating these strategies.

At a patient level, clinical judgment of the heart failure syndrome, management of comorbidities, in concert with optimally implemented disease-modifying therapies are of pivotal importance [25–27]. In addition, blood pressure, renal function and hyperkalaemia may limit up-titration of all recommended drugs [28]. Thismay be evenmore complicated by the fact that the number of drug classes shown to improve outcome in HFrEF is increasing [29]. Among potential solutions are start-low and go-slow dosing strategies, close monitoring of vital parameters and side-effects, the use of new potassium binders and angiotensin receptor/neprilysin inhibition. Critical appraisal and reduction of co-medication may also be beneficial. In addition, pharmacy care improves adherence to HF medications and quality of life, which was recently demonstrated by the PHARM-CHF investigators [30].

In concert with dedicated efforts of professional HF teams, well-informed patients and family caregivers may empower their participation in medical decisionmaking and contributes to earlier access of new therapies [5, 24]. Informed treatment choices are of particular relevance in guidance of decisions during advanced and palliative stages of care.

Limitations and strenghts

The CHECK-HF registry is a large-scale real-world registry of HF outpatient clinics in the Netherlands reflective of Western European countries. However, some limitations should be mentioned, such as the crosssectional design limiting follow-up data on patient outcomes. Some missing data exists, which might influence results. Our registry included only patients seen in secondary, but not in primary care, which limits the generalisability of our findings to the primary care setting. Information on actual protocols of diagnostic workup and medical decision-making strategies in centres was not collected. Notably, the CHECK-HF inclusion period was from 2013 till end of 2016, in which the CONNECT programme for Heart failure regional care had been in the initial

phase of implementation in regions. Therefore, we have not collected data on adoption of the CONNECT Heart Failure programme in the centres. Strengths of the study are the reflection of the true practice of large scale nationwide outpatient HF management with detailed information on medication prescription and dosage.

Conclusion

In this Dutch real-world registry of outpatient HF population, wide between-clinic ranges of demography, severity of heart failure and comorbidities of HF patients were observed. Also the prescription rates and prescribed dosages of guideline-recommended HF medication differed significantly, not fully explained by differences in the patient profiles. Thus, future research should lead to strategies to improve management of HF patients including reduction of practice variation.

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Supplementary content

Suppl. Table 1. Target daily doses of guideline-recommended therapy in patients with HFrEF

Beta blocker	
Bisoprolol	10 mg
Carvedilol	50 mg
Metoprolol succinate	200 mg
Nebivolol	10 mg
ACE inhibitor	
Captopril	150 mg
Enalapril	20 mg
Lisinopril	40 mg
Ramipril	10 mg
Perindopril	8 mg
ARB	
Candesartan	32 mg
Losartan	150 mg
Valsartan	320 mg
MRA	
Eplerenone	50 mg
Spironolactone	25 mg

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *MRA* mineralocorticoid receptor antagonist, *HFrEF* heart failure with reduced ejection fraction

Suppl. Table 2. Baseline characteristics in HFrEF patients (LVEF<40%) and range between centres

	Overall population	**Range**
Number of patients	5,701	25; 785
Age (years) (*n*=5,694)	71.4±11.8	66.9±11.8; 75.8±10.3
Male gender (*n*=5,677)	3,767 (66.4)	57.5; 82.9
BMI, kg/m2 (*n*=5,276)	27.2±5.1	25.9±3.7; 29.1±6.9
NYHA (*n*=5,643)		
I	839 (14.9)	0.0; 46.2
II	3,244 (57.5)	33.3; 87.5
III	1,449 (25.7)	7.7; 62.7
IV	111 (2.0)	0.0; 8.9
LVEF, % (*n*=4,880)	29.3±9.0	26.7±8.5; 38.1±16.5
Cause of HF (*n*=5,505)		
Ischaemic cause of HF	2,945 (53.5)	35.1; 69.3
Non-ischaemic cause of HF	2,560 (46.5)	30.7; 64.9

Suppl. Table 2. *(continued)*

	Overall population	Range
Systolic BP, mmHg (*n*=5,613)	124.4±20.2	111.5±18.3; 133.6±22.7
Diastolic BP, mmHg (*n*=5,615)	71.2±11.2	64.3±10.6; 75.8±12.9
Heart rate, bpm (*n*=5,624)	71.9±13.8	64.8±8.0; 77.6±16.8
Atrial fibrillation (*n*=5,625)	1,258 (22.4)	12.2; 56.0
LBBB (*n*=5,701)	1,050 (18.4)	0.0; 32.4
QRS ≥130 ms (*n*=4,824)	2,080 (43.1)	0.0; 58.1
eGFR (*n*=4,178)	61.2±24.9	48.5±26.2; 97.5±16.7
eGFR (*n*=4,178)		
<30	430 (10.3)	0.0; 19.5
30-59	1,676 (40.1)	0.0; 63.6
≥60	2,072 (49.6)	18.2; 100.0
Comorbidity (*n*=5,073)		
Hypertension	1,944 (38.3)	5.6; 76.7
Diabetes Mellitus	1,481 (29.2)	17.6; 51.4
COPD	900 (17.7)	6.7; 33.3
OSAS	320 (6.3)	0.0; 16.7
Thyroid disease	368 (7.3)	0.0; 12.2
Renal insufficiency †	2,741 (54.8)	28.6; 84.0
No relevant comorbidity	671 (15.0)	0.0; 33.3

† Defined as eGFR <60ml/min or a history of renal failure

BMI body mass index, *NYHA* New York Heart Association classification, *LVEF* left ventricular ejection fraction, *HF* heart failure, *HFrEF* HF with reduced ejection fraction; *BP* blood pressure, *LBBB* left bundle branch block, *eGFR* estimated glomerular filtration rate, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *COPD* chronic obstructive pulmonary disease, *OSAS* obstructive sleep apnoea syndrome

Suppl. Table 3. Baseline characteristics in HFmrEF patients (LVEF 40-49%) and range between centres

	Overall population	Range
Number of patients	1,574	3; 415
Age (years) (*n*=1,573)	73.7±11.7	68.1±12.8; 80.9±6.8
Male gender (*n*=1,571)	917 (58.4)	34.5; 100.0
BMI, kg/m2 (*n*=1,462)	27.5±5.4	24.0±7.0; 30.5±4.4
NYHA (*n*=1,558)		
I	284 (18.2)	0.0; 50.0
II	854 (54.8)	22.2; 90.0
III	392 (25.2)	5.5; 66.7
IV	28 (1.8)	0.0; 11.6
LVEF, % (*n*=1,299)	45.0±5.4	46.2±5.3; 48.8±9.0

Suppl. Table 3. *(continued)*

	Overall population	Range
Cause of HF (*n*=1,521)		
Ischaemic cause of HF	691 (45.4)	11.1; 70.0
Non-ischaemic cause of HF	830 (54.6)	30.0; 88.9
Systolic BP, mmHg (*n*=1,556)	129.5±21.6	113.5±17.5; 138.7±21.9
Diastolic BP, mmHg (*n*=1,560)	71.8±12.0	58.3±13.9; 77.2±8.6
Heart rate, bpm (*n*=1,554)	72.5±14.3	63.2±10.0; 79.3±17.9
Atrial fibrillation (*n*=1,559)	534 (34.3)	9.5; 71.4
LBBB (*n*=1,574)	216 (13.7)	0.0; 66.7
QRS ≥130 ms (*n*=1,320)	416 (31.5)	0.0; 100.0
eGFR (*n*=973)	56.2±23.7	35.8±3.0; 96.4±9.9
eGFR (*n*=973)		
<30	133 (13.7)	0.0; 45.5
30-59	439 (45.1)	0.0; 100.0
≥60	401 (41.2)	0.0; 100.0
Comorbidity (*n*=1,417)		
Hypertension	619 (43.7)	0.0; 81.8
Diabetes Mellitus	397 (28.0)	0.0; 66.7
COPD	291 (20.5)	0.0; 44.4
OSAS	116 (8.2)	0.0; 28.6
Thyroid disease	111 (7.8)	0.0; 33.3
Renal insufficiency †	745 (60.9)	0.0; 100.0
No relevant comorbidity	98 (9.0)	0.0; 38.9

† Defined as eGFR <60mL/min or a history of renal failure

BMI body mass index, *NYHA* New York Heart Association classification, *LVEF* left ventricular ejection fraction, *HF* heart failure, *HFmrEF* HF with mid-range ejection fraction; *BP* blood pressure, *LBBB* left bundle branch block, *eGFR* estimated glomerular filtration rate, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *COPD* chronic obstructive pulmonary disease, *OSAS* obstructive sleep apnoea syndrome

Suppl. Table 4. Prescription rates of HF medication according to ESC Guidelines 2012 versus 2016 per participating clinic (*n*=34), only for symptomatic patients

		Guideline-recommended pharmacotherapy (average % (min.-max.))				
		Beta blocker	**RAS inhibitor**	**MRA**	**Ivabradine**	**Diuretics**
ESC Guidelines 2012	HFrEF	80.2 (59.6-97.4)	80.4 (50.0- 97.0)	55.5 (30.6-86.8)	5.0 (0.0-40.9)	85.7 (65.9-100.0)
ESC Guidelines 2016	HFrEF	81.3 (64.5-96.0)	82.3 (54.0-97.3)	58.1 (34.7-88.0)	5.7 (0.0-40.0)	85.5 (65.9-100.0)
	HFmrEF	78.2 (30.8-100.0)	75.6 (33.3-100.0)	49.1 (23.6-100.0)	3.6 (0.0-50.0)	84.4 (63.6-100.0)
	HFsemiq	77.3 (0.0-100.0)	77.1 (33.3-100.0)	50.2 (0.0-100.0)	3.0 (0.0-30.8)	88.8 (69.2-100.0)

HF heart failure; *HFrEF* HF with reduced ejection fraction, *HFmrEF* HF with mid-range ejection fraction,
HFsemiq HF with semiquantitatively estimated left ventricular ejection fraction - though <50%, *ESC* European Society of Cardiology,
RAS renin-angiotensin system, *MRA* mineralocorticoid receptor antagonists

Suppl. Table 5. Prescription rates of HF medication according to ESC Guidelines 2012 versus 2016 per participating clinic (*n*=34)

			Guideline-recommended pharmacotherapy (*n* (%))				
			Beta blocker	**RAS inhibitor**	**MRA**	**Ivabradine**	**Diuretics**
ESC Guidelines 2012	HFrEF	Patients seen at HF clinic	6,303 (80.6)	6,358 (81.3)	4,204 (53.7)	382 (4.8)	6,543 (83.7)
		Patients not seen at HF clinic	240 (68.0)	288 (81.6)	123 (34.8)	2 (0.6)	225 (63.7)
		p-value	<0.01	0.88	<0.01	<0.01	<0.01
ESC Guidelines 2016	HFrEF	Patients seen at HF clinic	4,320 (81.6)	4,403 (83.2)	3,040 (57.4)	306 (5.7)	4,468 (84.4)
		Patients not seen at HF clinic	205 (69.0)	251 (84.5)	108 (36.4)	2 (0.7)	191 (64.3)
		p-value	<0.01	0.55	<0.01	<0.01	<0.01
	HFmrEF	Patients seen at HF clinic	1,151 (78.3)	1,134 (77.1)	674 (45.9)	49 (3.2)	1,178 (80.2)
		Patients not seen at HF clinic	32 (61.5)	34 (65.4)	13 (25.)0	0 (0.0)	31 (59.6)
		p-value	<0.01	0.05	<0.01	0.41	<0.01

Suppl. Table 5. *(continued)*

		Guideline-recommended pharmacotherapy (*n* (%))				
		Beta blocker	**RAS inhibitor**	**MRA**	**Ivabradine**	**Diuretics**
HFsemiq	Patients seen at HF clinic	832 (78.6)	821 (77.5)	490 (46.3)	27 (2.5)	897 (84.8)
	Patients not seen at HF clinic	3 (75.0)	3 (75.0)	2 (50.0)	0 (0.0)	3 (75.0)
	p-value	1.00	1.00	1.00	1.00	0.49

HF heart failure; *HFrEF* HF with reduced ejection fraction, *HFmrEF* HF with mid-range ejection fraction,
HFsemiq HF with semiquantitatively estimated left ventricular ejection fraction - though <50%, *ESC* European Society of Cardiology,
RAS renin-angiotensin system, *MRA* mineralocorticoid receptor antagonists

Suppl. Table 6. Prescription rates of HF medication according to ESC Guidelines 2012 versus 2016 per participating clinic (*n*=34)

			Guideline-recommended pharmacotherapy (*n* (%))				
			Beta blocker	**RAS inhibitor**	**MRA**	**Ivabradine**	**Diuretics**
ESC Guidelines 2012	HFrEF	Men	79.1 (54.9-96.1)	82.6 (66.7- 97.6)	52.8 (26.6-79.2)	4.2 (0.0-14.3)	81.6 (60.7-100.0)
		Women	82.0 (64.9-100.0)	78.9 (54.8- 96.1)	53.3 (26.4-100.0)	5.2 (0.0-28.6)	85.0 (73.2-100.0)
ESC Guidelines 2016	HFrEF	Men	79.7 (61.7-95.7)	84.2 (67.6- 97.7)	55.7 (30.0-83.3)	4.9 (0.0-31.8)	82.3 (60.2-100.0)
		Women	83.7 (64.5-100.0)	81.1 (57.1- 96.6)	57.7 (33.0-100.0)	6.3 (0.0-32.4)	85.7 (65.9-100.0)
	HFmrEF	Men	76.9 (0.0-100.0)	77.9 (33.3- 100.0)	44.0 (11.8-100.0)	3.1 (0.0-33.3)	76.6 (58.8-100.0)
		Women	79.0 (47.1-100.0)	75.2 (35.7- 100.0)	46.9 (0.0-100.0)	3.2 (0.0-17.6)	83.4 (50.0-100.0)
	HFsemiq	Men	78.3 (0.0-100.0)	79.4 (0.0- 100.0)	47.9 (0.0-100.0)	1.9 (0.0-28.6)	84.5 (66.7-100.0)
		Women	79.0 (0.0-100.0)	74.6 (0.0- 100.0)	43.4 (0.0-100.0)	3.4 (0.0-50.0)	85.5 (0.0-100.0)

HF heart failure; *HFrEF* HF with reduced ejection fraction, *HFmrEF* HF with mid-range ejection fraction,
HFsemiq HF with semiquantitatively estimated left ventricular ejection fraction - though <50%, *ESC* European Society of Cardiology, *RAS* renin-angiotensin system,
MRA mineralocorticoid receptor antagonists

Suppl. Table 7. Univariable analysis of predictors of HF medical treatment of HFrEF patients (LVEF<50%), Odds Ratios [95% confidence intervals]

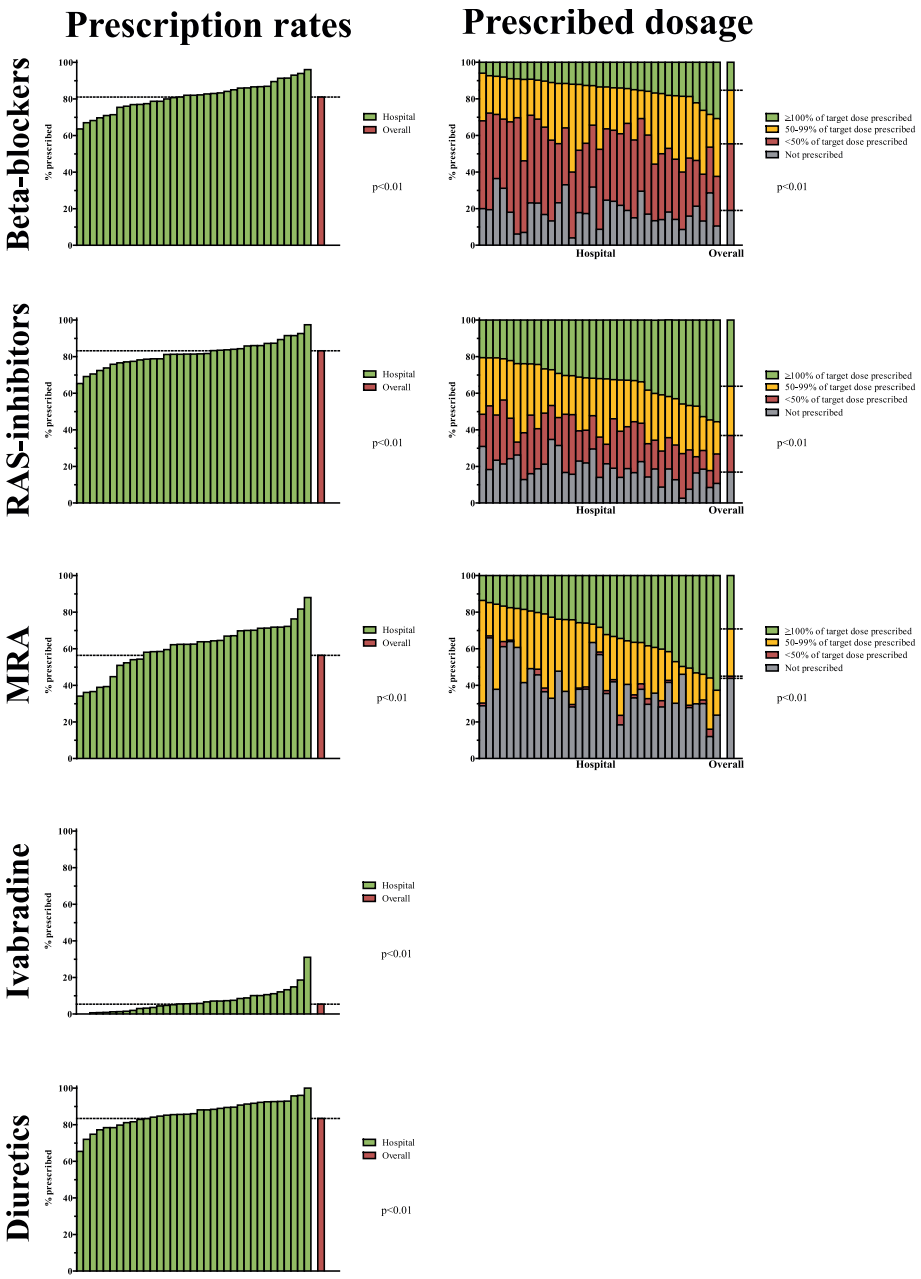
	Beta blocker	RAS inhibitor	MRA	Ivabradine	Diuretics
Gender	1.20 [1.07-1.35]	0.79 [0.70-0.88]	1.02 [0.93-1.11]	1.24 [1.01-1.53]	1.28 [1.13-1.45]
Age (per 10 years)	0.87 [0.83-0.92]	0.67 [0.64-0.71]	0.93 [0.89-0.96]	0.72 [0.67-0.78]	1.42 [1.35-1.48]
BMI	1.02 [1.01-1.03]	1.03 [1.02-1.05]	1.02 [1.01-1.03]	1.02 [1.00-1.04]	1.05 [1.04-1.06]
Systolic blood pressure (per 10 mmHg)	1.00 [0.97-1.03]	1.06 [1.03-1.09]	0.82 [0.80-0.84]	0.85 [0.80-0.90]	0.83 [0.81-0.86]
Diastolic blood pressure (per 10 mmHg)	1.05 [1.00-1.10]	1.09 [1.04-1.15]	0.82 [0.79-0.85]	0.82 [0.75-0.89]	0.74 [0.71-0.78]
NYHA classification	0.92 [0.85-0.99]	0.65 [0.59-0.70]	1.35 [1.27-1.44]	1.35 [1.16-1.56]	2.26 [2.06-2.47]
Heart rate (per 10 beats/min)	0.96 [0.92-0.99]	0.84 [0.81-0.87]	0.97 [0.94-1.00]	1.00 [0.93-1.08]	1.11 [1.06-1.16]
QRS duration (per 10 ms)	0.97 [0.96-0.99]	0.97 [0.96-0.99]	1.04 [1.02-1.05]	0.98 [0.94-1.01]	1.07 [1.05-1.09]
eGFR (per 10 ml/min)	1.02 [1.00-1.05]	1.17 [1.14-1.21]	1.00 [0.98-1.03]	1.04 [0.99-1.09]	0.81 [0.79-0.84]
Ischaemic aetiology	1.00 [0.90-1.11]	0.97 [0.86-1.09]	0.99 [0.91-1.08]	1.13 [0.91-1.40]	1.08 [0.97-1.22]
Hypertension	1.19 [1.05-1.35]	1.09 [0.97-1.22]	0.96 [0.87-1.05]	0.76 [0.59-0.97]	1.27 [1.11-1.45]
Diabetes	1.07 [0.93-1.22]	0.81 [0.71-0.92]	0.99 [0.89-1.10]	1.54 [1.21-1.95]	1.57 [1.35-1.82]
COPD	0.95 [0.82-1.11]	0.75 [0.65-0.87]	1.06 [0.94-1.19]	1.45 [1.10-1.92]	1.40 [1.19-1.66]
Renal insufficiency	1.02 [0.90-1.14]	0.49 [0.43-0.55]	1.07 [0.98-1.17]	0.82 [0.66-1.01]	2.96 [2.60-3.36]

† Defined as eGFR <60ml/min or a history of renal failure

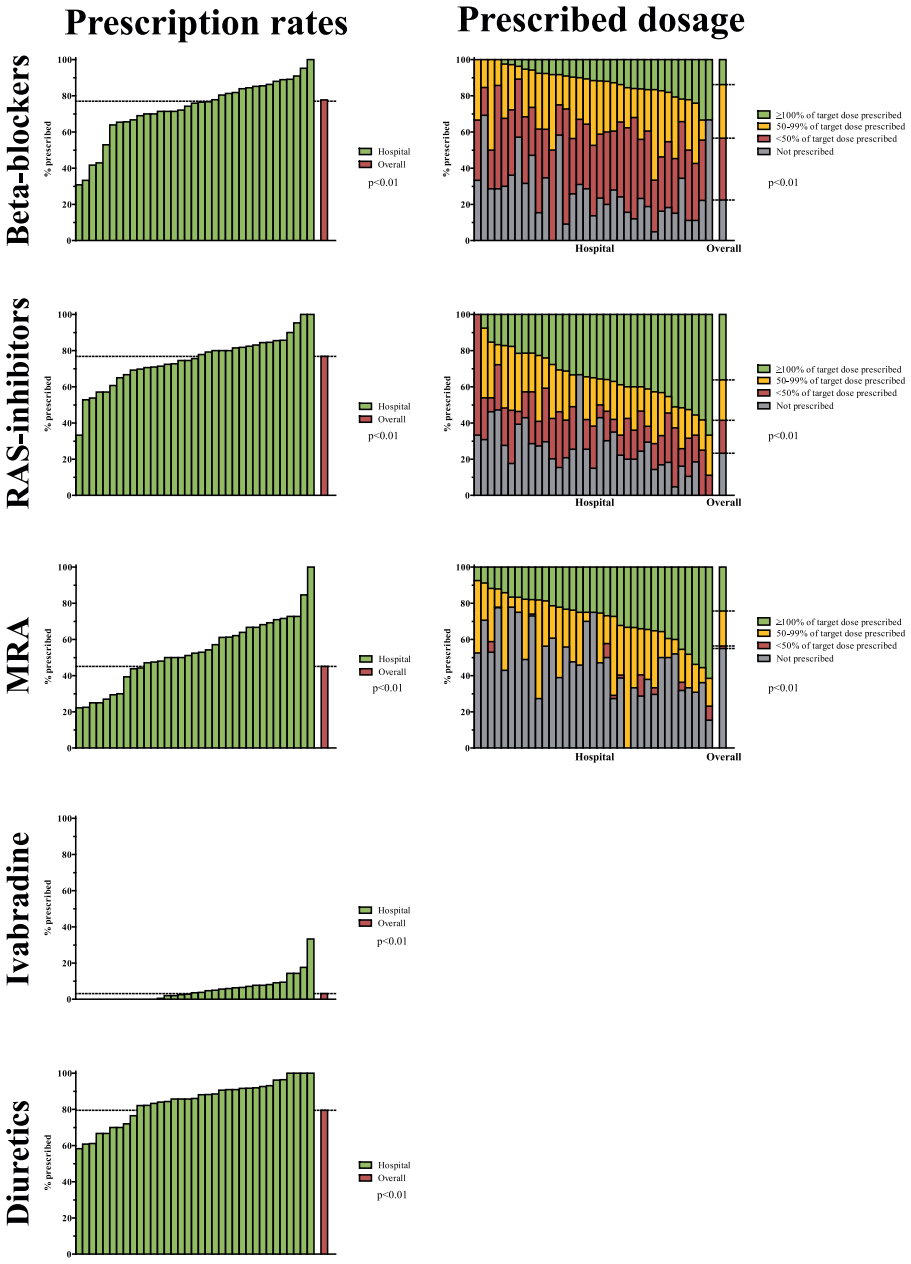
BMI body mass index, *NYHA* New York Heart Association, *LVEF* left ventricular ejection fraction, *HF* heart failure, *HFrEF* HF with reduced ejection fraction, *RAS* renin-angiotensin system, *MRA* mineralocorticoid receptor antagonists, *BP* blood pressure, *eGFR* estimated glomerular filtration rate, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *COPD* chronic obstructive pulmonary disease

Suppl. Table 8. Practical recommendations for optimal use of guideline-directed heart failure therapies

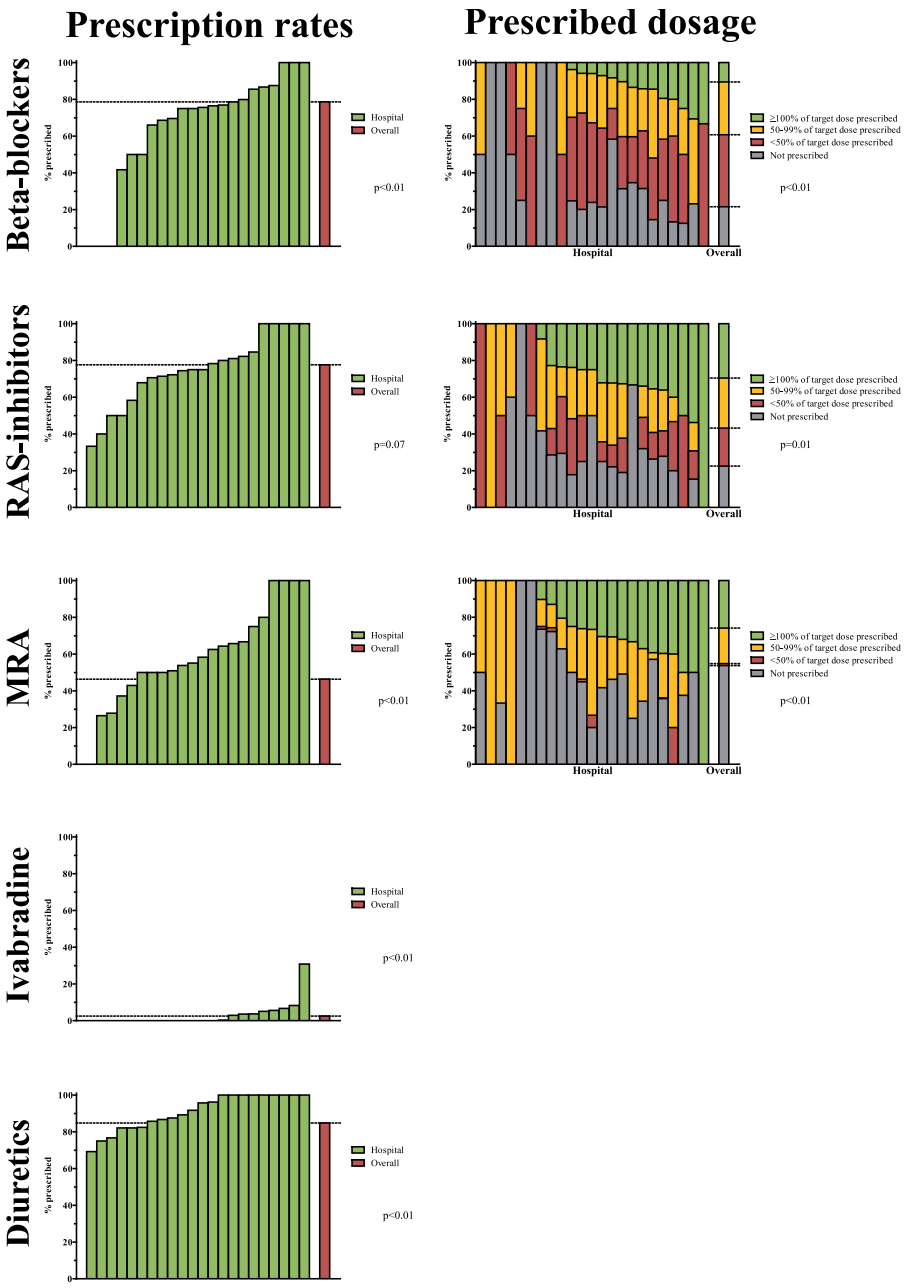
At hospital level, providing:
Multidisciplinary team (MDT) care programme
Trained allied professionals (e.g. nurse-specialists and physician assistants)
Life-long learning programme for health-care professionals
Transmural collaboration
Up-to-date diagnostic and therapeutic protocols
Nurse-directed or pharmacist-directed optimisation of recommended medication
Advanced and palliative care programme
e-Health solutions, telemonitoring facilities
Benchmarking and adopting best practices
Monitoring of adherence, clinical outcomes and patient reported outcomes
Periodic review of performance, improving heart failure care accordingly
At patient level, aimed at:
MDT is fully informed regarding medical history and social context
Assessing current condition and therapies
Management of comorbidities
Awareness of cognitive impairment and frailty
Matching patient profile and therapeutic options
Initiation, up-titration and maintenance of evidence-based therapies
Tailored dosing regimens and monitoring of blood pressure and heart rate
Addressing intolerabilities and side effects
Critical appraisal of polypharmacy
Patient education and counselling
Promoting self-management
Home-based monitoring, with implantable devices if applicable
In select patients: implantable pulmonary artery pressure monitoring
Addressing patient preferences and barriers
Involvement of family caregivers
Tailored end-of-life choices
Holistic approach preferably



Suppl. Fig. 1. Prescription rates (%) and prescribed dosages (%) of HF medication in HFrEF patients (LVEF <40%) per participating clinic (n = 34) (The left panels show the order of hospitals on the x-axis based on the percentage of prescription rate of each drug. The red bar is the overall prescription rate (%) and the green bars are the prescription rates (%) in each clinic. The same order is shown in the panels on the right). (*HF* heart failure, *HFrEF* heart failure with reduced ejection fraction, *LVEF* left ventricular ejection fraction, *RAS* renin-angiotensin system, *MRA* mineralocorticoid receptor antagonists)



Suppl. Fig. 2. Prescription rates (%) and prescribed dosages (%) of HF medication in HFmrEF patients (LVEF 40–49%) per participating clinic (n = 34) (The left panels show the order of hospitals on the x-axis based on the percentage of prescription rate of each drug. The red bar is the overall prescription rate (%) and the green bars are the prescription rates (%) in each clinic. The same order is shown in the panels on the right). (*HF* heart failure, *HFmrEF* heart failure with mid-range ejection fraction, *LVEF* left ventricular ejection fraction, *RAS* renin-angiotensin system, *MRA* mineralocorticoid receptor antagonists)



Suppl. Fig. 3. Prescription rates and prescribed dosages of HF medication in HF patients with semiquantitatively measured LV function per participating clinic (n = 27) (The left panels show the order of hospitals on the x-axis based on the percentage of prescription rate of each drug. The red bar is the overall prescription rate (%) and the green bars are the prescription rates (%) in each clinic. The same order is shown in the panels on the right). (*HF* heart failure, LV left ventricular, *RAS* renin-angiotensin system, *MRA* mineralocorticoid receptor antagonists)

9

Clinical profile and management of patients with heart failure with preserved ejection fraction in the CHECK-HF registry

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* Equal contributions

Under embargo

Submitted

B

Remote monitoring in chronic heart failure

Chapter 10
Remote monitoring of chronic heart failure patients: invasive versus non-invasive tools for optimizing patient management

Chapter 11
A randomized comparison of the effect of haemodynamic monitoring with CardioMEMS in addition to standard care on quality of life and hospitalisations in patients with chronic heart failure: design and rationale of the MONITOR HF multicentre randomized clinical trial

Chapter 12
Morning pulmonary artery pressure measurements by CardioMEMS are most stable and advocated to use for remote monitoring of pressure trends

Chapter 13
Monitoring pulmonary artery pressures in chronic heart failure patients and evaluating the treatment effect of MitraClip implantation for functional mitral regurgitation

10

Remote monitoring of chronic heart failure patients: invasive versus non-invasive tools for optimizing patient management

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Neth Heart J. 2020 Jan; 28(1):3-13

Abstract

Exacerbations of chronic heart failure (HF) with the necessity for hospitalisation impact hospital resources significantly. Despite all of the achievements in medical management and non-pharmacological therapy that improve the outcome in HF, new strategies are needed to prevent HF-related hospitalisations by keeping stable HF patients out of the hospital and focusing resources on unstable HF patients. Remote monitoring of these patients could provide the physicians with an additional tool to intervene adequately and promptly. Results of telemonitoring to date are inconsistent, especially those of telemonitoring with traditional non-haemodynamic parameters. Recently, the CardioMEMS device (Abbott Inc., Atlanta, GA, USA), an implantable haemodynamic remote monitoring sensor, has shown promising results in preventing HF-related hospitalisations in chronic HF patients hospitalised in the previous year and in New York Heart Association functional class III in the United States. This review provides an overview of the available evidence on remote monitoring in chronic HF patients and future perspectives for the efficacy and cost-effectiveness of these strategies.

Introduction

The management of patients with chronic heart failure (HF) places a high burden on health care resources due to the frequent follow-up visits combined with recurrent hospitalisations due to cardiac decompensation. [1] Early detection of HF deterioration is crucial to prevent HF-related hospitalisations, potentially improve overall survival and quality of life and lower the burden on health care resources. Remote monitoring of chronic HF patients can aid in the detection of HF deterioration; therefore several remote monitoring strategies have been developed. In this review, we provide an overview of available evidence on remote monitoring of chronic HF patients and provide further perspectives of anticipated developments in the remote care of HF.

Non-haemodynamic remote monitoring

Over the last few decades, several studies have investigated the use of non-haemodynamic remote monitoring. However, the results have been largely inconsistent. A recently updated Cochrane review included 41 randomised controlled trials (RCTs) investigating the use of structured telephone support (25 studies, 9332 patients) or non-invasive telemonitoring (18 studies, 3860 patients) compared with standard HF care. [2] This review showed a modest beneficial effect of remote monitoring on all-cause mortality and HF-related hospitalisations, although no effect on the overall hospitalisation rates was observed. However, the quality of the evidence of this review is limited by the many different inclusion and exclusion criteria for patients included in the studies and considerably heterogeneity of compared data. Also, the studies included used different intervention therapies, ranging from telephone calls only, weight monitoring to complex multiple-variable telemonitoring strategies making it difficult to conclude which component drives the effect. Additionally, the majority of selected individual studies (more than twenty) were neutral.

Multiple large multi-centre prospective clinical studies and RCTs have investigated multiple noninvasive remote monitoring strategies, ranging from symptom and body weight monitoring to complex and intensive strategies including body weight, blood pressure, electrocardiography and peripheral capillary oxygen saturation. The landmark studies of high quality design and well specified intervention show no consistent beneficial effect of non-haemodynamic remote monitoring in HF patients (Tab. 1). [3–11] Of specific note and most promising are the recent results of TIM-HF2 trial showing a

Table 1. Non-invasive remote monitoring in heart failure (*HF*) patients[a]

Trial/study	Author; journal; year	No. of patients	Parameter	Endpoint	Impact of HF hospitalization
TEN-HMS [5]	Cleland et al.; J Am Col Cardiol; 2005	426	Signs/symptoms, daily weights, BP, nurse telephone calls	HF hospitalisation	Non-significant
TEL-HF [4]	Chaudhry et al.; N Engl J Med; 2010	1653	Signs/symptoms, daily weights	HF hospitalisation	Non-significant
TIM-HF [7]	Koehler F et al.; Circulation; 2011	710	Signs/symptoms, daily weights	HF hospitalisation	Non-significant
INH [3]	Angermann et al.; Circ Heart Fail; 2012	715	Signs, symptoms, telemonitoring nurse coordinated	HF hospitalisation	Non-significant
WISH [10]	Lynga et al.; Eur J Heart Fail; 2012	344	Daily weights	HF hospitalisation	Non-significant
CHAT [9]	Krum et al.; Cardiovasc Ther; 2013	405	Monthly telephone-based automated telemedicine system	HF hospitalisation	Non-significant
BEAT-HR [11]	Ong et al.; JAMA Intern Med; 2016	1437	Signs, symptoms, daily weights, nurse communications	HF hospitalisation	Non-significant
TIM-HF2 [6]	Koehler F et al.; Lancet; 2018	1571	Web-based remote monitoring on daily weight, BP, pulse, ECG, peripheral capillary oxygen saturation, a self-related health status. ECG and BP machine at home	Reduction in the weighted average of 'the % of days lost due to unplanned CV hospital admissions or death'	HR 0.80; 95% CI 0.65–1.00

BP blood pressure, *CV* cardiovascular, *ECG* electrocardiography

[a] Demonstrating the landmark trials only, sample size >250 patients, discounting studies with only phone calls as intervention

benefit on all-cause mortality and cardiovascular hospitalizations of a well-structured but labour intensive 24/7 telemonitoring strategy, but remarkably showed no effect on quality of life. [6] Also, 'real-world' data, such as those from the Medicare database, did not show consistent benefits of non-haemodynamic remote monitoring strategies on mortality or hospitalisation rates. [12] Our conclusion is that although results are inconsistent for non-invasive telemonitoring, the simplicity makes it potentially useful for larger groups of HF patients at relatively lower risk or less symptomatic, where invasive telemonitoring may have more impact in sicker patients.

Remote monitoring using pacemaker/ICD devices

Multiple studies have investigated the remote monitoring abilities of implantable cardioverter defibrillator/cardiac resynchronisation therapy (ICD/CRT) devices in chronic HF patients to improve HF-related hospitalisation rates (Tab. 2). The MORE-CARE multi-centre RCT showed that remote monitoring of advanced diagnostics via CRT-D did not reduce mortality or hospitalisation rates, although the health care resource utilisation was reduced due to a reduction in outpatient follow-up visits. [13] Additionally, the DOT-HF, OptiLink and REM-HF trials investigated the use of remote monitoring using ICD/CRT devices, but all failed to show a reduction in HF-related hospitalization rates. [14–16] The DOT-HF trial even showed an increase in the number of HF hospitalisations in the remotely monitored groups. [16] The EFFECT study, a multi-centrer clinical trial, showed that remote monitoring of ICD in HF patients reduced mortality and cardiovascular hospitalisations, [17] and the COMMIT-HF trial showed that remote monitoring of ICD/CRT HF patients significantly reduces long-term mortality but not HF-related hospitalisations. [18]

Other patient outcomes have been investigated as well, with mixed results. The IN-TIME RCT showed that using the remote monitoring abilities of the ICD and CRT devices leads to a reduction of a combined endpoint of all-cause death, overnight HF-related hospitalisation, change in New York Heart Association (NYHA) class, and change in patient global self-assessment. [19] However, other trials found no significant effect on patient outcomes. [20, 21] The effect of remote monitoring using ICD/CRT devices has recently been investigated in a meta-analysis, including 11 RCTs (5702 patients). This meta-analysis showed a reduction in the number of outpatient visits in remotely monitored patients, although remote monitoring with an ICD/CRT device had no effect on mortality or HF-related hospitalisations rates in these patients. [22]

Table 2. Remote monitoring in heart failure (*HF*) patients using implantable cardioverter defibrillator/cardiac resynchronization therapy (*ICD/CRT*) devices

Trial/study	Author; journal; year	No. of patients	Parameter	Endpoint	Impact of HF hospitalization
DOT-HF [16]	Van Veldhuisen et al.; Circulation; 2011	335	Intrathoracic impedance	HF hospitalisation	Increased
OptiLink [14]	Brachmann et al.; Eur J Heart Fail; 2011	1002	Intrathoracic impedance	HF hospitalisation	Non-significant
EFFECT [17]	De Simone et al.; Europace; 2015	987	Remote monitoring via ICD, or CRT	HF hospitalisation	Reduced (IRR 0.54; 95% CI 0.24–0.62)
MORE-CARE [13]	Boriani et al.; Eur J Heart Fail; 2017	865	Remote monitoring of advanced diagnostics via CRT-D	HF hospitalisation	Non-significant
REM-HF [15]	Morgan et al.; Eur Heart J; 2017	1650	Remote monitoring via ICD, or CRT	HF hospitalisation	Non-significant
COMMIT-HF [18]	Kurek et al.; J Cardiovasc Electrophysiol; 2017	574	Remote monitoring via ICD, or CRT	HF hospitalisation/ All-cause mortality	Non-significant/ Reduced all-cause mortality (HR 0.24; 95% CI 0.14–0.41)
IN-TIME [19]	Hindricks et al; Lancet; 2014	716	Remote monitoring via ICD, or CRT	HF worsening score	OR 0.63 95% Ci 0.43–0.90

The MultiSENSE algorithm aims to predict the individualized risk for worsening of HF based on first and third heart sounds, thoracic impedance, respiration rate, the ratio of respiration rate to tidal volume, heart rate and patient activity. This could aid in the timely detection of HF worsening with the threshold retrospectively calculated by the algorithm. However, the overall sensitivity is only 70%. [23] Another algorithm with a similar aim is the HeartLogic algorithm. [24] To date, no clinical endpoint data or trial data are available and the technique is limited to certain ICD types and brands only.

The shift in remote HF care: haemodynamic (invasive) remote monitoring

In HF patients cardiac filling pressures rise weeks before an exacerbation of HF leading to a related hospitalisation. Symptoms of clinical congestion such as gain in body weight will occur about 2 weeks later, usually shortly before hospitalisation (Fig. 1). [25] Monitoring of cardiac filling pressures can be an effective strategy to detect upcoming HF decompensation, as it might provide a window of opportunity to intervene adequately and promptly, which is not possible with previous remote monitoring strategies. Therefore multiple implantable haemodynamic monitoring devices have been developed over the last few years. The ePAD (Medtronic, Dublin, Irland) device, an estimate pulmonary artery (PA) end-diastolic pressure device, can be implanted in the right ventricle and has been investigated in the COMPASS-HF trial. In this trial, NYHA class III/IV chronic HF patients were included and investigated as to whether remote haemodynamic monitoring using the ePAD could reduce HF-related hospitalisation, emergency or urgent care visits requiring intravenous therapy. This study did not find significant differences in its endpoint, although it was underpowered due to a lower inclusion rate. Furthermore, clinicians did not receive guidance on how to react to pressure changes. [26]

Left atrium pressures (LAP) can be directly measured using a LAP device. The tip of this device is implanted transvenously into the atrial septum oriented towards the left atrium, enabling remote LAP monitoring. This device was used only in the LAPTOP-HF trial, which aimed to investigate the safety and effectiveness of this sensor. However, the enrollment was stopped early due to a perceived excess of procedure-related complications. This is an important issue as the procedure needs an interatrial septum puncture and is placed in the left side of the heart with the risk of arterial side complications. However, in the patients already included in this trial, and followed for 12 months, a 41% reduction of HF-related hospitalisations was observed in the

patients with a LAP device. [27] Currently, the V-LAP™Left Atrium Monitoring systEm for Patients With Chronic sysTOlic and Diastolic Congestive heaRt Failure (VECTOR-HF) trial is investigating a new LAP device (V-LAP; Vectorious Medical Technologies Ltd., Tel Aviv, Israel) to assess the safety, performance and usability of this device in NYHA class III HF patients (NCT03775161).

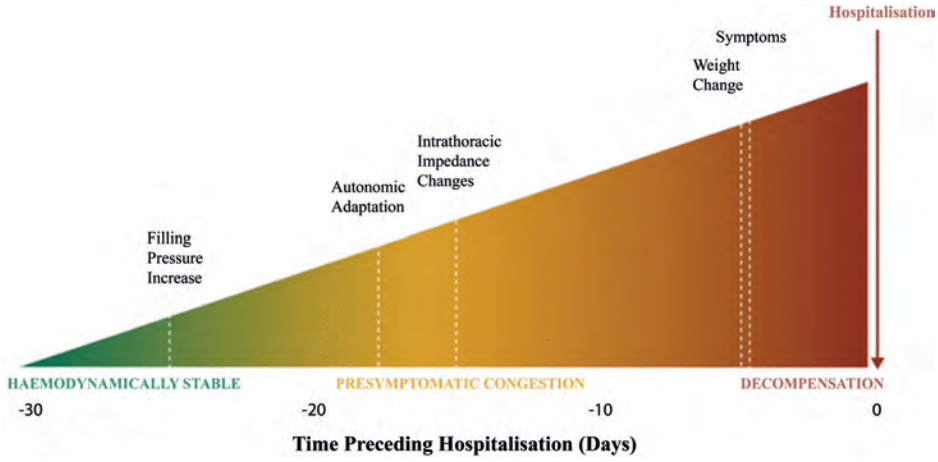

Fig. 1 Pathophysiology of decompensated heart failure. (Reprinted from [54], with permission)

Off all the remote monitoring strategies currently available, remote haemodynamic monitoring using the CardioMEMS HF system device (Abbott Inc., Atlanta, GA, USA) (Fig. 2) appears to be the most promising with respect to safety, durability and ability to prevent HF-related hospitalisations. The CardioMEMS is implanted into the PA and enables daily pulmonary artery pressure (PAP) readings. Treating physicians can react to these changes in PA trend data to maintain normal PAP levels, as a sign of a stable clinical status. Furthermore, these daily PAP readings can be used as a feedback mechanism after treatment changes, providing feedback on whether the treatment changes led to a sufficient decline of PAPs. These strategies can lead to individualised HF therapy.

The CardioMEMS consists of a coil combined with a pressure-sensitive capacitor sealed in a capsule, forming an electrical circuit that resonates at a specific frequency when it is electromagnetically coupled with an external antenna. [28] This antenna provides the power for the device, so the device is completely free from batteries or leads. At both sides of the capsule, a loop is placed to ensure that the CardioMEMS remains at the implanted position until the endothelialisation is complete, approximately 3–4 weeks after implantation. When pressure is applied, the resonant frequency changes via a characteristic pattern and is received by the external antenna. The antenna converts

this signal into a pressure waveform and sends it to a secure website, where it can be monitored. The device is implanted during a right heart catheterisation, with access via the femoral vein. An appropriate target location, based on vessel size and location, is identified on a pulmonary arteriogram. The CardioMEMS delivery system is advanced to the target location over a guidewire, where the CardioMEMS is released. After implantation, the device is calibrated using PAP obtained with a Swan Ganz catheter.

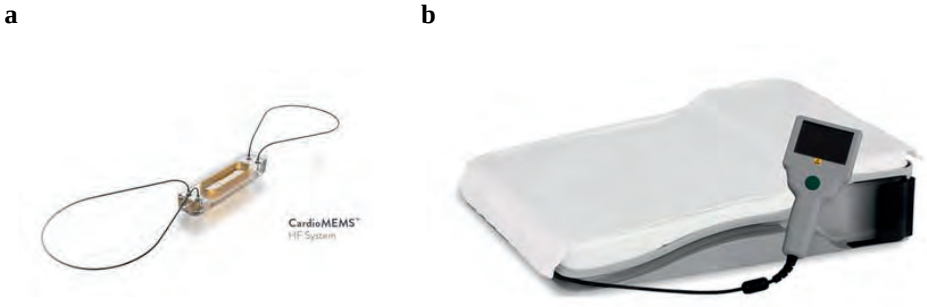

Fig. 2 CardioMEMS HF system, consisting of the pulmonary artery pressure sensor (a) and the patient electronics system (b) used to take daily pressure readings. (Courtesy of Abbott, Inc.)

Two studies have validated the PAP measured by the CardioMEMS, with cardiac filling pressures measured by Swan-Ganz catheterisation or echocardiography directly after implantation and after 6 months of follow-up. [29, 30] Swan-Ganz measurements showed a good correlation with mean PAP assessed by CardioMEMS (r^2= 0.90at implantation and r^2=0.94at follow-up, p< 0.01). [30] Furthermore, a good correlation (r^2= 0.80 at implantation and r^2= 0.75, both p<0.01at follow-up) was found between PAP measurements by the CardioMEMS and estimated pressure measurements by echocardiography. [29]

Safety

The safety of the CardioMEMS has been investigated in the CHAMPION trial. A total of 15 serious adverse events occurred during all implantation attempts in the CHAMPION trial. [31] In total, 1% (n= 8) of patients developed a device-related adverse event, and 1% (n= 7) developed a procedure-related adverse event. The following events were reported: four bleeding events, three anticoagulation-related hospitalisations, two pre-existing atrial dysrhythmia exacerbations during implantation, two febrile illnesses, one pulmonary in situ thrombus during implantation that was treated with anticoagulation, one cardiogenic shock, one case of atypical chest pain, and one delivery-system failure requiring a snare to remove the delivery system. [32] An analysis of the post-marketing

data of more than 5500 CardioMEMS implantations showed that 2.8% of all CardioMEMS patients experienced an adverse event. [33] Most adverse events were a recalibration of the system (n= 35) or access-site-related bleeding (n= 15). The reported adverse event rates are comparable with those of a standard right heart catheterisation, which is considered a safe procedure. [34] The recent US Post Approval Study (PAS) reported a device- or system-related complication in 0.3% of all patients, and a sensor failure in only 0.1% of all patients, which confirms the safety and durability of this technique.

Clinical efficacy

The CardioMEMS was investigated for the first time in the CHAMPION trial. [32] In this trial, 550 patients with NYHA class III HF and at least one hospitalization in the last year received a CardioMEMS and were randomised. Of the patients in the intervention group, the haemodynamic information was available to the treating physicians, and the physicians were instructed to react on pressure changes. In the control group, the CardioMEMS readings were not available to the physicians, and these patients received only the standard care. Using the haemodynamic feedback in the intervention group led to a significantly higher number of medication changes, especially diuretics and vasodilator changes, compared to the control group. [35] Furthermore, remote monitoring with the CardioMEMS device led to a significant reduction in mean PAP [32, 36]; similar results were observed in a real-world setting. [37]

The effectiveness of the CardioMEMS in preventing HF-related hospitalisations has been investigated in multiple studies (Fig. 3). [32, 36, 38, 39] During the first 6 months of remote monitoring of HF patients, the HF hospitalisation rates declined by approximately 30% [32, 38] compared with standard care. During the long-term follow-up, the sustained reduction was approximately 33%. [31, 38, 39] Also, all-cause hospitalisation rates were reduced: 45% at 6 months [38] and 16% at 18 months of follow-up. [31] None of these studies were powered to observe mortality differences; however, the CHAMPION trial showed a strong trend towards survival benefit in HF and reduced ejection fraction (HFrEF) patients monitored with the CardioMEMS system (p= 0.06). [40]

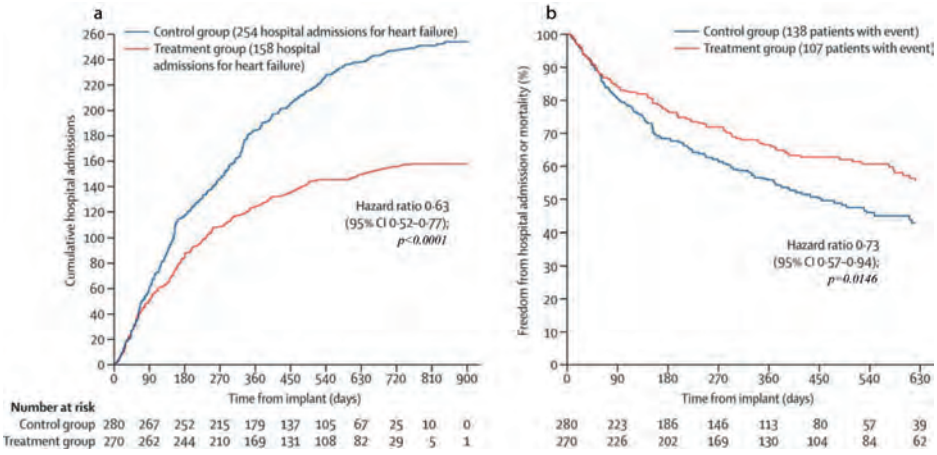

Fig. 3 Cumulative heart-failure-related hospitalisations during the entire period of randomised single-blind follow-up (a), and freedom from first heart-failure-related hospitalisation or mortality (b) in the CHAMPION trial. (Reprinted from [32], with permission)

The recently presented PAS results confirm the consistent treatment benefit with CardioMEMS in chronic HF patients, reducing the number of HF hospitalisations in a more contemporary setting. The PAS study showed a 58% reduction in HF-related hospitalization in the first year after CardioMEMS implantation compared with 1 year before implantation. Furthermore, a reduction in HF hospitalisations, mortality and all-cause mortality was observed after CardioMEMS implantation. However, patients included in the PAS study were their own historical controls and there has been no randomised comparison to standard care without PA monitoring.

CardioMEMS and evidence in HFpEF patients

In a real-world setting, remote monitoring using the CardioMEMS leads to a similar reduction in mean PAP in both HFrEF and HFpEF patients. [37] Interestingly, in the CHAMPION trial, a larger reduction of HF-related hospitalisations in HFpEF patients compared with HFrEF patients was observed after at least 6 months of remote monitoring. [40, 41] Besides the alleged benefit of spironolactone in the United States (US) and European participants of the TOPCAT trial [42] with spironolactone, this is the first evidence of a treatment or tool to improve the outcome in HFpEF patients.

Standard care in chronic HF

Recently two large HF registries have been published, the CHAMP-HF registry [43] from the USA and the CHECK-HF Registry [44] from The Netherlands. These two registries showed the differences in standard care between the USA and Western Europe. The prescription rates of RAS inhibitors (82.3% vs 59.9%), beta-blockers (80.6% vs 66.8%) and mineralocorticoid receptor antagonist (MRA) (54.8% vs 33.1%) in HFrEF patients were much higher in the CHECK-HF registry compared to the CHAMP-HF registry (Fig. 4a). Furthermore, the prescribed dosages differed between the two registries, with higher prescribed dosages for RAS inhibitors in the CHECK-HF registry and higher dosages for MRA in the CHAMP-HF registry (Fig. 4b) Differences in the HF readmission rates were observed between the USA and Europe. [45, 46] The generalizability of the US findings in terms of clinical effectiveness when using the CardioMEMS device in addition to standard care is therefore limited, and additional costs cannot be directly extrapolated between the two different health care structures. Additional research is needed in the European setting. In Germany, the CardioMEMS European Monitoring Study for Heart Failure (MEMS-HF) study was set up as a post-marketing study to test the safety and clinical effectiveness in a European setting but lacks a control group. [47]

Cost-effectiveness of CardioMEMS

The cost-effectiveness of remote monitoring using the CardioMEMS is highly relevant. Using the US CHAMPION trial data the incremental cost-effective ratio (ICER, cost per quality-adjusted life-year) for the US setting has been calculated. [32, 48–50] These studies estimated an increase in the quality-adjusted life-years in the CardioMEMS group of between 0.28 and 0.58, with incremental costs between $4282 and $20,079, compared with standard care patients. This results in an estimated ICER in the USA of between $13,379 and $71,462, which are additional costs in order to gain one quality-adjusted life-year in patients monitored with the CardioMEMS device. Sensitivity analyses demonstrated that the cost-effectiveness of the CardioMEMS is highly influenced by device costs, costs of routine outpatient care, hospitalisation rates, mortality rates and duration of remote monitoring using the CardioMEMS.

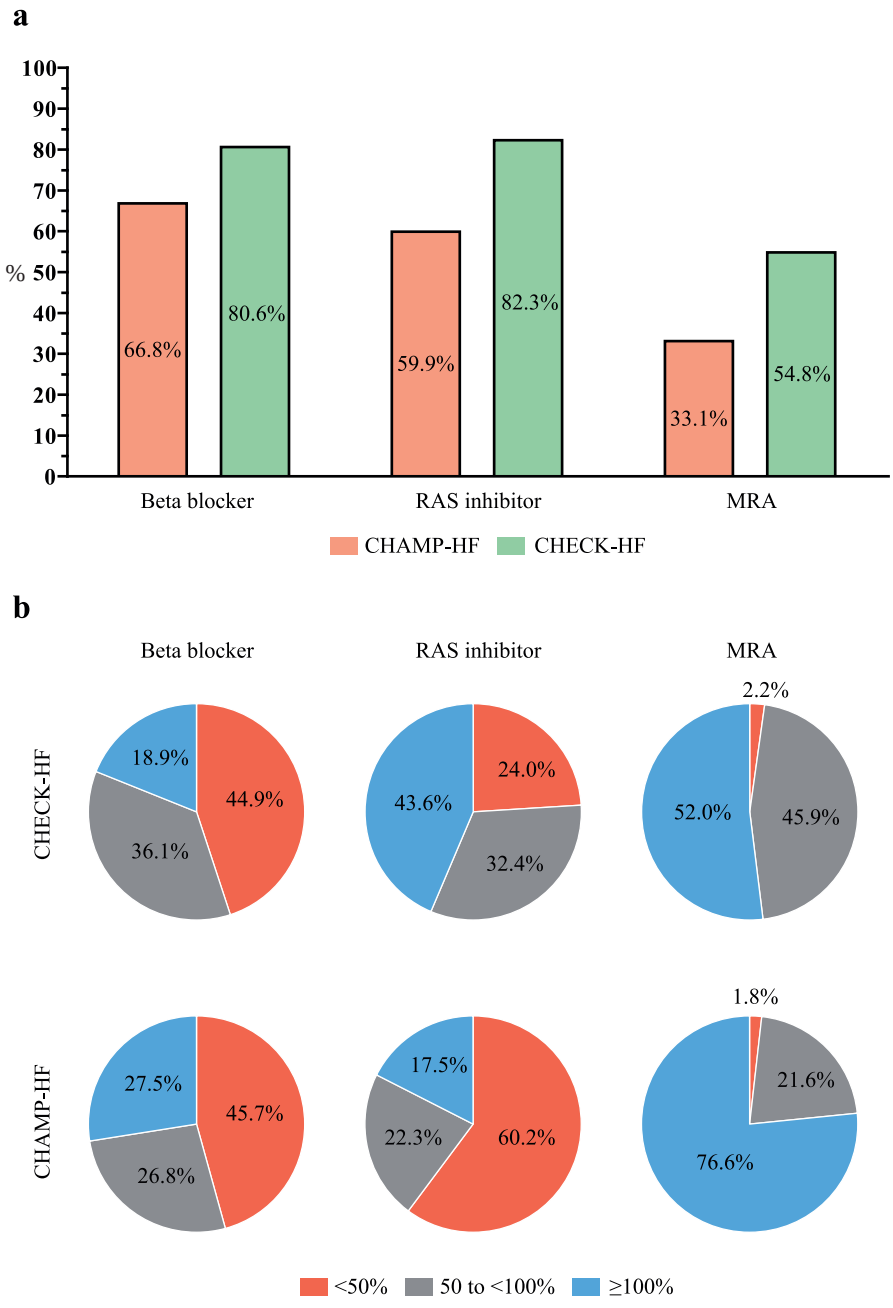

Fig. 4 Differences between the United States and the Netherlands in the use of (a) and dosing of (b) guideline-recommended medication in patients with heart failure and reduced ejection fraction in the CHAMP-HF [43] and CHECK-HF [44] registries. MRA mineralocorticoid receptor antagonist (Adapted from [43, 44], with permission)

There are no patient-level data for cost-effectiveness analyses in Western Europe. With assumptions and estimations based on extrapolating data from the CHAMPION trial and despite the large differences in standard care and financial systems, Cowie et al. [51] calculated the ICER in the European setting, which was approximately between €22,555 (for the Netherlands) and €23,814 (for Germany). However, all these analyses used data on the reduction of HF hospitalization from the CHAMPION trial and used different estimated mortality rates from population-based cohorts for the cost-effectiveness analyses.

Health care utilisation

Two studies investigated the potential reduction of health care utilisation achieved by using the CardioMEMS. [38, 52] In a real-world Medicare database, 1-year remote monitoring with the CardioMEMS led to an $11,260 cost reduction for HF hospitalisations compared with 1 year before the CardioMEMS implantation. [38] Based on the effects reported in the CHAMPION trial, and the expected prevalence and hospitalisation costs in Germany, remote monitoring with the CardioMEMS could lead to an overall cost reduction of 106,000,000 in Germany in 2021. [52]

As shown above, remote monitoring of PAP with the CardioMEMS in chronic HF patients leads to more medication changes and a larger reduction of PAP compared with patients receiving standard care, indicating that these patients receive more individualized HF care. In the US, this strategy was effective in reducing the number of HF-related and all-cause hospitalisations. It was suggested that this strategy could improve mortality rates and has been shown to be cost-effective. However, as discussed earlier, some important differences in HF care exist between the USA and Europe.

Recommendation of ESC 2016 guidelines on remote monitoring

The 2016 ESC guidelines report on the lack of consistent evidence for non-haemodynamic telemonitoring or remote monitoring in HF patients. The guidelines state that remote monitoring may be considered in selected patients to improve HF outcome with individual approaches such as CardioMEMS to reduce the risk of HF admissions and multi-parameter monitoring with ICD (in-time approach) to improve outcome in HFrEF patients with a level IIb class B recommendation. [53]

Conclusion

In recent years, many remote monitoring strategies have been developed, and development continues at a rapid rate. Non-invasive remote monitoring of symptoms and signs, as well as weight, has not been proven to be effective in improving outcome measurements. Also, the monitoring of biomarkers or thoracic impedance has not been shown to be beneficial. Invasive or haemodynamic measures of remote monitoring are developed with right-sided (CardioMEMS) and left-sided (LA devices) sensors. The LAPTOP-HF trial with LA devices was stopped early for safety reasons. The CardioMEMS is the most promising (invasive) remotemonitoring tool currently available. The haemodynamic information allows for a window of timely and adequate intervention based upon raised PAP, preventing an upcoming HF decompensation. Additionally, its safety and durability have been tested and confirmed in post-marketing studies. However, important information on the effect on the quality of life and cost-effectiveness is still lacking in a Western European setting, which is currently being investigated in the MONITOR-HF study.

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11

A randomized comparison of the effect of haemodynamic monitoring with CardioMEMS in addition to standard care on quality of life and hospitalisations in patients with chronic heart failure: design and rationale of the MONITOR HF multicentre randomized clinical trial

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* Equal contributions

Neth Heart J. 2020 Jan; 28(1): 16-26

Abstract

Background: Assessing haemodynamic congestion based on filling pressures instead of clinical congestion can be a way to further improve quality of life (QoL) and clinical outcome by intervening before symptoms or weight gain occur in heart failure (HF) patients. The clinical efficacy of remote monitoring of pulmonary artery (PA) pressures (CardioMEMS; Abbott Inc., Atlanta, GA, USA) has been demonstrated in the USA. Currently, the PA sensor is not reimbursed in the European Union as its benefit when applied in addition to standard HF care is unknown in Western European countries, including the Netherlands.

Aims: To demonstrate the efficacy and cost-effectiveness of haemodynamic PA monitoring in addition to contemporary standard HF care in a high-quality Western European health care system.

Methods: The current study is a prospective, multicentre, randomised clinical trial in 340 patients with chronic HF (New York Heart Association functional class III) randomised to HF care including remote monitoring with the CardioMEMS PA sensor or standard HF care alone. Eligible patients have at least one hospitalisation for HF in 12 months before enrolment and will be randomised in a 1:1 ratio. Minimum follow- up will be 1 year. The primary endpoint is the change in QoL as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ). Secondary endpoints are the number of HF hospital admissions and changes in health status assessed by EQ-5D-5L questionnaire including health care utilisation and formal cost-effectiveness analysis.

Conclusion: The MONITOR HF trial will evaluate the efficacy and cost-effectiveness of haemodynamic monitoring by CardioMEMS in addition to standard HF care in patients with chronic HF.

Introduction

In Western European countries such as the Netherlands, chronic heart failure (HF) is estimated to occur in 1.5–2.0% of the population. [1, 2] In the Netherlands, the prevalence was 227,000 patients in 2017, and the number of HF hospital admissions is high at 29,011 admissions per year with an average hospital stay of 9 days. [1, 2] The overall hospital burden from HF hospitalisations will rise rapidly in the coming decade due to aging of the population and better survival following myocardial infarctions. The main public and personal burden of HF is clustered in patients with New York Health Association (NYHA) functional class III and IV, who most often need to be hospitalised. Approximately 25% of all Dutch HF patients are in NYHA class III based on the latest CHECK HF registry findings. [3] Contemporary treatment of chronic HF shows a reasonably high adherence to European guidelines for the recommended drugs, when compared to US data in the CHAMP-HF registry. [4, 5] Still, both registries show considerable room for improvement in HF therapy considering target or optimal dosing of medication. [4, 5] So clearly, despite optimal medical treatment, there is a considerable residual risk, especially for patients in NYHA class III. The main problem for care givers and patients is timely recognition of a daunting cardiac decompensation and, if recognised, to react adequately and promptly.

Remote monitoring and telemonitoring initiatives have received wide attention for their promise in detecting early signs of decompensation and guiding HF therapy. Proactive guided treatment could optimize treatment further and prevent clinical deterioration. Such an approach could reduce HF hospitalisations and relieve the large burden of chronic HF exacerbations for the current health care systems. However, numerous telemonitoring programmes which were based on remote signs of clinical congestion such as weight or symptoms or impedance measurements through pacemakers have been largely disappointing. [6–15] From a physiological point of view, weight gain and symptoms of HF are late signs of an exacerbation of HF. New management strategies should focus on markers preceding the exacerbation of HF. It has been recognised that a period of decompensation starts with a rise in (intracardiac) filling pressures. A chain of events from haemodynamic (asymptomatic) congestion transits to clinical congestion.

CardioMEMS (Abbott Inc., Atlanta, GA, USA) is a small sensor capable of measuring pressures in the pulmonary artery (PA) on a daily basis. PA pressures can be used as an invasive haemodynamic surrogate marker of filling pressures, which has been shown

to precede a period of decompensation for several weeks. This time window would allow the physician to intervene before clinical symptoms arise and act in a proactive way to avert an exacerbation of HF by adjusting the dose of diuretics or vasodilators. In line with this hypothesis, the CHAMPION trial in the USA demonstrated a significant 37% reduction in HF hospitalisations with PA monitoring applied in addition to standard care in patients with chronic HF. [16, 17] Observations in post-marketing studies (with historical controls) were consistent and confirm the low-risk and safe procedure as well as the durability of the device. [17–20] Despite the innovation in patient management, several profound differences exist in the organisation of HF care (HF outpatient clinic and HF nurses), level of standard care, as well as financial structure of the health care systems in Europe and the USA, which mean that the results of this one trial cannot be translated directly. Additionally, individual trial data in a European setting are lacking and clinical and financial data can only be extrapolated from US data, [21, 22] in the knowledge that the costs and setup of the US health care system are not comparable to the European situation. We therefore designed the MONITOR HF randomised clinical trial to evaluate the effectiveness and cost-effectiveness from a European perspective in the Netherlands.

Methods

Study design

The MONITOR HF trial is an investigator-initiated, multicentre, randomised clinical trial enrolling 340 patients with chronic HF NYHA class III and at least one HF hospitalisation in the previous 12 months. In total, 20 Dutch hospitals, distributed over the country, agreed to participate (Fig. 1; Electronic Supplementary Material, Appendix Tab. 1). Sites without previous experience with CardioMEMS will go through a learning curve of two patients for sensor implantation and pressure management, who do not participate in the main trial but are followed according to study protocol. Alternatively, added centres can proctor two patients in an experienced centre. The MONITOR HF trial aims to test the effect of PA monitoring in addition to standard HF care on quality of life (QoL), the number of HF hospitalisations and cost-effectiveness in a Dutch health care system. Four populations for analysis are defined in the MONITOR HF trial: intention-to-treat, as-treated and per-protocol (time until implant after randomisation (maximum 3 weeks per protocol)) and safety analysis. The principal analysis for the primary effectiveness endpoint will be performed in the intention-to-treat population.

Fig. 1 Participating centres in the Netherlands

The MONITOR HF trial is sponsored by the Dutch Ministry of Health and National Health Care Institute (Zorginstituut, Nederland) as part of a conditional coverage programme in the Netherlands for the health-care-related costs. The study and data management are performed by the CRO Erasmus MC University Medical Centre (Sponsor).

Type of patients

Patients with chronic HF (≥3 months) in NYHA functional class III and at least one hospitalisation for HF (or emergency ward visit resulting in intravenous diuretic therapy) in the 12 months prior to enrolment are eligible for the trial. The diagnosis of HF is made according to the criteria set out in the 2016 European Society of Cardiology (ESC)

guidelines for the treatment of HF. [23] Patients with HF and reduced ejection fraction (HFrEF), mid-range (HFmrEF) or preserved ejection fraction (HFpEF) are eligible for the trial. The inclusion and exclusion criteria are presented in Tab. 1 and 2.

Table 1. Inclusion criteria. In order to be eligible to participate in this study, a subject must meet all of the following criteria

1	Written informed consent obtained from subject aged ≥18 years
2	Diagnosis of chronic heart failure[a] (≥3 months) in NYHA functional class III with 1 HF hospitalisation within 12 months (defined as an admission for HF longer than 6h and/or use of i.v. diuretics) or emergency ward visit for HF resulting in i.v. diuretic therapy (independent of EF %)
3	HF subjects with reduced EF (HFrEF) should be treated according to national and international (ESC) guidelines for optimal or maximum tolerated doses of HF medication and evaluated for ICD or CRT-D therapy, if indicated
4	Subjects with a BMI≤ 35. Subjects with BMI> 35 will require their chest circumference to be measured at the axillary level<65 inches or 165 centimetre (related to distance of the sensor to the pillow)
5	Subjects willing and able to comply with the follow-up requirements of the study and able to comply with the daily readings

[a] According to the definition given in the 2016 ESC guidelines for heart failure. [10] In line with good clinical practice, a patient cannot participate in any other interventional study or active telemonitoring programme (on HF parameters) during the study

NYHA New York Heart Association, *HF* heart failure, *EF* ejection fraction, *ESC* European Society of Cardiology, *ICD* implantable cardioverter-defibrillator, *CRT-D* cardiac resynchronization therapy defibrillator, *BMI* body mass index

Table 2. Inclusion criteria

1	Subjects with an active infection
2	Subjects with a history of recurrent (>1) pulmonary embolism or deep vein thrombosis
3	Subjects who have had a major cardiovascular event (e.g. myocardial infarction, open heart surgery, stroke) within the past 2 months
4	Subjects with a CRT implanted <3 months prior to enrolment and implantation of the sensor (in order to avoid manipulation of lead)
5	Subjects with an estimated GFR< 25ml/min (obtained within 2 weeks of the baseline visit), refractory to diuretic therapy, or on chronic renal dialysis
6	Subjects with complex congenital heart disease or mechanical right heart valve(s)
7	Subjects with known pulmonary arterial hypertension (WHO category 1 or 4/5) in whom PA pressure is most likely not responsive to cardiac treatment
8	Subjects scheduled for or likely to undergo heart transplantation or receive a ventricular assist device within 6 months of baseline visit
9	Subjects with known coagulation disorders or allergy to acetylsalicylic acid and/or clopidogrel

CRT cardiac resynchronisation device, *GFR* glomerular filtration rate, *PA* pulmonary artery

Randomisation

At the baseline visit, patients will be randomised in a 1:1 ratio for standard care plus CardioMEMS PA monitoring versus standard HF care with written and signed informed consent. Crossover is not allowed per study protocol and leads to termination of the patient's participation in the study. After randomisation, the sensor is to be implanted within 3 weeks per protocol in those randomised to CardioMEMS and a second informed consent form will be signed for use of the Merlin.net website.

CardioMEMS system

The CardioMEMS HF system includes an implantable wireless sensor with delivery catheter, a patient and hospital electronics system and a patient database (Integrated Merlin.net website for patient data management). [16] The sensor measures PA pressure using MEMS (micro-electromechanical systems) technology and requires neither battery nor leads (wireless). The sensor is implanted in a branch of the left PA via a transvenous catheter inserted through the femoral vein. The sensor is 15mm in length, 3.4mm in width and 2mm thick. The sensor remains in the PA as a permanent implant which endothelialises completely (Fig. 2). A 4-week course of acetylsalicylic acid and clopidogrel is recommended in those patients without anticoagulation or platelet inhibition. [16] Clinicians are informed about the daily CardioMEMS derived PA and PA trends over time via Merlin.net (diagnostic tool in disease management). A study operating procedure will be available for clinicians to help them guide HF therapy, most importantly based on a significant rise in PA pressure over time, aiming for normal PA pressures avoiding progressive clinical congestion, or additionally, a significant fall in PA pressure over time avoiding chronic hypovolaemic triggers. The device is FDA approved and CE marked for use in chronic HF patients in NYHA class III and with one HF hospitalisation in the previous year (NYHA classes, Tab. 3).

Fig. 2 a The CardioMEMS sensor (with permission of Abbott Inc.). **b** The CardioMEMS HF system patient unit including antenna (with permission of Abbott Inc.). **c** Location of the CardioMEMS sensor in the left pulmonary artery (with permission of Abbott Inc.)

Table 3. New York Health Association classification of heart failure symptoms

NYHA class I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc
NYHA class II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity
NYHA class III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100m). Comfortable only at rest
NYHA class IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients

Standard care

In patients with HFrEF, standard care is defined as treatment according to the recommendations in the national and ESC guidelines for HF with up-titrating recommended HF therapies to maximum tolerated or optimal dosages and to evaluate the patient for an ICD/CRT-D when indicated. [23] For HFpEF (and HFmrEF) treatment recommendations are lacking, but in accordance with the 2016 ESC guidelines it is advised to focus on optimal management of comorbidities and cardiovascular risk factors such as hypertension and atrial fibrillation. [23] All Dutch hospitals have a structured HF outpatient clinic with specialized HF nurses who are supervised by a cardiologist with experience or specific interest in HF treatment. At these outpatient clinics, patients are seen for the uptitration of HF drug therapies at frequent intervals to reach optimal or maximum tolerated dosages of evidence-based medication. Treatment choices are at the discretion of the physician. Further, patients are counselled, e.g. about the aetiology of their HF, diet, fluid and salt restrictions, as well as the importance of treatment compliance and of abstaining from tobacco use and minimising alcohol consumption. Patients are instructed when to contact the outpatient clinic in case of alarming symptoms or abnormal weight gain. After hospital discharge, patients are generally seen by the HF nurse within 2 weeks, and we estimate that patients visit these outpatient clinics on average 3 times/year to see the nurse and at least 2 times/year to see the cardiologist depending on their clinical need and ongoing therapeutic decisions.

Hypothesis

We hypothesise that the CardioMEMS HF system applied in addition to standard care will improve QoL and reduce HF hospitalisations in patients with chronic HF.

Clinical study

Inclusion window/enrolment

The planned inclusion phase is 24 months. Twenty centres have initially been selected to start including patients in this study. In anticipation of a stable inclusion rate, we calculate a mean inclusion rate of 0.7 patients per centre per month to reach a sample size of 340 patients in 2 years. Patient inclusions are competitive between centres. If, at 6 months, the inclusion rate is lower than 50% of that expected, the number of sites can be increased, if necessary.

Duration of follow-up

All patients will be followed for at least 12 months, resulting in a minimum follow-up of 12 months (for the last patient included) and a maximum follow-up of 36 months (for the first patient included) according to the above-mentioned enrolment schedule. The follow-up visits are scheduled at 3, 6, and 12 months and every 6 months thereafter (Fig. 3).

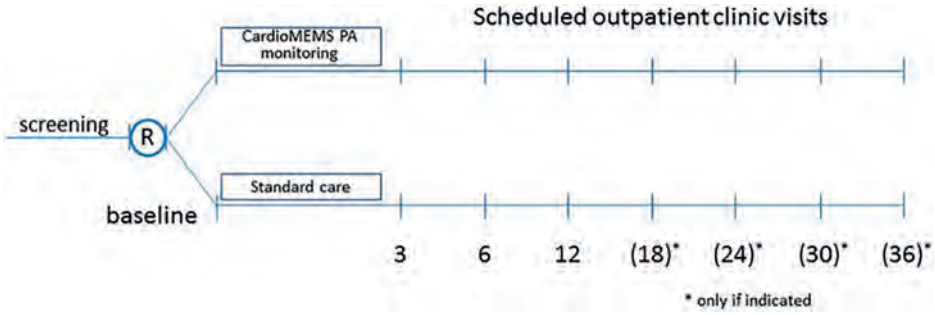

Fig. 3 The MONITOR HF trial follow-up scheme. Randomisation at baseline visit

Patient visits

At baseline demographics, medical history and medication use are evaluated. An echocardiogram is part of the baseline visit (type of HF) as well as a detailed laboratory assessment, QoL questionnaires (Kansas City Cardiomyopathy Questionnaire (KCCQ) and EQ-5D-5L) and a 6-min walk test (6MWT). [24, 25] During follow-up visits, an electrocardiogram (ECG) is recorded in all patients, NYHA class is established, and a physical examination is performed, including vital parameters and standard laboratory assessments, which will consist of renal function and natriuretic peptides (NTproBNP or BNP). Serum samples are stored at regular intervals for a biobank at Durrer Center for Cardiovascular Research. A 6MWT is performed at baseline, 6 and 12 months of follow-up. Serial echocardiography is performed at baseline, 12 months and 24 months of follow-up. The KCCQ is performed at baseline, 3, 6 and 12 months, EQ-5D-5L at baseline,

3, 6, 12 and 24 months of follow-up. An iMTA Medical Consumption Questionnaire (iMCQ) for health care utilization and health technology assessment (HTA) analyses is performed prospectively at 3, 6 and 12 months. [26] Changes in medication and reasons for change are recorded in a detailed logbook. In another detailed logbook, information on patient contacts is recorded, including the reason for contact, direction of contact and location (telephone, general practitioner, outpatient clinic, emergency ward, clinic).

Outcome measures

Primary endpoint: Change in QoL as assessed with the KCCQ HF questionnaire

The KCCQ questionnaire is conducted at baseline (t= 0), and at follow-up intervals of 3, 6 and 12months' follow-up after randomisation in both treatment arms. Primary analysis is based on change in KCCQ scores at 12 months (Tab. 4). The KCCQ questionnaire assesses QoL in HF patients and has undergone extensive validation in HF populations. [27, 28]

Table 4. Study endpoints

Primary endpoint	Quality of life as measured by the KCCQ HF questionnaire at 12 months' follow-up
Secondary endpoint	The number of HF hospitalisations during follow-up
	Health status as measured by the EQ-5D-5L questionnaire

KCCQ Kansas City Cardiomyopathy Questionnaire, *HF* heart failure

Secondary endpoints

- The number of HF hospitalisations during followup, defined as an unscheduled admission for HF longer than 6h and/or the need for intravenous diuretics for decongestion of the patient.
- Change in health status as assessedwith the EQ-5D-5L questionnaire.

Other endpoints will be all-cause mortality; all-cause hospitalisations; scheduled HF hospitalisations, composite of all-cause mortality and cumulative HF hospitalisations; cardiovascular mortality; days alive outside of the hospital; days in hospital; emergency ward visits (or equivalent), composite of HF hospitalisations and emergency ward visits for HF, change in NYHA class, health care utilisation, number of patient contacts, change in baseline PA pressure; number ofmedication changes.

Statistical analysis

Sample size

The conditional coverage agencies requested 90% power on QoL endpoints and at least 85% for the secondary endpoint HF admissions in order to have adequate estimates of effect sizes for cost-effectiveness analyses (which are dependent on this set of variables). We decided to aim for 90% statistical power to detect an at least 6-point difference in KCCQ overall summary (KCCQ-OS) score between randomised treatment groups [27]; we calculated, at an alpha level of 0.05 and standard deviation (SD) of 15, group sizes of N1 133 and N2 133 patients (total sample size 266 patients). With an anticipated 10% withdrawal rate, we will need to include 292 patients in total. For the secondary endpoint of HF admissions, we used two assumptions of estimated treatment effect size and estimated event rates of HF hospitalisations in the Netherlands. The long-term results of the CHAMPION trial, more comparable to our follow-up length, showed a reduction of 33% in HF hospitalisations compared to controls (182 HF hospitalisations vs 279 HF hospitalisations, in 270 and 280 patients treated with CardioMEMS vs standard care, respectively; average follow-up 18 months) and the Dutch COACH trial provided an event rate of 2.03% per month in a comparable but slightly less sick cohort of chronic HF patients. [16, 17, 29] Under these assumptions, at least 85% statistical power at an alpha level of 0.05, and a treatment effect size of CardioMEMS of 33% and event rate of 2.0% per month in the control group, when N1 164 and N2 164 patients, a total of 328 patients is to be included. For the secondary endpoint, EQ-5D-5L improvement in health status, 90% statistical power to detect a significant difference of 0.06at an alpha level of 0.05 and SD 0.18, a sample size of N1 155 and N2 155 totalling 310 patients is needed, and by including a 10% early withdrawal rate a total sample size of 340 patients is to be included. Therefore, the total sample size of the trial required to adequately answer the research questions is 340 patients.

Data analysis

Data will be summarised using univariate statistics (number, mean, standard deviation, median) or frequency (number, percentage). For baseline characteristics, between-group comparisons will be performed with the $\chi 2$ test for categorical variables and two-sample t-tests for continuous variables. The primary time-point for effectiveness analyses on improvement of QoL is 12 months. Change in the KCCQ-OS from baseline to 12 months will be compared between the intervention and standard care groups. Additionally, a linear mixed-effects model will be used to compare change in the KCCQ-OS over time between the randomly allocated treatment groups to account for missing data and longitudinal trends. The effect of CardioMEMS in comparison to standard care

in changes of KCCQ clinical summary and KCCQ-OS scores is compared using repeated measurement analysis of covariance adjusted for baseline KCCQ score. EQ-5D-5L scores will be analysed in a comparable manner. The secondary endpoint in the study is the number of HF hospitalisations during follow-up. A Cox proportional hazard regression model with Anderson-Gill method for recurrent events will be used for analysis of clinical events (HF hospitalisations, mortality rates). Additionally, Cox proportional hazard models are implemented to analyse time to first events, including mortality and hospitalisation. Hospitalisation rates and mortality rates are estimated using the Kaplan-Meier method, and p-values are computed using the log-rank test. All reported analyses are performed using the intention-to-treat principle. All statistical tests will be 2-sided with a significance level of 0.05.

Cost-effectiveness analysis

The cost-effectiveness analyses will be conducted in accordance with the Dutch guidelines for HTA and will calculate incremental-cost-effectiveness ratio (ICER) per quality-adjusted-life-year (QALY) gained both from a societal as well as health care perspective. For cost-effectiveness analyses, the EQ-5D-5L is the required standard tool to use. In addition, iMCQ, a generic instrument for measuring medical costs [26], will be used together with costs from the Dutch costing manual. [28] Cost-effectiveness will be evaluated by use of a decision analytical model, e.g. a Markov cohort simulation, developed to capture the clinical events and costs for the current and a (hypothetical) cohort of patients. The number of states (e.g. alive or dead; NYHA class; hospitalised; after a cardiovascular event) and transitions between these states distinguished in the cost-effectiveness model will be chosen based upon the available evidence regarding the natural history of disease and treatment pathways. Survival probabilities beyond the trial period can be estimated by fitting a parametric survival model to the trial data. For patients who are alive, the period of survival can be weighted by patients' utility measured with the EQ-5D-5L. Similarly, the out-of-hospital period will be weighted by patient utility EQ-5D-5L. Missing data in the EQ-5D-5L questionnaires can be adjusted for using linear effect models or multiple imputations. Costs evaluated in the model included those for sensor implantation and device, care, HF hospitalisation, medication changes, number of visits, and end-of-life support for those who died. To extrapolate costs beyond follow-up, we will make use of standardised estimates of health-care spending from the Netherlands. [30] Total costs and QALYs will be modelled according to the time (in intervals) patients spent in each health state. The ICER will be evaluated against the appropriate severity-weighted threshold for cost-effectiveness.

Trial structure, registration and organisation

The MONITOR HF trial is designed, implemented and overseen by an independent executive board and steering committee. The study was evaluated by scientific committees (ZonMW) and councils of the National Health Care Institute and patient councils. Site and data management is performed by the CRO Erasmus MC trial organisation. An independent data safety monitoring board (DSMB) has been established and will review safety data on an ongoing basis during the trial in accordance with the DSMB charter. An independent clinical endpoint committee (CEC) has been established, blinded to study group assignment, and will review and adjudicate all deaths and hospitalisations using prospectively defined criteria in the CEC charter. The adjudicated data are used for outcomes regarding hospitalisations and deaths. The DSMB and CEC are organised and led by an external independent organisation (Cardialysis, Clinical Trial Research Centre). The clinical trial is structurally monitored by independent monitors from the research trial organisation. The study complies with good clinical practice in accordance with the Declaration of Helsinki and the laws and regulations applicable in the Netherlands, including the European Union General Data Protection Regulations, as the clinical trial has been approved by the appropriate medical ethics committee and review board (Erasmus MC, MEC 2018-1563). The clinical trial was registered under the number NL7430 (NTR7672, clinical trial registration number) on 12 December 2018. The study started enrolment on 1 April 2019.

Discussion

This multicentre, randomised clinical trial (MONITOR HF) will evaluate the efficacy and cost-effectiveness of remote PA monitoring with CardioMEMS applied in addition to standard care in patients with chronic HF, from a European perspective. The benefits of remote monitoring with CardioMEMS were demonstrated in the CHAMPION trial of 550 participants in the US, who were studied between 2007 and 2009 [14], and have been confirmed in several large-scale post-marketing registries. [15–17]. The MONITOR HF trial will provide contemporary trial data on the effectiveness of CardioMEMS in a highly organised European health care system where HF patients are routinely followed in dedicated HF outpatient clinics after an HF admission. The recently published CHAMP-HF and CHECK-HF registries highlight the differences in guideline adherences between the Netherlands and the USA. [3–5] Additionally, profound differences exist between Europe and the USA as regards the organisation of health care as well as financial structures. The current study will provide the individual data necessary to perform calculations on cost-effectiveness of remote monitoring from a European health care perspective.

In the CHAMPION trial, QoL was not a primary endpoint and data are only available on small subsets of patients with a short follow-up. [16] The current trial has QoL as a primary endpoint, which is a novel aspect in telemonitoring but is emerging as a relevant clinical endpoint in HF trials. Additionally, QoL might hypothetically be valued most by the patient, as living longer in poor health might not be the main focus of choice. For the secondary endpoint, the number of HF hospitalisations, it is most likely that rehospitalisation rates differ between the USA and Europe, and we expect a lower event rate in the Dutch health care system with dedicated HF nurses and HF outpatient clinics as the organisation of standard care differs. [29] Dedicated HF outpatient clinics and structured HF care after HF admissions are emerging throughout Europe as standard HF care, including multidisciplinary team approaches, heart teams, and cardiac rehabilitation programmes as advocated in the 2016 ESC guidelines. [23] The recently published US Post Approval Study (PAS) confirms the consistent treatment benefit with CardioMEMS in chronic HF patients, reducing the number of HF hospitalisations in a more contemporary setting. [20] However, the patients included in the PAS study were their own historical controls and no randomised comparison to standard care without PA monitoring was made. However, the main inference of the PAS is the consistent safety of the implantation procedure and the durability of the sensor without sensor failures. [20]

From a financial point of view, a cost-effectiveness analysis using the US CHAMPION trial data calculated an ICER for costs per QALYs of $29,593 for CardioMEMS based on US health care data. [21] Extrapolating the US data to European health care systems, such as those in the UK, the Netherlands and Germany, showed that PA-pressure-guided HF therapy is anticipated to be cost-effective, but the intervention increases costs compared with usual care by £10,916 over a time horizon of 10 years while the ICER is estimated to be £19,274 with a reduction in admissions. [22] The analysis did not include staff time, due to a lack of data concerning this variable. Running the model with estimated staff time included resulted in an increased ICER of between £22,342 and £25,464 per QALY gained. [22] No individual data from European systems are currently available.

Other forms of telemonitoring and available evidence

Several studies have been performed using non-haemodynamic parameters of remote monitoring such as signs and symptoms of HF, blood pressure or daily weights. These studies have shown no effect on HF hospitalisations. [6–15] Clearly, simple markers such as weight or blood pressure are inadequate for monitoring fluid status and if the variation in weight is caused by decompensation, treatment comes too late and cannot prevent

a hospitalisation. Additionally, some studies have investigated natriuretic peptides to guide HF therapy, but these were not successful in reducing HF hospitalisations. [10] Other studies with non-haemodynamic parameters of remote monitoring have focused on information from ICD devices using intrathoracic impedance or other specific combinations of parameters in algorithms. [13–15] None of these studies have shown any actual benefit in reducing the number of hospitalisations. Most recently, the TIM-HF 2 trial was one of the first studies to show a small benefit of remote monitoring in HF patients with regard to length of hospital stay, despite its labour intensity (fully staffed telemedicine centre).[11]

The 2016 ESC guidelines report on the lack of consistent evidence for non-haemodynamic telemonitoring or remote monitoring in HF patients. The guidelines state that remote monitoring may be considered in selected patients to improve HF outcome with individual approaches such as CardioMEMS to reduce the risk of HF admissions and multi-parameter monitoring with ICD (in-time approach) to improve outcome in HFrEF with a level IIb class B recommendation. [23]

Future developments and potential impact

The most essential concept remains the shift from remote monitoring with (late) signs of clinical congestion to parameters of (early) haemodynamic congestion, which precede all above non-haemodynamic parameters by several weeks and provides a window of proactive intervention in order to prevent further exacerbation of HF. In this way, it makes sense that nonhaemodynamic parameters have not made a significant impact in remote monitoring of HF patients to date despite their simplicity and the relatively low effort involved, for instance in monitoring weight. The current trial sets out to evaluate the benefit of CardioMEMS remote monitoring versus standard care in relation to QoL and HF hospitalisations as well as cost-effectiveness in the Netherlands. If proven effective, this has important implications for countries with similar health care structures and levels of HF care in Western Europe. The field of remote monitoring is most likely to develop further with additional tools for patient control and pressure feedback with more sophisticated monitoring websites or tools and patient self-management. The HF path of care will evolve into a more structured approach integrating remote monitoring to achieve a proactive, preventive approach to patient care instead of passive, symptom-driven care delivery. Remote monitoring has the potential to lower the overall hospital burden (number of outpatient visits, admissions and resources used) of HF in an attempt to keep the stable patient out of hospital and the unstable patient in hospital only if refractory to remote interventions at home.

Strengths and limitations

The current trial is important as it is the first randomised clinical trial in Europe comparing haemodynamic remote monitoring by CardioMEMS with a control group in chronic HF. The trial is adequately powered to test the efficacy of CardioMEMS (in addition to standard care) in improving QoL and reducing HF hospitalisations as compared to standard care. Additionally, this trial will provide further contemporary data with CardioMEMS in addition to the CHAMPION trial and post-marketing registries. As randomisation is essential in efficacy studies (but lacking in post-marketing studies), the current European trial is the first with a control group of standard HF care after the US CHAMPION trial. This MONITOR HF trial will not have a sham procedure in consultation with the MEC and patient councils for a variety of reasons. A sham procedure and sham measurements every day during 3 years of follow-up was deemed unethical with a futile risk, patient efforts and costs. Furthermore, we argue that daily sham measurements (with the sensor turned off, but with its costs) are not a part of current standard care and would impact the true comparison with standard care as it is actually delivered. We recognise that the lack of a sham procedure may introduce a potential bias in the standard care arm. However, this effect can be of any magnitude, direction and degree for each individual patient, either positive or negative (as the technique is most likely not suited for all), and therefore it will be complex to completely quantify the placebo effect (and directions). We will keep precise track of medication changes in response to abnormal readings of PA pressure and HF admissions as well as detailed records of health care utilization rates, to provide objective proof of subjective improvements. Finally, despite the mentioned limitations, proactive monitoring and interventions based upon pre-symptomatic pressure shifts are needed to achieve any actual sustained benefit of the device. The design of the current trial and the involvement of HTA experts from the start of the project ensures high-quality data for future cost-effectiveness analyses and modelling from a Western European perspective, including detailed health care utilisation data.

Conclusions

The MONITOR HF randomised clinical trial compares haemodynamic remote monitoring with the CardioMEMS PA sensor in addition to contemporary standard care versus standard care in improving QoL and reducing HF hospitalisation in patients with chronic HF in NYHA class III independent of left ventricular function. In addition, the study will evaluate health care utilisation and cost-effectiveness in Western Europe from a societal and health care perspective.

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12

Morning pulmonary artery pressure measurements by CardioMEMS are most stable and advocated to use for remote monitoring of pressure tends

Crnko S, Brugts JJ, Veenis JF, De Jonge N, Sluijter JPG, Oerlemans MIF, Van Laake LW

Under embargo

Submitted

13

Monitoring pulmonary artery pressures in chronic heart failure patients and evaluating the treatment effect of MitraClip implantation for functional mitral regurgitation

Veenis JF, Van Mieghem NM, Caliskan K, Manintveld OC, Brugts JJ

EuroIntervention 2019 Aug 29; 15(5):418-419

In chronic heart failure (HF) patients, functional mitral valve regurgitation (FMR) is a common finding and is associated with worse outcome. The position of the MitraClip™ (Abbott Vascular, Santa Clara, CA, USA) as a therapeutic option is still debated after the publication of the MITRA-FR and COAPT trials, showing conflicting results.

A 51-year-old male, with a history of severely dilated, non-ischaemic cardiomyopathy, severe FMR, actively on the heart transplant (HTx) waiting list, remotely monitored with the CardioMEMS™ sensor (Abbott Vascular), developed persistent elevated pulmonary artery pressires (PAPs) (mean 42 mmHg), despite high-dose diuretics, which were limited by prerenal insufficiency. Swan-Ganz measurement demonstrated no reversibility of pulmonary hypertension (PH) (mean PAP [mPAP] 42 to 35 mmHg), wedge pressure (23 to 22 mmHg) or transpulmonary gradient (TPG) (19 to 13 mmHg) after intravenous administration of nitroglycerine at maximal tolerated dosage (due to a significant drop in systemic blood pressure). The Heart Team judged that the patient was not a good candidate for an HTx at this stage due to the high pressures.

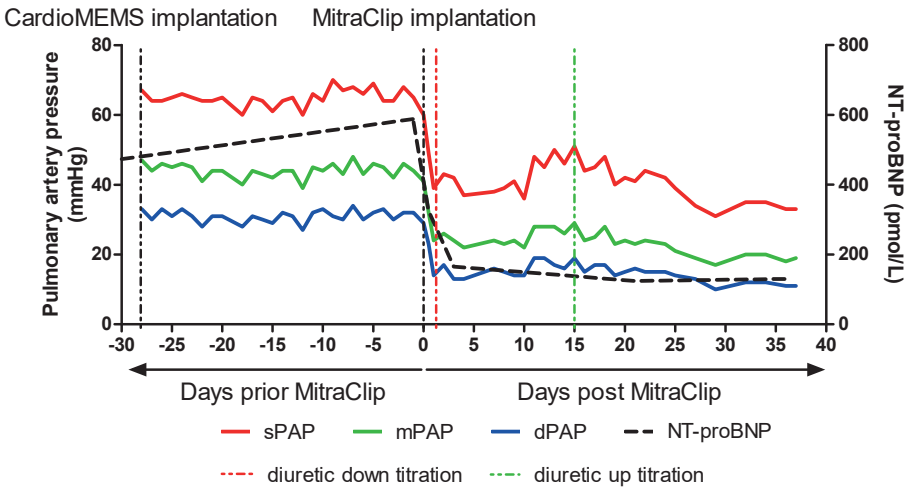

Figure 1. pre- and post-MitraClip daily PAP readings

In this setting, it was unclear how much the severe FMR contributed to the PH. The Heart Team decision was made for a MitraClip implantation. On the day of implantation, mPAP was 45 mmHg. After successful implantation of two MitraClips, FMR was reduced to mild on echocardiography, and mPAP dropped to 32 mmHg. In the following days, mPAP dropped to 23 mmHg (**Figure 1**). NT-proBNP decreased from 579 pmol/L (normal <14 pmol/L) pre implantation to 165 pmol/L four days post implantation. Kidney function

(estimated glomerular filtration rate [eGFR]) improved from 62 ml/min to 72 ml/min and, based on the normalised PAPs, the diuretic dosage was decreased, and the patient was discharged in a good clinical condition. During follow-up, the CardioMEMS showed a gradual rise of PAP, on which the diuretic dosage could be titrated again to maintain normal PAP at the normal home setting. A Swan-Ganz measurement was repeated approximately 1.5 months after MitraClip implantation (mPAP 19 mmHg, wedge pressure 12 mmHg, TPG 7 mmHg), confirming the CardioMEMS readings. Subsequently, the patient returned to active status on the HTx waiting list.

The CardioMEMS offers valuable and unprecedented information to the treating physician to monitor the effects of therapy modifications, such as medication or dosage changes[1], or valvular interventions such as a MitraClip implantation. This unique "at home" haemodynamic feedback for the treating clinicians allows further therapy optimisation.

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C

Remote monitoring of left ventricular assist device supported patients

Chapter 14
Remote monitoring for better management of LVAD patients:
the potential benefits of CardioMEMS

Chapter 15
Monitoring pulmonary pressures during long-term continuous-flow left ventricular assist device and fixed pulmonary hypertension: redefining alleged pathophysiological mechanisms?

Chapter 16
Design and rationale of haemodynamic guidance with CardioMEMS in patients with a left ventricular assist device: the HEMO-VAD pilot study

Chapter 17
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Short term results from the HEMO-VAD pilot study

Chapter 18
Safety and feasibility of a hybrid construction of hemodynamic guidance by pulmonary artery pressure monitoring and left ventricular assist device management: Main findings of the proof of concept HEMO-VAD study

14

Remote monitoring for better management of LVAD patients: the potential benefits of CardioMEMS

Veenis JF, Brugts JJ

Gen Thorac Cardiovasc Surg. 2020 Mar; 68(3):209-218.

Abstract

Left ventricular assist devices (LVAD) are frequently used in the treatment of end-stage heart failure (HF), and due to the shortage of heart donors and destination programs, it is likely to keep on growing. Still, LVAD therapy is not without complications and morbidity and rehospitalization rates are high. New ways to improve LVAD care both from the side of the patient and the physician are warranted. Remote monitoring could be a tool to tailor treatment in these patients, as no feedback exists at all about patient functioning on top of the static pump parameters. We aim to provide an overview and evaluation of the novel remote monitoring strategies to optimize LVAD management and elaborate on the opportunities of remote hemodynamic monitoring with CardioMEMS, at home in these patients as the next step to improve care.

Introduction

Epidemiological data on end-stage heart failure (HF) is scarce. Estimations performed by the America Heart Association suggest that < 1% of all HF patients are in end-stage HF. [1] Other studies estimated that approximately 5–10% of the HF population develop at some moment in life advanced HF despite optimal medical treatment. [2] These patients become refractory for medical therapy and are frequently hospitalized and have high mortality rates, leaving heart transplantation or left ventricular assist device (LVAD) implantation as the only treatment options. Due to shortness in available heart donors, LVAD implantation rates continue to rise. [3, 4]

Despite new LVAD designs and technological improvements, LVAD care remains very complex and associated with high mortality and with many rehospitalization and outpatient contacts. [3, 5, 6] The main reason for hospitalization is gastrointestinal (GI) bleeding or LVAD-related (driveline) infection, followed by decompensated HF and arrhythmia. [7, 8] Due to the growing number of patients treated with a LVAD, combined with the high hospitalization and complication rates, LVAD care places a high burden on hospital resources, with many logistical challenges with available hospital beds, as many other departments are not familiar with LVAD devices, so LVAD patients preferably are admitted at a cardiology ward despite non-cardiac admission indications.

It is difficult for pump optimization to be available in a short time at the outpatient clinic and so it is only based on echocardiographic images and static pump parameters.

Patient self-management and remote monitoring is an important part of chronic HF care, to prevent admission. Due to the complexity of LVAD care, remote monitoring has the potential to provide valuable information to help the physician in structured decision making. It has been suggested that remote monitoring of pump parameters, combined with remote monitoring of blood pressure, pacemaker-related parameters, coagulation values, and driveline exit parameters could improve LVAD care. [9] However, many of these investigations are still unexplored, and not yet tested in large populations. We aim to provide an overview of these new technological advances for the remote monitoring of LVAD patients.

The LVAD and hemodynamics

Different LVAD designs, pump mechanisms (axial or centrifugal), and implantation techniques are used. The two most common used LVADs are the HeartMate 3 (HM3,

Abbott Inc, Atlanta, GA, USA) and the HVAD (Medtronic Inc, Framingham, MA, USA) (Fig. 1. Both are centrifugal pumps, placed in the pericardial space. The HM3 uses a fully magnetic levitated pump rotor, whereas the HVAD uses passive magnetic and hydrodynamic thrust bearings. [10–12]

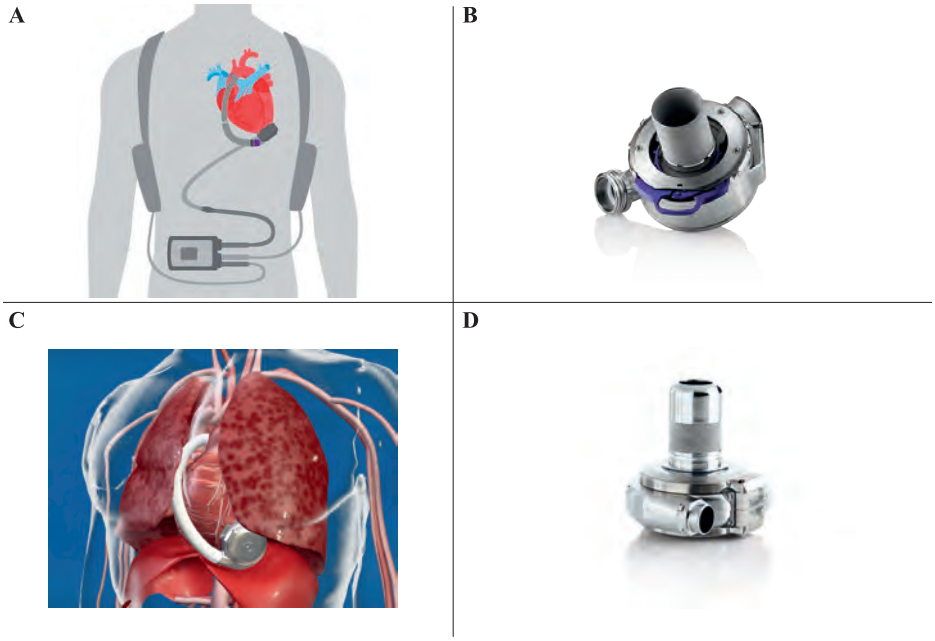

Fig. 1 Schematic presentation of the HeartMate 3 (**a**) and HeartWare LVAD (**c**), and close-ups of the pump house and inner work (**b, d**, resp) Courtesy of Abbott, Inc. and Medtronic, Inc. to provide the illustrations

Common LVAD-related complications

LVAD care can be lifesaving, however, it is also associated with several LVAD-related complications, such as right ventricular (RV) failure, LVAD-related infection, cardiac arrhythmia, hemolysis and thrombosis, GI bleeding due to angiodysplasia and renal dysfunction. [13] An overview of the incidence rates of common LVAD complications in HM3 and HVAD LVADs is presented in Table 1.

RV failure is a serious hemodynamic complication, occurring in up to 20–30% of the LVAD patients. [14–17] Signs of RV failure are elevated central venous pressure (CVP) and manifestations of elevated CVP, such as edema, ascites or increasing renal dysfunction. [18]

Table 1. Common LVAD-related complications

	HeartMate 3			HeartWare		
	Short term	**Medium term**	**Long term**	**Short term**	**Medium term**	**Long term**
RV-failure	8,0	10,0-14,7	14,0-31,7	-	25,4	-
Resulting in RVAD implantation	4,0	4,0-6,7	3,2-4,0	2,1-4,0	1,4-3,3	6,0
Bleeding	30,0	25,1-38	42,9-50,0			
GI-bleeding	4,0	6,0-8,0	20,0-27,0	3,3-4,3	9,9-12,7	-
Resulting in surgical intervention	12,0	10,2-14,0	12,2-16,0	12,0-16,0	14,3-14,8	20,0
Infection	20,0	35,2-36,0	52,0			
Driveline infection	2,0	11,7-16,0	23,8-24,0	0,0-3,6	12,1-16,9	18,0
Sepsis	8,0	9,1-16	13,8-22,0	2,0-3,0	11,4-17,2	10,0
Suspected or confirmed pump thrombosis	0,0	0,0	1,1	0,0	2,1	-
Resulting in surgical intervention	-	-	0,0	0,3	4,2	-
Stroke	4,0	5,4-12,0	10,1-24,0			
Ischemic	0,0	3,9-4,0	6,3-24,0	3,3-5,0	7,1-14,1	4,0
Hemorrhagic	4,0	1,5-8,0	4,2-8,0	0,0-2,1	5,7-12,7	8,0
Cardiac arrhythmia	28,0	34,0	37,6	-	-	-
Ventricular	-	-	23,8	2,0-10,2	20,7-20,8	4,0
Supra-ventricular	-	-	17,5	14,8-15,0	20,0-21,4	-
Organ dysfunction						
Renal dysfunction	10,0	10,0	13,2	5,1-10,0	8,6-9,6	10,0
Hepatic dysfunction	2,0	2,0	4,2	1,8-2,1	2,9-4,8	6,0
Respiratory dysfunction	14,0	16,0	23,8	14,0-16,0	20,0-22,0	16,0
References	[24]	[15, 17, 24]	[15, 16, 26]	[25, 28]	[18, 25, 26]	[28]

Short term defined as < 1 month; medium term defined as 6–12 months; long term defined as 2 years; – data not available

RV right ventricle, *RVAD* right ventricular assist device, *GI* Gastrointestinal

Tamponade, which can develop shortly after LVAD implantation, is a feared complication, occurring in up to 20% of the LVAD patients. [19] Symptoms usually occur in a late stage, and common hemodynamic signs, such as tachycardia, shock or pulsus paradoxus can be masked by the LVAD pump. [20] Late tamponade can be hard to visualize on echocardiography until the patient is in shock, and the first sign might be a drop in pump parameters. [21, 22]

GI bleeding is a common complication in LVAD patients, affecting up to 20–30% of the patients. [14–17, 23–25] GI bleeding has different presenting symptoms, 50% of patients present with melena, 25% with unexplained anemia, 15% with hematochezia and 10% with hematemesis. [26]

LVAD-related infections occur in 10–25% of the LVAD patients in the first 3 months after LVAD implantation. [14–16, 23–25, 27] Presenting symptoms are fever, erythema at the driveline site, or purulent fluids from the driveline exit site.

Pump thrombosis affects approximately 15% of axial-flow LVAD, and 1% of centrifugal-flow LVADs. [14–16, 23, 25] Pump thrombosis is characterized by signs of worsening HF in the patients, which cannot be explained otherwise, abnormal pump parameters and signs of hemolysis in laboratory results, such as elevated LDH. [28, 29]

Quality of life

All the above-mentioned LVAD-related complications affect the mortality and morbidity of LVAD patients. However, the complications and the hospitalizations due to these complications also affect the quality of life of LVAD patients. Especially in patients with an LVAD as the destination therapy, quality of life should be the main focus. [30] Remote monitoring of LVAD patients could aid in improving the quality of life of LVAD patients. By earlier detection of LVAD-related complications, earlier intervention is possible, potentially reducing the number of rehospitalizations. Additionally, LVAD settings and the patient's status could be better monitored, allowing for better optimization of the pump settings, improving the pump function. [31]

Monitoring strategies

Non-invasive remote monitoring

An overview of remote monitoring strategies in LVAD patients is showed in Table 2. One of the keystones in traditional ambulant HF management is the active participation of patients with their medical care team. The use of noninvasive remote monitoring, or structured telephone monitoring in HF patients, has been investigated in multiple trials showing different results. [32] A recent Cochrane review showed that the use of non-invasive and structured telephone remote monitoring reduced mortality and HF-related hospitalizations. [32]

At this moment, there is one study that investigated the use of a structured telephone remote monitoring system in LVAD patients. [33] This retrospective study investigated 96 LVAD patients, among who 25 received bi-weekly telephone calls, consisting of an inquiry about LVAD parameters, alarms, blood pressure, INR, body weight, temperature, driveline exit status, symptoms and presence of edema. They found after 2 years a better overall survival in the intervention group (89% vs. 57%, p = 0.027), however, there was no effect on time free of readmission between the groups.

Table 2. Remote monitoring strategies

	Number of patients	Main finding	Refs.
Non-invasive remote monitoring			
Schloglhöfer, et al.	96	At 2 year of follow-up, using bi-weekly telephone calls (consisting of an inquiry about LVAD parameters, alarms, blood pressure, INR, body weight, temperature, driveline exit-status, symptoms and presence of edema) the overall survival was significantly better compared to standard care (89% vs. 57%, p=0.027); but no significant difference in time free of readmission	32
Remote antithrombotic monitoring			
Dionizovik-Dimanovski, et al.	50	Moderate correlation between INR measured using a POC device and in a central laboratory(correlation coefficient of 0.83)	34
Joshi, et al.	41 samples	Good correlation between INR measured by a POC device and in a central laboratory(correlation coefficient of 0.96)	35

Table 2. *(continued)*

	Number of patients	Main finding	Refs.
Bishop, et al.	11	Using a POC INR measurement device at home leads patients to be more often within therapeutic range compared with regular INR measurements at a central laboratory (44% vs. 31%, p=0.026)	36
Gavalas, et al.	956 samples	The statistical performance of positive urine hemoglobin to predict LDH ≥600IU/L is: sensitivity 60.4%; specificity 85.5%; PPV 42.7%; NPV 92.4%	39
Remote pump monitoring			
Pektok, et al.	5	Demonstrates the feasibility of remote pump parameter monitoring, providing additional information to the treating clinicians	41
Kawahito		Adding a vibration sensor to an LVAD could adequately detect pieces of silicone, acting like thrombi, at the four most common thrombus locations	43
Bishop, et al.	6	In patients with no or minimal AoV regurgitation, adding a specific algorithm could adequately predict AoV opening	47
Intrathoracic impedance			
Bartoli, et al.	1	Demonstrates the potential utility of intrathoracic impedance measurements in a patient with an LVAD, with an increased intrathoracic impedance preceded intravascular volume depletion and dangerous LVAD dysfunction	49
Implantable hemodynamic monitoring devices			
Feldman, et al.	27	Using remote monitored PAP, by the CardioMEMS, leads to a large reduction of PAP and an optimized timing of LVAD-implantation compared to those receiving standard care	54
Hubert, et al.	4	Significant correlation between left atrial pressure sensor, and pump speed, LV and LA size and pulmonary capillary wedge pressure (r=0.92-0.99, p<0.05)	55

POC point-of-care, *LDH* lactate dehydrogenase, *PPV* positive predicting value, *NPV* negative predicting value, *AoV* aortic valve, *LVAD* left ventricular assist device, *PAP* pulmonary artery pressure, *LV* left ventricle, *LA* left atrial

Remote antithrombotic monitoring

LVAD care is associated with thromboembolic complications, such as pump thrombosis, which could be a lifethreatening complication, thus showing the need for adequate chronic anticoagulation. [7] However, LVADs are also associated with bleeding events, particularly GI bleeding, thus requiring a small target window of chronic anticoagulation to minimize the risk of bleeding events. [7, 34] The development of accurate point-of-care (POC) INR monitors made patient self-testing possible. In patients with other indications for anticoagulation therapy, self-testing led to a higher percentage of time in the therapeutic range. [35] Two studies showed a moderate to good correlation between the INR measured by the POC system and laboratory results. [36, 37] Bishop et al. [38] compared 11 LVAD patients using a POC-INR monitoring system or regular laboratory INR monitoring in the outpatient setting. Patients using a POC system were significantly more frequently tested (7.4 vs. 21.4 days, $p < 0.01$), and were more often within the therapeutic range (44% vs. 31%, $p = 0.03$). Furthermore, they investigated the potential differences in the number of bleeding or thromboembolic events, however, due to the small sample size, no significant difference was found. Self-testing in LVAD patients has the potential to increase the frequency of INR monitoring. By doing so, dosage changes can be made more often, leading to a higher percentage of "time in therapeutic INR range". This could contribute to reducing the number of thromboembolic and bleeding events in LVAD patients, but has not been shown yet.

The diagnosis of pump thrombosis is complex, consisting of an evaluation of symptoms of HF, pump parameters, echocardiographic analysis and serum lactate dehydrogenase (LDH). LDH is a sign of hemolysis, and probably one of the most reliable markers of pump thrombosis. [39, 40] LDH monitoring is usually only performed during regular outpatient clinic follow-up visits, leading to potential delays in pump thrombosis detection of weeks. Gavalas et al. [41] demonstrated a good correlation between a simple dipstick urine analysis for urine hemoglobin and serum-measured LDH. Absent of urine hemoglobin had a negative predicting value for LDH ≥ 600 IU/L (significant hemolysis) of > 90%, thus indicating the potential use for easy remote monitoring at home of pump thrombosis in LVAD patients.

Remote pump monitoring

Although experience with remote monitoring especially in ICDs and CRTs is growing [42], experience with a remote monitoring function within an LVAD system is limited. However, the first experiences with remote monitoring of pump parameters have been described. [43, 44] The HeartAssist 5 and aVAD LVADs have these remote

monitoring functions, allowing to transmit pump parameters, such as pump speed, rounds per minute (rpm) and pump flow, as well as errors, to a website accessible to the care team. This new information can be used in earlier detection of pump complications. Hypovolemia and LVAD thrombosis could be detected by a downward LVAD flow trend. [44]

Furthermore, new technologies and algorithms are developed which use the LVAD parameters and help with troubleshooting, and patient monitoring. Detection of vibrations as a sign of mechanical failure is widely used in the biomechanical industry, however, it is not yet used in LVAD management. Kawahito [45] investigated the use of a vibration sensor in combination with an LVAD detect pump thrombosis. This study investigated vibration signals caused by pieces of silicon, acting like actual thrombi, attached at the four most common locations for thrombus in an LVAD: the total area of the bottom of the impeller, an eccentric shape on the bottom of the impeller, a circular shape around the shaft top and an eccentric shape on the top of the impeller. Thrombi at these specific locations can be detected by specific vibration signals, indicating the potential use for early detection of pump thrombosis in LVAD patients.

The aortic valve opening rate is an important aspect of LVAD care. When the aortic valve is not opening the risk of adverse cerebrovascular events increases [46] and commissural fusion can occur, one of the causes of aortic valve regurgitation. [47] Bishop et al. [48] described a novel algorithm to analyze in patients with no or minimal aortic valve regurgitation whether the aortic valve is opening or not. This algorithm uses the electric current waveforms provided by the HeartMate-II LVAD and analyzes this data using a modified Karhunen–Loève transformation. The algorithm could accurately predict aortic valve opening and closing. This algorithm can also be used in an automatic regulation program which can automatically change the rpm settings of the LVAD based on this physiological feedback to maintain a predefined aortic valve opening rate.

Intrathoracic impedance

Remote intrathoracic impedance monitoring is possible in the newer ICD and CRT devices. A drop in intrathoracic impedance is seen during pulmonary congestion, as an early sign of HF decompensation. Due to the remote monitoring function of newer ICD and CRT devices, the intrathoracic impedance can be used to detect HF decompensation at an earlier stage. Multiple studies investigated whether remote monitoring of intrathoracic impedance could lead to a better outcome in chronic HF patients. A recent systematic review [49] showed that intrathoracic impedance was associated with lower

health care costs due to a reduction in planned hospital visits, despite a slight increase in unplanned visits. However, the use of remote impedance monitoring did not affect all-cause or cardiac mortality.

At this moment, there is only one case report [50] describing the use and potential benefits of remote monitoring of intrathoracic impedance in LVAD patients. This patient experienced shortly after LVAD implantation an increase in the impedance as a sign of intravascular fluid depletion. The patient was admitted and treated with fluid repletion and the impedance was increased. This case showed that intrathoracic impedance measurements in LVAD patients might provide some information on their fluid status. However, the use of remote monitoring of impedance in chronic HF holds limited additional value, and it is unclear whether this will be better in LVAD patients.

Implantable hemodynamic monitor devices

Due to the failure of simple non-invasive and intrathoracic impedance remote monitoring strategies to improve the outcome of chronic HF patients, new, wireless implantable hemodynamic monitor systems were developed. These systems measure filling pressures, and work according to the hypothesis that filling pressures will increase before other signs of decompensated HF occur, as shown in Fig. 2. As has been shown, intracardiac pressures will rise weeks before patients are hospitalized due to decompensated HF. [51] Recently, Abraham provided an overview of multiple implantable hemodynamic monitor devices, which were developed in recent years. [52] In chronic HF patients, one of the most promising techniques is the CardioMEMS system (Abbott Inc, Atlanta, GA, USA) (Fig. 3). This device is implanted in the pulmonary artery during right-heart catheterization, and consists of a pressure-sensitive capacitor combined with a coil and can be powered by coupling this electrical circuit with an external antenna. When powered, the capacitor resonates, which is received by the external antenna. When pressure by the pulmonary artery pressure (PAP), is applied, the frequency of resonated energy changes via a characteristic pattern and can be converted into a pressure wave. This system has been shown in clinical trials as well as in real-world clinical practice to be effective in reducing HF hospitalization rates by maintaining normal PAP. [53, 54]

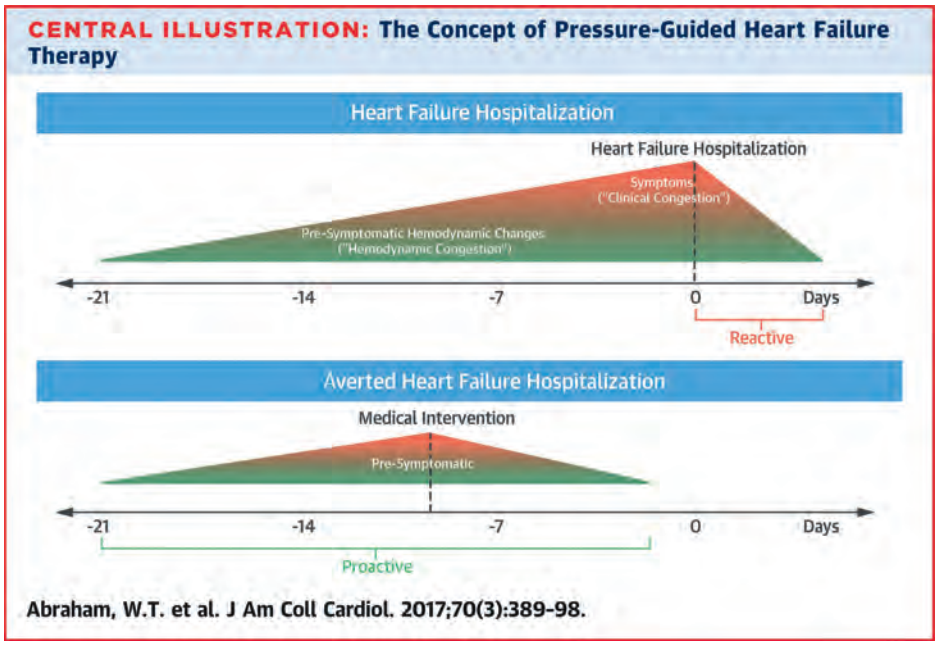

Fig. 2 Hypotheses of pressure monitored and guided heart failure management Reprinted from Abraham [52], 2017, with permission from Elsevier

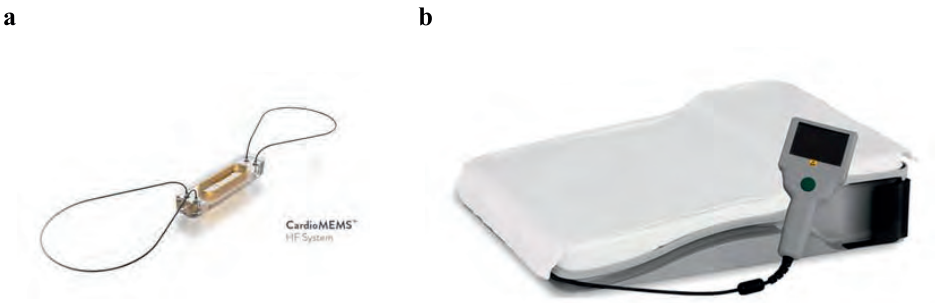

Fig. 3 CardioMEMS HF system, consisting of the pulmonary artery pressure sensor (**a**) and the patient electronics system (**b**) used to take daily pressure readings Courtesy of Abbott, Inc. to provide the illustrations

A subgroup analysis of the CHAMPION trial, the initial clinical trial investigating the CardioMEMS, consisting of 27 chronic HF patients, who received an LVAD, showed that patients who received an LVAD were sicker, and had a higher PAP when compared to the group who did not receive an LVAD. [55] The intervention group received more medical changes, based on the hemodynamic feedback provided by the CardioMEMS compared to the control group. However, the PAP did not decrease significantly in the patients who received an LVAD, indicating that a lack of decrease of PAP can be a sign of refractory

HF, and thus providing useful information in the timing of an LVAD implantation. Post-LVAD implantation, the PAP dropped in both groups, however, using the hemodynamic feedback in the intervention group, the PAP dropped even lower. This indicates that the use of the PAP provided by the CardioMEMS leads to a better and more optimal LVAD management, leading to a better pump function.

Hubbert et al. [56] investigated in four LVAD patients an implantable left atrial pressure (LAP) monitor, the Titan LAP monitoring system (ISS Inc. Ypsilanti, MI). They showed a significant correlation between LAP and pump speed, LV and left atrial size and the pulmonary capillary wedge pressure, thus indicating the potential use of pressures obtained by an implantable hemodynamic monitor for optimization of the pump settings during a ramped speed test.

Potential impact of implantable hemodynamic monitoring

We believe that the implantable hemodynamic monitors hold more potential in LVAD patients than currently shown. Using the daily pressure readings, which provide real-time insight into patients' fluid status, the clinicians could optimize patients shortly prior to the LVAD implantation, thereby improving patients' status and their clinical outcome. Also, this hemodynamic information provides direct feedback on medical changes made. We believe that using this hemodynamic feedback will lead to better optimization, thus improving patients' status and potentially improving their clinical outcome. [57] Furthermore, optimizing patients will lead to a better decongestion and thereby better unloading of the RV, thus, reducing the impact of the LVAD implantation on the RV and reducing the risk of RV failure.

Changes in filling pressures post-LVAD implantation might indicate potential postoperative complications. An increase in filling pressures might indicate a tamponade, since the venous return reduces due to inflow obstruction due to elevated pressures in the pericardium. An earlier detection and thereby earlier intervention might prevent late-stage tamponade and more severe complications.

Multiple complications, such as pump thrombosis, hemodynamic important arrhythmias or aortic valve regurgitation, will lead to congestion. Similar to chronic HF patients, in LVAD patients filling pressures will rise as a result of congestion. [58] A rise in filling pressures might indicate one of these complications is occurring. Hospitalization and the worsening outcome can potentially be prevented by acting on rising filling

pressures. Furthermore, investigating the waveforms and rhythm could provide insight into potential arrhythmias.

A drop in filling pressures might indicate a loss of circulating volume, which might point to a GI bleeding.

LVAD therapy will increase cardiac output, and thereby increase the renal perfusion and resolve the congestion, lowering the renal venous pressure and thereby improving the renal function. [59] Filling pressures might aid in optimizing LVAD therapy, and thus improve the renal function even further.

Fixed pulmonary hypertension is an absolute contraindication for heart transplantation. In these patients, the by ischemic stunned right ventricle will be unable to overcome the elevated afterload and is most likely to fail immediately after heart transplantation. In patients with fixed pulmonary hypertension, LVAD therapy can be used as a bridge to candidacy for heart transplantation, since LVAD therapy is more effective in treating fixed pulmonary hypertension, compared to medical therapy alone. [60] Pulmonary hypertension should be evaluated periodically using a right-heart catheterization, as recommended by the ISHLT guidelines to evaluate whether the patient has become eligible for heart transplantation. [61] However, remote hemodynamic monitoring could replace these periodically right-heart catheterizations, and provide daily feedback on hemodynamic changes. Providing continues insight when a patient could be considered eligible for heart transplantation.

Recently, it has been shown that preforming hemodynamically guided ramp testing could reduce the number of LVAD-related complications and the number of hospitalizations. [31, 62, 63] However, this technique is limited by the need for frequent Swan-Ganz measurements, which increases the risk of bleeding events. Using the hemodynamic information provided by the CardioMEMS, this limitation could be overcome and allowing for easy hemodynamic optimizing of LVAD pump settings.

Future perspectives: design of the HEMO-VAD study to guide LVAD management by hemodynamic feedback

To investigate the potential impact of an implantable hemodynamic monitor in LVAD patients, we designed the HEMOVAD pilot study. [64] In this study, we will investigate ten consecutive end-stage HF patients, who are accepted for LVAD implantation. These

patients will receive prior to LVAD implantation a CardioMEMS device, which will be used for daily hemodynamic monitoring to optimize patients prior to LVAD implantation and monitoring of complications and patient status after LVAD implantation.

Conclusion

Many remote monitoring strategies are currently investigated and developed for LVAD patients, ranging from non-invasive telephone monitoring programs to implantable hemodynamic monitoring systems. Based on results from trials investigating the use of remote monitoring of regular heart failure, it is warranted to study these devices in LVAD patients. This technique holds the potential to provide additional information for determining the optimal LVAD implantation window, optimizing the patients prior to and post-LVAD implantation, and monitoring for LVAD-related complications to identify the patients most likely to benefit from such therapy and for early discovery of its complications.

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Monitoring pulmonary pressures during long-term continuous-flow left ventricular assist device and fixed pulmonary hypertension: redefining alleged pathophysiological mechanisms?

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Abstract

Pulmonary hypertension (PH) type II (classified by the World Health Organization) is a common complication in chronic left-sided heart failure. In advanced heart failure therapy, fixed PH is an absolute contraindication for heart transplantation after which a left ventricular assist device (LVAD) is the only remaining option. With remote monitoring, we can now continuously evaluate the pulmonary artery pressures during long-term LV unloading by the LVAD. In this case, we demonstrate that fixed PH can be reversed with LVAD implantation, whereby previous thoughts of this concept should be redefined in the era of assist devices.

Introduction

In patients with chronic left-sided heart failure (HF), pulmonary hypertension (PH) (classified by the World Health Organization as group 2) is a common complication.[1] PH occurs in up to 60% of the patients with severe left ventricular systolic dysfunction, and up to 70% in patients with HF with preserved ejection fraction.[2] HF causes chronic pulmonary congestion, resulting in elevated pulmonary capillary wedge pressure (PCWP). The right ventricle (RV) adapts slowly over time in order to overcome the increasing PCWP, leading to increasing pulmonary artery pressures (PAPs). Over time, this process results in pulmonary capillary and arterial remodelling. The vascular wall stiffens and loses its elasticity and ability to compensate for the higher pressures, resulting in elevated pulmonary vascular resistance (PVR). Additionally, several pulmonary diseases affect the PVR and cause PH. At screening for candidacy for heart transplantation (HTx), the standard procedure is to perform a right heart catheterization (RHC) to study these aspects in detail. If at the Swan–Ganz measurement the patient has PH, we perform a vasodilator test to evaluate the reversibility of PH and PVR. Reversibility is crucial in potential HTx candidates. Because the RV of the donor heart will not be capable to build up PAPs to overcome the fixed high PVR, after a period of stunning by ischemia, the RV is most likely to fail immediately. Left ventricular assist device (LVAD) therapy can be successful in lowering PAPs by unloading the left ventricle, which will aid in the treatment of PH caused by left-sided heart disease.[3] However, limited data are available on the topic whether fixed PH can be reversed as well. The acute and chronic effects of LVAD therapy on PH have not been clearly investigated. The recently introduced CardioMEMS sensor offers the possibility to study this concept, because it allows for remote daily monitoring of PAPs, even in LVAD patients,[4] as we have shown in our case.

Case report

A 53-year-old man with a history of severe dilated cardiomyopathy was admitted with progressive HF, despite maximal tolerated medical therapy. During the admission, the patient was screened for both HTx and LVAD implantation. The RHC revealed a cardiac output of 3.8 L/min, PAP 61/31 mmHg (mean 43), PCWP 28 mmHg, and PVR 316 dynes/s/cm5 (3.9 Woods). During the vasodilator test of reversibility, intravenous nitroglycerin was up-titrated to maximum tolerated dosage (100 µg/min) without inducing systemic hypotension; PAP [47/23 mmHg (34)], PCWP (20 mmHg), and the PVR (295 dynes/s/cm5 , 3.7 Woods) remained elevated, confirming the diagnosis of

fixed PH. In the multidisciplinary heart team, the patient was rejected as candidate for HTx owing to irreversible PH and was accepted for LVAD (HeartMate 3, Abbott Inc, Atlanta, GA, USA) as bridge to transplant or destination therapy. A CardioMEMS device was implanted, followed by LVAD implantation 2 weeks later. Post-operatively, the LVAD support provided additional room for further up-titration of the medical therapy. Echocardiography and PAPs were used to uptitrate renin–angiotensin system inhibition, mineralocorticoid receptor antagonist, and diuretics and the LVAD speed settings. The patient recovered well with an uncomplicated course and was discharged home.

In the outpatient setting, haemodynamic feedback provided by the CardioMEMS was used for further treatment optimization. A combination of hydralazine/isosorbide dinitrate was started and slowly up-titrated resulting in a small decline in PAP. However, this was limited owing to complaints of dizziness.

Approximately 160 days after LVAD implantation, the patient was admitted owing to dehydration and hypotension due to insufficient intake, which was identified by the sudden drop in PAPs. During admission, antihypertensive medication and diuretics had to be lowered or stopped, allowing the renal function to recover. After discharge, medication was up-titrated again to maximum tolerated dosage, limited once more by complaints of dizziness. Even though further up-titration of medication was not possible, the mean PAP (mPAP) continued to decline gradually and then finally normalized. Approximately 290 days post-LVAD implantation, a consistent mPAP < 25 mmHg was reached. During follow-up, the patient regularly underwent echocardiography, demonstrating a stable RV function and only a minor tricuspid valve regurgitation, suggesting that the decline in mPAP was caused by reversibility of the ‘fixed’ PH and was not due to a decline in RV function. Currently, the candidacy for HTx is re-evaluated, and likely no cardiac issues will be raised for acceptance on the waiting list.

Discussion

This case report demonstrates for the first time the continuous follow-up of PAP data in a LVAD patient with fixed PH, for up to 300 days post-LVAD implantation. This case demonstrates that LVAD therapy is a successful treatment for lowering PAP in patients with fixed PH, additional to optimal medical treatment. The reversibility of PH and candidacy for HTx thereby become a more dynamic state, which changes views on these programmes in light of expanding LVAD programmes.

The increase of left ventricular filling pressure leads to an increase in post-capillary pressure and elevated PCWP in the pulmonary circulation. This leads to endothelial dysfunction, making the vascular walls less flexible owing to smooth muscle cell hypertrophy and hyperplasia, increasing the PVR. Thereby, PH arises, followed by remodelling of the arterial wall. This is characterized by medial hypertrophy and intimal fibrosis. Longstanding PH can grow to a state of fixed PH. Current data are conflicting about the reversibility of severe or fixed PH, with some data suggesting that LVAD therapy can reverse fixed PH. However, it remains unclear whether this is caused by remodelling of the pulmonary vascular wall or LV unloading and remodelling. Furthermore, the cut-off between fixed and reversible PH is unclear, and there is no agreement on the time needed to reach irreversibility.[5]

Continuous-flow LVADs unload the left ventricle and lower the cardiac filling pressures. As has been shown previously, LVAD therapy is more effective in treating 'fixed' PH than is maximal medical therapy.[3,5] The CardioMEMS device allows for daily PAP readings (Figure 1) and was used to observe the haemodynamic changes after medication changes. As shown in this case, up-titrating the medical therapy to maximal tolerated dosage did not lead to a normalization of the PAPs. However, as shown, during the longer-term follow-up, the PAPs slowly declined, and after 0.5 to 1 year of LVAD support, the PAPs normalized with an mPAP < 25 mmHg. These results show the natural decline of PAP while on LVAD support besides the haemodynamic effects of maximal tolerated medical therapy.

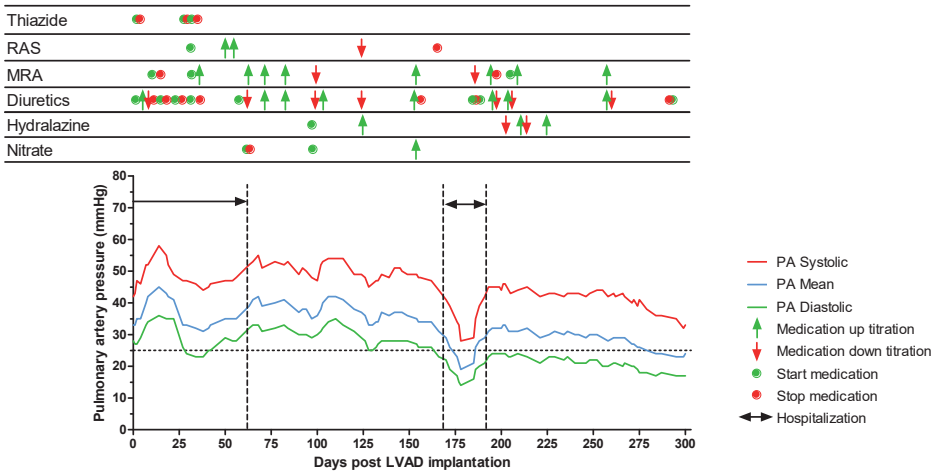

Figure 1 Daily pulmonary artery pressure readings and medication changes. LVAD, left ventricular assist device; MRA, mineralocorticoid receptor antagonist; PA, pulmonary artery; RAS, renin–angiotensin system.

Previous studies investigating the reversibility of fixed PH were limited to repeated invasively measured PAP readings, instead of continuous PAP readings. So the timing of reversibility of fixed PH is still unclear.

Mikus et al. investigated the reversibility of PH during LVAD support at 6, 12, and 18 months of follow-up and concluded that the biggest reduction in PAP will occur within the first 6 months post-LVAD implantation.[5] In contrast, our case shows a slow decline in PAP over time in which the PAP of our patient normalized only after 300 days on LVAD support. This result suggests that the decline of PAP can occur past the 6 months suggested in the previous study.

Reversibility of fixed PH is very important because fixed PH is a contraindication for HTx. When HTx is performed in a patient with fixed PH, the stunned RV of the donor could not overcome the high afterload and fails owing to elevated PVR. RV failure is a major cause of both mortality and morbidity after LVAD implantation as well (20–50% of patients).[6] By lowering PAP, there is more potential to improve or maintain RV function at long-term LVAD support, which is essential, especially in destination therapy. This could help in the longterm survival of LVAD patients who depend on a good working RV for a proper functioning LVAD. This case demonstrates that the haemodynamic feedback, provided by the CardioMEMS, can be used to optimize medical therapy also in LVAD patients. And this provides feedback on haemodynamic changes, which could help to detect problems such as dehydration or decompensation in earlier stages.

Conclusions

Continuous-flow LVAD can reverse fixed PH, even after a period of 6 months on LVAD support. The CardioMEMS sensor enables to monitor and guide the treatment of PH in patients with an LVAD and severe PH.

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Design and rationale of haemodynamic guidance with CardioMEMS in patients with a left ventricular assist device: the HEMO-VAD pilot study

Veenis JF, Maninveld OC, Constantinescu AA, Caliskan K, Birim O, Bekkers JA, Van Mieghem NM, Den Uil CA, Boersma E, Lenzen MJ, Zijlstra F, Abraham WT, Adamson PB, Brugts JJ

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Abstract

Aims: We aim to study the feasibility and clinical value of pulmonary artery pressure monitoring with the CardioMEMS™ device in order to optimize and guide treatment in patients with a HeartMate 3 left ventricular assist device (LVAD).

Methods and results: In this single-centre, prospective pilot study, we will include 10 consecutive patients with New York Heart Association Class IIIb or IV with Interagency Registry for Mechanically Assisted Circulatory Support Classes 2–5 scheduled for implantation of a HeartMate 3 LVAD. Prior to LVAD implantation, patients will receive a CardioMEMS sensor, for daily pulmonary pressure readings. The haemodynamic information provided by the CardioMEMS will be used to improve haemodynamic status prior to LVAD surgery and optimize the timing of LVAD implantation. Post-LVAD implantation, the haemodynamic changes will be assessed for additive value in detecting potential complications in an earlier stage (bleeding and tamponade). During the outpatient clinic phase, we will assess whether the haemodynamic feedback can optimize pump settings, detect potential complications, and further tailor the clinical management of these patients.

Conclusions: The HEMO-VAD study is the first prospective pilot study to explore the safety and feasibility of using CardioMEMS for optimization of LVAD therapy with additional (remote) haemodynamic information.

Introduction

As the prevalence and incidence of heart failure (HF) keeps increasing, more and more patients develop end-stage HF despite improved medical management.[1–3] About 10–15% of the HF patients develop advanced HF every 3 years and become refractory to drug therapy, leaving heart transplantation or haemodynamic support by left ventricular assist device (LVAD) implantation as the only therapy option.[1]

Experience with LVADs is rapidly growing worldwide; however, mortality and morbidity of this advanced therapy remains high. LVAD therapy is life-saving but remains an intensive complex treatment with high rehospitalization rates and outpatient clinic contacts.[4] Recently, novel LVAD designs have improved post-operative outcomes with a marked reduction in pump thrombosis and cerebrovascular accidents,[5] but bleeding, driveline infections, and long-term right ventricle (RV) failure continue to impair the long-term efficacy of this intervention.[6–8] Patients with long-term LVAD therapy remain particularly vulnerable for RV failure, with up to 20–40% of the patients developing early RV failure [5,9,10] and 15% late RV failure.[11] Severe RV dysfunction remains the leading cause of death in the first month after LVAD implantation.[12,13] There is a growing clinical demand for physicians to have better ways to predict response to treatment as well as tailor clinical management in these patients. Currently, the pump controller only reflects a fixed number of rotations per minute (rpm) and notifications of a calculated pump flow and pulse index of the device itself but no actual haemodynamic feedback.

The CardioMEMS™ pulmonary artery (PA) sensor allows frequent remote monitoring of haemodynamic information, with proven effectiveness in reducing HF hospitalizations by maintaining normal pulmonary artery pressure (PAP) as surrogate markers of filling pressures (which rise in eminent decompensation) in chronic HF patients.[14,15] An innovation would be to combine two state-of-the-art strategies such as LVAD therapy and guidance by PA monitoring in order to improve the outcome in this complex patient category and reduce the high burden of complications by early detection of pressure shifts. New insights will be provided by such haemodynamic feedback in order to tailor therapy in this patient group as well as to learn more on RV dynamics and pulmonary hypertension during long-term treatment with daily haemodynamic data. In order to study the feasibility and clinical value of the hybrid construction of CardioMEMS and HeartMate 3 (HM-3), we present the pilot study design to address this hypothesis in LVAD patients.

Study design

This is an investigator-initiated, single-centre, prospective pilot study enrolling 10 consecutive patients who undergo a scheduled semi-elective or elective implantation of an HM-3 LVAD. The decision for LVAD therapy will be established by heart team consensus. Before LVAD implantation, all patients will receive a Swan–Ganz right heart catheterization, and a CardioMEMS PA sensor will be implanted to measure PAP. This study has been approved by the ethics committee (MEC no. 2017-342), and the study will be conducted according to the Helsinki declaration, with all patients providing informed consent prior to participation. The study is registered at clinicaltrails.gov under NTR 2017-6804.

Study population

The HEMO-VAD pilot study involves 10 patients with New York Heart Association functional Class IIIb or IV with Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Classes 2–5, who undergo a scheduled implantation of an HM-3 LVAD at the Erasmus MC Thoraxcentre, Rotterdam, The Netherlands. Inclusion criteria are presented in Table 1, and exclusion criteria are presented in Table 2.

Table 1. Inclusion criteria

- Age ≥ 18 years
- LVEF < 25%
- NYHA Class IIIb or NYHA Class IV with INTERMACS classes 2-5
- Scheduled for LVAD implantation within 1 month after heart team consensus
- Life expectancy > 1 year
- Body surface area ≥ 1.2 m^2 and chest circumference, at the axillary level, of less than 65 inches if BMI >35kg/m^2
- Signed informed consent form

BMI, body mass index; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; NYHA, New York Heart Association.

Table 2. Exclusion criteria

- No signed informed consent form
- INTERMACS 1 emergency LVAD implantations
- Patients with a known coagulation disorder or hypersensitivity to aspirin
- Intolerance to anticoagulant or antiplatelet therapies
- Patients with contra-indications for the PAP sensor device, which will include active infection, a history of deep vein thrombosis or recurrent pulmonary embolism, mechanic right heart valve, or unable to tolerate Swan ganz.

Table 2. *(continued)*

- History of pulmonary embolism within 30 days prior to enrollment or history of recurrent (>1 episode) pulmonary embolism and/or deep vein thrombosis
- History of stroke within 90 days prior to enrollment, or a history of cerebrovascular disease with significant (>80%) uncorrected carotid stenosis
- Serum creatinine ≥ 221 umol/L or CKD-EPI eGFR < 25 ml/min not related to cardiac condition or the need for chronic renal replacement therapy
- Psychiatric disease/disorder, irreversible cognitive dysfunction or psychosocial issues that are likely to impair compliance with the study protocol and LVAD management

CKD-EPI, Chronic Kidney Disease–Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; PAP, pulmonary artery pressure.

Objectives and endpoints

The objectives of this study are as follows:

- to investigate the feasibility and safety of using haemodynamic guidance by the CardioMEMS PA sensor in LVAD HM-3 patients,
- to investigate the information provided by haemodynamic data of CardioMEMS PA sensor in relation to incident LVAD complications prospectively, and
- to study haemodynamics (PAP) preoperatively and post-operatively of LVAD surgery.

The proposed impact and goals of haemodynamic guidance in LVAD patients are further shown in Table 3. All study endpoints are shown in Table 4.

Table 3. Proposed impact and goals of CardioMEMS in LVAD

Phase A: Pre-LVAD optimization phase	· Improve patient selection pre-LVAD implantation · Evaluate timing of LVAD implantation · Optimizing clinical patient status towards surgery, INTERMACS class pre-LVAD implantation
Phase B: Clinical phase	Guide post cardiac surgery treatment Early discovery of major complication, such as: · RV failure · Tamponade · Infection
Phase C: Out-patient monitoring phase	Guide LVAD therapy remotely Evaluate further improvement of PA guided LVAD pump settings Decrease the high rate of HF related hospitalizations (70% first year) Early discovery of late complications of LVAD Evaluate pulmonary hypertension on LVAD therapy

HF, heart failure; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory; LVAD, left ventricular assist device; PA, pulmonary artery; RV; right ventricle.

Table 4. Study endpoints

Primary end points
- Safety of the hybrid construction of CardioMEMS and LVAD
- Feasibility of the hybrid construction of CardioMEMS and LVAD
- Clinical endpoints, defined as: • Number of HF-related hospitalizations • Number of LVAD related complications (such as tamponade, RV failure, GI bleeding, infection, pump thrombosis and hemolysis)
Secondary endpoints
- The number of improvements in INTERMACS classes during pre-operative optimization phase
- Clinical endpoints, defined as: • Number of HF-related hospitalizations • Number of LVAD related complications
- Time to reach optimal condition for surgery in the pre-operative phase (days)
- Predictive value of PAP during follow-up in out-patient clinic LVAD patients of risk of RV failure, GI bleeding, suboptimal fluid balance and development of long-term aortic valve insufficiency
- Monitoring of PAP and pulmonary hypertension, and reversibility of pulmonary hypertension in LVAD patients
- Detection of arrhythmia and heart rate monitoring with CardioMEMS in LVAD
- Feasibility of pump optimization using CardioMEMS during rpm test, and number of pump changes
- Changes in quality of life (KCCQ, EQ-5D-5L, PHQ-9)
- 6MHWD post HM-III implantation and changes during out-patient clinic phase
- HF medication changes (counts and TDD) during pre-LVAD implantation phase, post-LVAD implantation phase and out-patient clinical phase
- Iron deficiency before and after LVAD treatment, incidence of GI bleeding and the relationship with PAP and early discovery of occult blood loss
- Change in renal function in relation to PAP and diuretic medication dosage
- LDH, PAP and the incidence of pump thrombosis and hemolysis in LVAD patients
- Number of days hospitalized, number of days requiring inotropic support, and number of physical contact in the out-patient clinic
- Percentage of days PAP in goal range, changes in PAP from baseline and analysis of PAP waveforms in LVAD

GI, gastrointestinal; HF, heart failure; HM-3; Heart Mate 3; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; KCCQ, Kansas City Cardiomyopathy Questionnaire; LDH, lactate dehydrogenase; LVAD, left ventricle assist device; PAP, pulmonary artery pressure; PHQ-9, Patient Health Questionnaire 9; rpm, rotations per minute; RV, right ventricle; TDD, total daily dose; 6MHWD, 6 min hall walk distance.

Study overview: CardioMEMS allocation and patient flow

The study can be divided into three phases (A–C), as is shown in Figure 1. The different phases are described below.

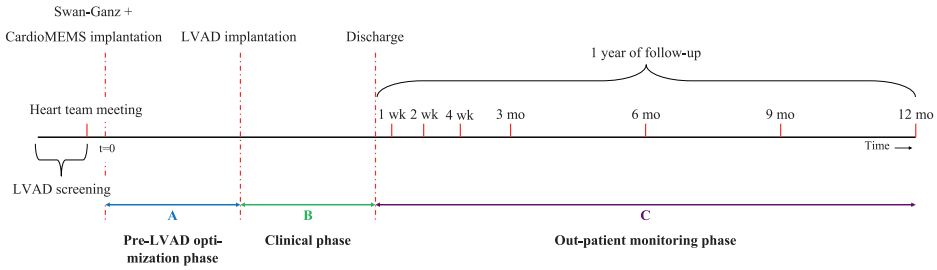

Figure 1 Study overview. LVAD, left ventricular assist device.

Phase A: Pre-left ventricular assist device optimization phase (1 week)

Every consecutive patient, who is accepted by the heart team for scheduled LVAD implantation (both destination therapy and bridge to transplant), is screened for eligibility to participate in the HEMO-VAD study. After the heart team decision has been taken to plan an LVAD implantation, the CardioMEMS sensor is implanted as soon as possible, that is, at 0–1 day. LVAD implantation is to be scheduled with the aim within 1 week in semi-elective to elective patients, with minimum 1 day and maximum within 4 weeks after heart team consensus.

After enrolment and informed consent, but prior to HM-3 implantation, subjects will be implanted with the CardioMEMS HF system. The baseline visit (t = 0) includes the day of the right heart catheterization (Swan–Ganz) occurring in all patients and the implantation of the CardioMEMS PA sensor in the left lower lobe PA. PAP data will be utilized to guide adjustments of medical therapy (e.g. diuretics, vasodilators, and inotropes or phosphodiesterase inhibitors) for optimization of the haemodynamic status prior to HM-3 implantation, with the aim to improve the pre-LVAD INTERMACS class, which is one of the best parameters of outcome. The main objective is to ensure optimal status to decompress venous congestion (unloading) of the RV and mean PAP (mPAP) below 25 mmHg. Recommendations for these adjustments will be provided with options for the physician as deemed clinically appropriate.

In this PAP-guided phase prior to LVAD implantation, the physician will use the PAP obtained by the sensor to optimize the patient condition and fluid status proceeding towards LVAD surgery. This contains optimal fluid status (euvolemia) and lowered

right heart pressures (unloading the RV) to optimal capacity as judged by the treating clinician, laboratory values, and echocardiographic parameters. The clinician normally uses a treatment course of phosphodiesterase inhibitors or inotropes and titrates diuretics, angiotensin-converting enzyme inhibitors, and nitrates dosages. Another aspect of the pre-LVAD optimization phase is to learn more on optimal timing window of LVAD surgery. When optimal timing window to proceed to LVAD surgery is reached, the HM-3 implantation follows. Based on clinical judgement or clinical urgency, this timing can be adjusted.

Phase B: Clinical phase

After LVAD implantation, the patients will be admitted to the intensive care unit (ICU), where patients will receive regular care. At the ICU, potential interference between the implanted PAP sensor, LVAD controller, and potential other equipment will be tested, as an important part of the feasibility and safety of this novel hybrid construction. In addition to the regular care, daily pressure readings provided by the CardioMEMS system will be used to guide HF treatment, according to the predefined goals: diastolic PAP will be targeted and maintained between 8 and 15 mmHg as well as mPAP below 25 mmHg. Furthermore, PAP changes might indicate the presence of complications such as RV failure, infection, or cardiac tamponade, on top of echocardiography in an earlier stage. At the moment, haemodynamic recordings after LVAD implantation are very limited in the current literature to provide insights in these mechanisms. Recently, a retrospective sub-analysis of the CHAMPION trial provided some information of PAP changes after LVAD implantation, suggesting that additional haemodynamic information has the potential to improve LVAD management.[16] However, information during the hospitalization for LVAD implantation and during potential LVAD-related complications is still lacking.

When clinically stable, patients will be transferred to the HF department. Patients will receive the usual care, and at least once a day, pressure readings will be continued. Haemodynamic feedback will be used for optimizing HF medication titration, leading to tailored therapy (maintain normal PAP), and evaluating haemodynamic changes during potential complications. During admission, LVAD care echocardiography will be performed to optimize pump settings (rpm testing), as is standard care, only with additional pressure feedback for the CardioMEMS system, which will be analysed separately. Furthermore, patients will be trained in using the LVAD device, controller, and exchange batteries as well as operating the home monitoring unit and instructed to take daily PAP measurements.

Phase C: Outpatient monitoring phase (long-term follow-up)

Throughout the long-term follow-up period and subsequent hospitalizations, the pressure data upload will be performed at least daily using the home monitoring system and the Merlin.net website. Pressures will be reviewed remotely at least once a week and more frequently when pressures are outside the target range, on the Merlin.net website, with anticipation of treatment alterations based on maintaining normal PAP. Patients will be followed during regular outpatient clinic visits, approximately at 1, 2, and 4 weeks and 3, 6, 9, and 12 months. During these visits, patients will receive standard care, expanded with specific blood, urinary, and echocardiography parameters, as well as questionnaires on quality of life, and the performance status will be assessed.

Parameters of interest

Primary study parameter(s) of CardioMEMS device

Daily PAP measurements will be performed in the preoperative period towards LVAD implantation, direct post-operative period on ICU, clinical department, and the regular outpatient clinic setting. Measurements record systolic PAP, diastolic PAP, mPAP, mean trend, and heart rate.

Our study protocol will further study PAP in relation to the following:

- serial lactate dehydrogenase levels, international normalized ratio values, and pump thrombosis;
- serial creatinine clearance, urinary samples, and kidney dysfunction;
- serial iron status and gastrointestinal bleeding incidence; and
- serial measurements of quality of life at 3, 6, and 12 months.

Other parameters of interest

Baseline Swan–Ganz measurements (including cardiac index, systolic PAP, diastolic PAP, mPAP, wedge pressures, RV pressures, right atrial pressures, and PA pulsatility index) are recorded at baseline during CardioMEMS implantation (protocol describing the Swan–Ganz procedure and CardioMEMS implantation is described in detail in Table 5). Vasoreactivity is tested during the LVAD screening, using continuous administration of an i.v. vasodilating agent, such as nitroglycerin, in increased dosage. During the entire study, at regular intervals, clinical parameters (such as heart rate, blood pressure, weight, and symptoms of congestion), laboratory results (including standard routine care laboratory results, renal function, haemolysis parameters, iron status, and biomarkers), urine analysis (proteinuria), LVAD parameters log file (rpm, flow, pulse index, power, pulsatility index events, and suction events), echocardiography

parameters (such as ventricle dimensions, valve patency, ventricle and vena cava dimensions, tricuspid annular plane systolic excursion, and rpm measurements), electrocardiogram, performance status (New York Heart Association and INTERMACS classification, and 6 min hall walk test), and quality of life questionnaires (EQ-5D-5L, Kansas City Cardiomyopathy Questionnaire, and Patient Health Questionnaire 9) will be assessed.

Table 5. Swan-Ganz and CardioMEMS implantation protocol:

1.	Insert, using ultrasound guidance, a 7F balloon-tipped Swan-Ganz pulmonary artery catheter through the femoral vein
2.	Obtain standard Swan Ganz right heart catheterization pressure reading at RA, RV, PA and pulmonary capillary wedge pressure. Preferably right pulmonary artery.
3.	Obtain the cardiac output using thermodilution (using 10 ml NaCl 0.9% per measurement), calculated as the average of at least three adequate measurements
4.	Introduce the adequate pigtail shaped into the venous sheath and localize the pigtail with fluoroscopy into the left lower pulmonary artery. And perform a standard pulmonary artery angiogram of the left lower pulmonary artery
5.	Perform standard measurements of vessel size and re-assure maximum vessel size diameter and anatomical requirements (inner vessel diameter must be > 7 mm) suited for CardioMEMS
6.	Insert the CardioMEMS catheter in the left lower pulmonary artery targeted vessel site, and confirm adequate positioning by fluoroscopy
7.	Turn the catheter switch button to release the wires of the CardioMEMS sensor which fixes itself in the pulmonary artery. Confirm adequate positioning of the device by the radiopaque markers with fluoroscopy
8.	Re-introduce the Swan Ganz catheter and position the catheter in the right pulmonary artery. Start calibrating and equilibrate the CardioMEMS pressure readings with the simultaneous Swan Ganz pressure readings (nulling of the sensor). Perform baseline measurements and calibration three times and confirm measurements and baseline recordings are identical
9.	Remove Swan Ganz catheter. Remove the venous sheath from the femoral vein. At preference of the operator, use a closure device for the femoral vein, manual compression or pressure bandage at the venous puncture site

PA, pulmonary artery; RA, right atrium; RV, right ventricle.

Device description and implantation procedure

The device description and implantation procedure of the CardioMEMS HF sensor system (Abbott Inc., Atlanta, GA, USA)[17] and of the HM-3 LVAD (Abbott Inc., Pleasanton, CA, USA) have been published previously.[18]

Statistical analysis

For the purpose of this study, all data will be recorded on a case report form and introduced into the study database environment. All patient data will be collected by a

dedicated research fellow or PhD student. Baseline quantitative data will be presented with mean ± standard deviation or median with interquartile range when appropriate. In general, statistical analyses in this pilot study will be descriptive in nature. The data will be summarized using descriptive statistics (e.g. N, mean, standard deviation, median, minimum, and maximum) or frequency (e.g. N, %) as appropriate. Changes in PAP will be measured as area under the curve of PAP relative to the baseline. Changes in quality of life (assessed using EQ-5D-5L, Kansas City Cardiomyopathy Questionnaire, and Patient Health Questionnaire 9) will be analysed. The primary time point for safety analyses is 6 months post-enrolment. The time point for analyses of feasibility and haemodynamic performance is at 6 and 12 months post-enrolment.

Discussion

The HEMO-VAD pilot study is the first prospective study investigating haemodynamic guided management of HM-3 LVAD patients with an implantable pressure sensor (CardioMEMS). The primary goal is to assess the safety and feasibility of this hybrid construction and evaluate its additive value in optimizing treatment in LVAD patients. Reaching and maintaining optimal fluid status and maximizing optimal medical treatment and timing of surgery towards LVAD therapy (preoperative and post-operative stages) are the main focus. Additionally, this study will evaluate the use of frequent remote measurement of PAP to discover early and late complications of LVAD therapy during hospitalization. Finally, we evaluate whether direct haemodynamic feedback can influence outpatient clinical management and optimize pump settings on top of current standard care.

Left ventricular assist device therapy is a complex entity with high risk of mortality and morbidity without clear tools to predict outcome or complications during treatment.[9,19–23] From a haemodynamic point of view, RV failure is the most common serious complication after LVAD implantation. RV failure after LVAD implantation can be divided into early or late RV failure (<4 weeks and >4 weeks after implantation, respectively). Early RV failure occurs in as much as 20–40% [5,9] and late RV failure in 15% of LVAD patients.[11] Preoperative assessment of RV function is essential in LVAD screening but dependent on filling status and right heart pressures. Prolonged elevated PAP is a major cause of RV failure, but pulmonary hypertension alone is not a contraindication for LVAD implantation, unless there is already severe RV failure pre-LVAD. One of the caveats is that RV failure after LVAD implantation is highly unpredictable.[5,12] Current risk assessment scores have limited predictive value and clinical usefulness for predicting

LVAD-related complications, especially RV failure. [9,10,24] Recently, the EUROMACS-RHF risk score has been developed and aims to predict early RV failure and associated mortality after LVAD implantation.[10] At the moment, the best predictive variable for RV failure post-LVAD implantation is RV function prior to surgery as assessed by echocardiography, which largely depends on fluid status, vascular resistance, degree to which pulmonary pressures are elevated, and severity of tricuspid valve regurgitation. Echocardiography can be used to evaluate RV function but correlated poorly with the development of RV failure. Right heart catheterization is the gold standard to assess RV workload and function; however, this is an invasive procedure, performed at one moment in time, and greatly depends on loading conditions at that moment. More tools are needed to adequately predict and assess the risk of post-LVAD RV failure.

We hypothesize that PAP is key in the preoperative stage to deliver the patient to the surgeon in optimal decongested state to lower the impact of the surgery on the RV. After implantation, we hypothesize that PAP can be used as a marker of treatment success of left ventricular (LV) unloading by the LVAD with insight into residual fixed vascular resistance, which may be a target for therapies with the goal of protecting RV function by reducing afterload. Additionally, PAP information may predict potential complications of LVADs such as occult bleeding, haemolysis, or pump thrombosis in association with the fixed measurement from the pump. Better prediction of upcoming RV dysfunction, directed by measuring PAP combined with optimization of therapy based on haemodynamic feedback, might lead to a better LV unloading, lowering the PAP and lowering chances of RV failure.

As described previously, pulmonary hypertension alone is not a contraindication for LVAD implantation. Often PAP and pulmonary vascular resistance normalize several months after LVAD implantation, which cannot be matched by any medical therapy. Furthermore, LVAD implantation appears to be the best tool for reversal of 'fixed' pulmonary hypertension.[12] However, continuous data of PAP after LVAD implantation are not available at this moment. This study will provide novel insights of changes in PAP data during LVAD therapy.

Despite existing risk scores,[21,25–27] an adequate measuring tool for determining the ideal LVAD implantation timing is still missing. Multiple studies [13,21,26,27] demonstrated that sicker and more instable patients, indicated by a lower INTERMACS profile, had worse survival outcome than less sick patients, indicated by a higher INTERMACS profile.

It has been shown that an improvement in risk score shortly before LVAD implantation lead to a better outcome after LVAD implantation.[25] We hypothesize that the haemodynamic feedback, provided by the implantable haemodynamic monitoring, will lead to a tailor made, optimized medical therapy pre-LVAD. By doing so, we think that the patient will get in an optimal clinical condition, potentially rising the INTERMACS class from 2 to 3, or 3 to 4. Furthermore, we hypothesize that haemodynamic feedback provides additional information in order to determine the optimal timing of LVAD implantation. We hypothesize that optimizing the patients' clinical condition and the timing of LVAD implantation will lead to a better clinical outcome.

Other research areas of interest

Pulmonary artery pressure data provided by the CardioMEMS during LVAD therapy provide a unique opportunity of a wealth of novel haemodynamic data.

In the post-operative period, one of the major complications of LVAD is bleeding (40%) or tamponade requiring surgical intervention (20%).[20,22] The clinical diagnosis of tamponade is often missed in this complex patient group, as the pump keeps on providing flow even in the late stages of tamponade.[20] In case of tamponade, we expect to detect a decrease in PAP if the pericardial fluid impairs the filling of the right side of the heart; at the left side, located pockets could also impair pump function and increase PAP. CardioMEMS might be a valuable tool to detect the changes in a much earlier stage. In contrary, a major post-operative bleeding might lead to a drop in PAP due to loss of circulating volume. Additionally, in the outpatient clinical phase, the haemodynamic data could provide important feedback on development of frequent complications such as gastrointestinal bleeding (20–40%),[19,28] pump thrombosis (8–10%),[23] or renal dysfunction (12%) [21] at an earlier stage.

As described previously,[29] filling pressures will rise as a result of congestion. Congestion can be a sign of development of aortic valve regurgitation and pump dysfunction (kinking outflow graft or bent relief), resulting in higher PAP. For example pump thrombosis leads to LVAD dysfunction and impaired LV unloading. This will lead to signs and symptoms of HF and pulmonary congestion.[23,30]

Additionally, considering renal function,[8] lowering PAP by better unloading LV and providing better cardiac output will improve renal function. However, when kidney failure occurs and patients' urine production declines, PAP might rise. We will study these issues with separate research subthemes within the HEMO-VAD pilot study.

Limitations

The design of our study has some limitations. Due to the pilot study design we include only a small number of patients, with the aim to test the feasibility of this hybrid construction. Also, we have not included a control group in the study design, because of the observational nature. Still, the current study is the first prospective study investigating this new hybrid combination of CardioMEMS with an LVAD providing a wealth of novel haemodynamic data. After feasibility is demonstrated, we need to test the clinical value of this concept in a large-scale randomized clinical trial in patients scheduled for LVAD therapy as is currently anticipated.

Conclusions

The HEMO-VAD study will test the safety and feasibility of the hybrid construction of PAP measurements by the CardioMEMS device and LVAD therapy during 6 and 12 months of follow-up.

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Remote hemodynamic guidance before and after LVAD implantation: Short term results from the HEMO-VAD pilot study

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Abstract

Aims: Left ventricular assist device (LVAD) therapy remains to be affected by several severe LVAD-related complications. Additional tools to optimize and identify high-risk patients for adverse clinical outcomes are needed. We aimed to assess the safety, feasibility, and effectiveness of a hybrid construction of using CardioMEMS monitoring in patients before LVAD surgery and during LVAD therapy to optimize patient management as a proof of concept.

Methods and results: Ten patients (NYHA≥III; INTERMACS 2-5) accepted for (semi-) elective LVAD surgery were included and received a CardioMEMS ≤2 weeks before surgery. The aim was to optimize filling pressure to decongest the kidney and unload the right ventricle (RV) using hemodynamic data on top of physical examination and blood biomarkers. Patients were categorized whether hemodynamic optimization was achieved (mean pulmonary artery pressure (mPAP)≤25mmHg (n=4) vs. mPAP>25mmHg (n=6)) pre-LVAD surgery. Primary endpoints were CardioMEMS device safety and a combined endpoint of all-cause mortality, acute kidney injury, renal replacement therapy, and/or right ventricle failure at 3 months follow-up.

No device or system-related complications, or sensor failure of CardioMEMS, and no interference with the LVAD occurred during measurements. The combined end-point occurred most often in non-optimized CardioMEMS patients compared to hemodynamic optimized CardioMEMS patients (83%, 0%, p=0.007).

Conclusions: This pilot study demonstrates that combining CardioMEMS monitoring with LVAD therapy is safe and generates the hypothesis that using continuous hemodynamic data pre-LVAD surgery can improve patient outcome post-LVAD surgery. Patients with an mPAP>25mmHg pre-LVAD surgery, despite medical management, identify a very high-risk group for adverse clinical outcomes.

Introduction

Chronic heart failure (HF) is a complex clinical syndrome with increasing prevalence and incidence worldwide[1]. If HF progresses, patients can become refractory to medical therapy, leaving heart transplantation or left ventricular assist device (LVAD) surgery as advanced HF treatment options. Due to a shortage of available heart donors, LVAD therapy is increasingly used[2]. Despite growing experience with LVAD and technical improvements, overall survival remains affected by several severe LVAD-related complications, such as right ventricular (RV)-failure, acute kidney injury (AKI), LVAD-related infections, and major bleeding events[3-6]. The short term (≤3 months) mortality rate remains high, at approximately 10%[2]. Improving patient status shortly pre-LVAD surgery can improve post-LVAD surgery outcomes[7].

Identifying the ideal patients, as well as the timing of LVAD surgery, is essential in advanced HF management. Physical examination, laboratory results, and echocardiography are parameters that can be used pre-operatively but have limited predictive value for the outcome post-surgery. Many risk-scores are developed and provide some guidance in determining high-risk patients, but do not provide tools to optimize the patient pre-LVAD surgery[3, 8-11]. Congestion of the kidneys, indicated by an elevated central venous pressure (CVP), is associated with a higher risk of AKI and mortality[12]. Additional tools to optimize and assess the ideal LVAD surgery window are needed.

Recently, remote monitoring using the CardioMEMS device, an implantable pulmonary artery pressure (PAP) sensor, has shown to be safe and effective in preventing HF-related hospitalization in chronic HF patients[13, 14]. This technique could also be used as an additional tool to optimize patients during the work-up for LVAD surgery, allowing for hemodynamic optimization of patients going for surgery, unloading the RV, and decongestion of the kidney. This approach might improve the timing of surgery and might identify patients at high-risk for worse outcomes, e.g., RV-failure, where additional assistance (RV back-up) is necessary during, and shortly after surgery. Post-LVAD surgery, hemodynamic data could be used to remotely monitor patients as a hybrid construction with the static pump measurements provided by the LVAD at the out-patient clinic and at home.

The HEMO-VAD (HEMOdynamic guidance with CardioMEMS in patients with a left Ventricular Assist Device) pilot study assessed the safety and feasibility of combining

CardioMEMS with LVAD therapy. Furthermore, the study tests the hypothesis that combining the hemodynamic data provided by CardioMEMS in the pre-operative period towards LVAD surgery can improve patient selection, timing window, and overall surgical outcome. This is the first study evaluating this concept in a structured manner pre- and post-operatively to study this promising combination of techniques to optimize patient management.

Methods

The design and methods of the HEMO-VAD pilot study, an investigator-initiated, prospective pilot study, has been published in detail elsewhere [15]. In brief, all consecutive patients accepted by the heart team for LVAD surgery (HeartMate 3, HM3), both as destination therapy (DT) and bridge to transplantation (BTT), in the Erasmus MC Thorax Center, Rotterdam, between November 2017 and March 2019 were screened for study eligibility. In total, ten chronic HF patients with New-York Heart Association (NYHA) functional Class ≥III and Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Class 2-5, scheduled for (semi-) elective LVAD implantation were enrolled (Figure 1). Patients with significant RV dysfunction, indicated by a tricuspid annular plane systolic excursion (TAPSE) measurement ≤13 mm [16], were excluded from participation in this study. All patients provided informed consent, the local medical ethics committee approved the study (MEC nr. 2017-342), and the study complies with the Declaration of Helsinki.

CardioMEMS patients

All enrolled patients underwent CardioMEMS implantation at baseline (moment of acceptance within one day, per protocol), allowing for daily PAP monitoring in the pre-operative period towards LVAD surgery. The daily hemodynamic information, on top of standard care, was used to guide the adjustments in the medical treatment to hemodynamically optimize the patients prior to LVAD surgery. During the optimization phase, the central aim was to adjust the diuretic dosage to reach euvolemia and vasodilator therapy to aim for a normal mean PAP (mPAP) ≤25 mmHg. The timing of surgery was determined by normalized PAP, the urgency of surgery at the discretion of the physician, no responding pressure trend to medical changes, or a maximum period of two weeks. Post-LVAD surgery, the PAP readings were used in addition to regular care on the intensive care unit (ICU) and clinical ward, as well as at the out-patient clinic, to HF treatment and fluid (substitution) therapy and to optimize pump settings, targeting for a diastolic PAP between 8 and 15 mmHg as well as an mPAP ≤25 mmHg.

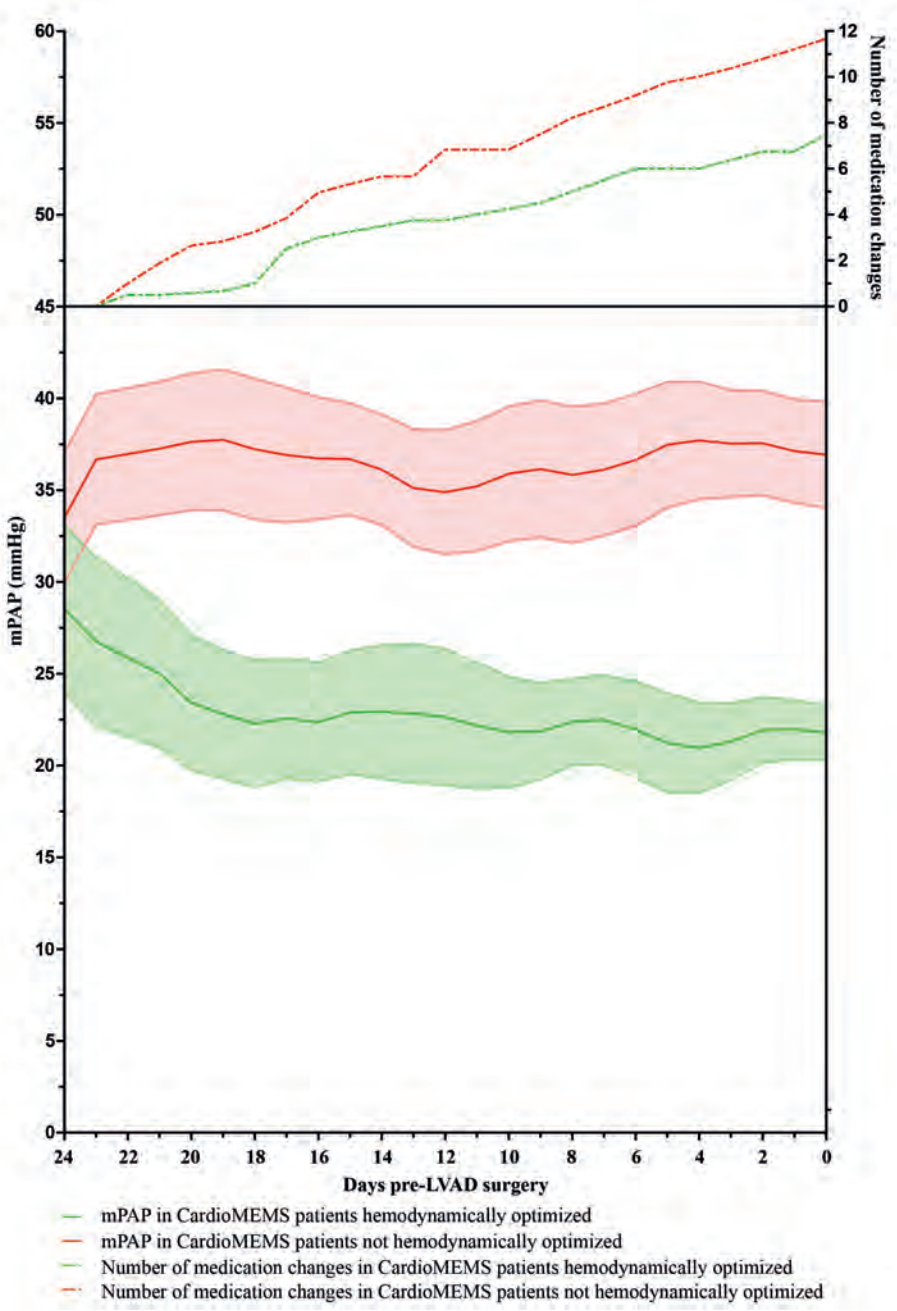

Figure 1. Optimization phase (pre-LVAD implantation): mPAP and number of medication changes from CardioMEMS implantation up to LVAD surgery according to hemodynamically optimized status pre-LVAD surgery

Colored area indicates ±1SE

Safety endpoints

The endpoints of the safety analysis were freedom of sensor failures at 3 months, freedom of device-related complications at 3 months, and the presence of signal malfunction or interference with the CardioMEMS device and HM3.

Clinical endpoints

The primary clinical endpoint of this analysis was the 3 months outcome after LVAD surgery, assessed as a composite endpoint of all-cause mortality, AKI and/or renal replacement therapy (RRT), and RV-failure. Secondary endpoints were all-cause mortality, AKI and/or RRT, RV-failure, as well as all-cause hospitalization-free survival, changes of mPAP pre- and post-LVAD surgery, the number of medication changes pre- and post-LVAD surgery, and changes in laboratory results (NT-proBNP, eGFR, bilirubin), quality of life (assessed using the EQ-5D-5L, Kansas City Cardiomyopathy Questionnaire (KCCQ) and Patient Health Questionnaire-9 (PHQ-9) questionnaires) and functional performance defined as 6-minute walking distance.

AKI was defined as a minimal 1.5 times increase of baseline serum creatinine during the first seven days post-LVAD implantation, according to the kidney disease improving global outcome criteria [17]. RV-failure was defined as continuous inotropic support for ≥14 days, or nitric oxide ventilation for ≥48 hours [18].

Statistical analysis

Continuous data are expressed as median and interquartile range and compared by the Mann-Whitney U-test. Categorical data are expressed as counts and percentages and compared by the two-sided Fishers' exact test. The probability of survival/ combined endpoint was calculated using the Kaplan-Meier method and compared using the log-rank test (time-to-first event analysis). Changes in quality of life between baseline and 6 months of follow-up within and between patient groups were analyzed using the repeated ANOVA test. A two-sided P value of 0.05 or lower was considered statistically significant.

The CardioMEMS patients were stratified based on mPAP provided by the CardioMEMS, into two groups: patients who could be hemodynamically optimized, defined as a pre-LVAD surgery mPAP≤25mmHg and those who could not be hemodynamically optimized, defined as a pre-LVAD surgery mPAP>25mmHg.

All statistical analyses were performed using Statistical Package for Social Sciences, version 25.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of all patients are presented in Table 1. In the entire cohort, the median age was 60 [52-63] years, 70% of patients were men, and the median left ventricular ejection fraction was 19% [13-24]. At baseline, the patients had a median TAPSE of 16 [15-20]mm, and a median systolic, diastolic, and mean PAP of 45 [39-50], 25 [21-30] and 33 [28-36]mmHg, respectively, at baseline. The median pulmonary capillary wedge pressure (PCWP) was 14 [11-29]mmHg, and the cardiac output was 3.9 [3.5-5.3]L/min.

Table 1. Baseline characteristics

	Overall population (n=10)	**Not hemodynamic optimized patients** (n=6)	**Hemodynamic optimized patients** (n=4)	**p-value**
Age (years)	60.1 [52.4-63.0]	60.3 [51.6-66.3]	58.7 [53.4-61.9]	0.670
Male gender (%)	7 (70.0)	4 (66.7)	3 (75.0)	1.000
BMI (kg/m^2)	27.2 [23.1-28.6]	27.2 [23.5-29.2]	24.8 [21.5-30.6]	0.670
Systolic BP (mmHg)	98.5 [89.0-108.5]	101.5 [88.8-115.3]	95.5 [89.3-102.5]	0.593
Diastolic BP (mmHg)	66.5 [57.0-72.8]	65.5 [50.3-81.3]	66.5 [60.8-70.0]	0.915
Heart rate (/min)	70.0 [67.5-78.0]	70.0 [64.3-84.0]	71.5 [68.5-75.3]	0.829
History				
Myocardial infarction	4 (40.0)	4 (66.7)	0 (0.0)	0.076
CABG	2 (20.0)	2 (33.3)	0 (0.0)	0.467
PCI	0 (0.0)	0 (0.0)	0 (0.0)	-
Atrial fibrillation	4 (40.0)	3 (50.0)	1 (25.0)	0.571
Diabetes Mellitus	4 (40.0)	2 (33.3)	2 (50.0)	1.000
Renal insufficiency	8 (80.0)	5 (83.3)	3 (75.0)	1.000
TIA/CVA	2 (20.0)	1 (16.7)	1 (25.0)	1.000
Laboratory values				
Creatinine (µmol/L)	159.5 [124.5-191.0]	174.5 [156.5-206.0]	121.0 [109.5-152.0]	0.032
e-GFR (mL/min)	38.5 [31.5-47.5]	33.5 [27.8-39.0]	50.0 [40.5-63.3]	0.019
NT-proBNP (pmol/L)	476.5 [297.8-565.0]	531.5 [328.8-655.0]	372.0 [263.3-544.5]	0.522
Bilirubin (µmol/L)	13.0 [10.5-20.3]	11.0 [8.3-20.3]	15.0 [12.5-19.8]	0.238
Echocardiogram				
Left ventricular ejection fraction (%)	19.0 [13.0-24.0]	19.0 [12.0-27.5]	17.5 [15.0-20.0]	1.000
TAPSE	16.0 [15.0-20.3]	18.0 [15.0-21.0]	16.0 [15.3-19.8]	0.826

Table 1. *(continued)*

	Overall population (n=10)	Not hemodynamic optimized patients (n=6)	Hemodynamic optimized patients (n=4)	p-value
Right heart catheterization				
RA pressure (mmHg)	5.5 [3.0-10.5]	5.0 [3.0-11.0]	5.0 [2.5-7.5]	0.392
Systolic PAP (mmHg)	44.5 [38.8-49.8]	46.5 [42.3-58.8]	39.5 [26.0-47.0]	0.165
Diastolic PAP (mmHg)	25.0 [20.8-29.5]	27.5 [24.0-34.0]	22.0 [13.3-24.8]	0.042
Mean PAP (mmHg)	32.5 [27.8-36.0]	33.5 [31.3-42.5]	28.5 [17.3-34.5]	0.238
PAP index	3.28 [1.76-6.50]	3.05 [1.27-8.17]	4.58 [2.20-6.00]	0.831
PCWP (mmHg)	13.5 [10.5-29.0]	19.5 [7.5-38.8]	13.0 [11.3-16.3]	0.670
Cardiac output (L/min)	3.89 [3.48-5.25]	3.69 [3.33-6.75]	4.10 [3.83-4.68]	0.522
HF therapy at baseline				
Loop diuretics	100 (100.0)	6 (100.0)	4 (100.0)	-
Beta-blocker	9 (90.0)	5 (83.3)	4 (100.0)	1.000
Vasodilators	7 (70.0)	4 (66.7)	3 (75.0)	1.000
MRA	7 (70.0)	4 (66.7)	3 (75.0)	1.000
Anticoagulation	10 (100.0)	6 (100.0)	4 (100.0)	-
ICD therapy	10 (100.0)	6 (100.0)	4 (100.0)	-
CRT-D	7 (70.0)	4 (66.7)	3 (75.0)	1.000

BMI, Body Mass Index; BP, Blood Pressure; CABG, Coronary Artery Bypass Graft; COPD, Chronic Obstructive Pulmonary Disease; TIA, Transit Ischemic Attack; CVA, Cerebrovascular Accident; e-GFR, estimated Glomerular Filtration Rate; TAPSE, Tricuspid Annular Plane Systolic Excursion; RA, Right Atrial; PAP, Pulmonary Artery Pressure; PCWP, Pulmonary Capillary Wedge Pressure; MRA, Mineralocorticoid Receptor Antagonist; ICD, Implantable Cardioverter Defibrillator; CRT, Cardiac Resynchronization Therapy

Safety & feasibility

The freedom of device or system-related complications of CardioMEMS was 100%, and the freedom of sensor failures of CardioMEMS was 100%, including no interference with the LVAD HM3 during measurements. In all patients, a clinically useful daily PA signal was achieved pre- and post LVAD surgery at the ICU, ward, and at home.

Pulmonary artery pressure

The median duration of the optimization phase before the planned elective LVAD surgery was 9 [6-12] days in patients who were not hemodynamically optimized (n=6) and 6 [5-10] days in patients who were hemodynamically optimized (n=4). Despite a lower number of medication changes during the optimization period, the decline in mPAP was larger in the patients who were hemodynamically optimized compared with those not hemodynamically optimized, as shown in Figure 1. In all patients who could

not be hemodynamically optimized, a combination of diuretics, as well as Enoximone, was used in an attempt to optimize these patients. During the optimization phase, three out of four hemodynamically optimized patients had an improvement in INTERMACS class (1.00 [0.25-1.75]). In contrast, one not hemodynamically optimized patient had an improvement, three patients remained in a similar INTERMACS class, and two patients had a worsening INTERMACS class (0.00 [-1.00-0.25]. Of the hemodynamically optimized patients, all proceeded towards LVAD-surgery because optimal mPAP were achieved. In the not hemodynamically optimized patients, three patients proceeded towards LVAD-surgery because the mPAP did not respond to changes, two patients because they excided the two weeks threshold and one patient at the discretion of the physician.

After LVAD surgery, in both patient groups, an initial increase in mPAP was observed, most likely by the fluid substitution at the ICU period, followed by a decline in both patient groups, as shown in Figure 2. Patients who were not hemodynamically optimized had more medication changes compared with the patients who were hemodynamically optimized.

Clinical outcome and LVAD-related adverse events

The combined endpoint of all-cause mortality, AKI/RRT, or RV-failure occurred 83.3% of the CardioMEMS patients who were not hemodynamically optimized. In comparison, no events occurred in the CardioMEMS patients who were hemodynamically optimized (0.0%), p=0.017 (Figure 3A). All-cause mortality occurred in 16.7% of the CardioMEMS patients who were not hemodynamic optimized, while no deaths occurred in the CardioMEMS patients who were hemodynamically optimized (0.0%) (p=0.414, Figure 3B). Both AKI and/or RRT, as well as RV-failure, occurred the least in the CardioMEMS patients who were hemodynamically optimized (0.0% and 0.0%, respectively) compared CardioMEMS patients who were not hemodynamically optimized (83.3% and 66.7%, respectively) (p=0.017 and p=0.054, respectively, Figure 3C and 3D).

All-cause hospitalization-free survival

The all-cause hospitalization-free survival did not significantly differ between the patient groups during the first 3 months post-LVAD surgery (p=0.665), as shown in Supplementary Figure 1. The all-cause hospitalization-free survival was 75.0% in the CardioMEMS patients who were hemodynamically optimized, and 60% in those who were not hemodynamically optimized.

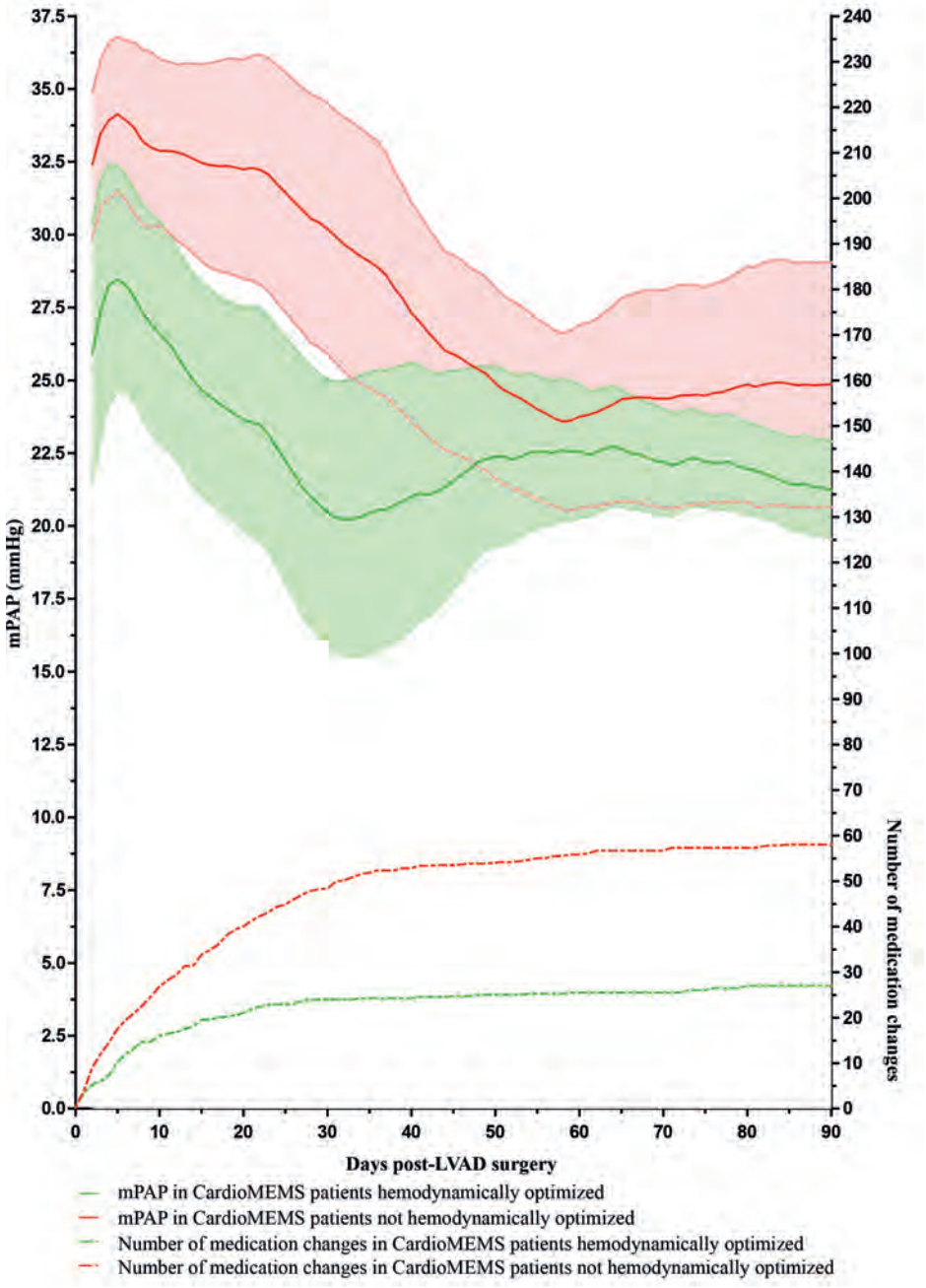

Figure 2. Out-patient monitoring phase: Mean mPAP and mean number of medication changes up to 90 days post-LVAD surgery according to hemodynamically optimized status pre-LVAD surgery

Colored area indicates ±1SE

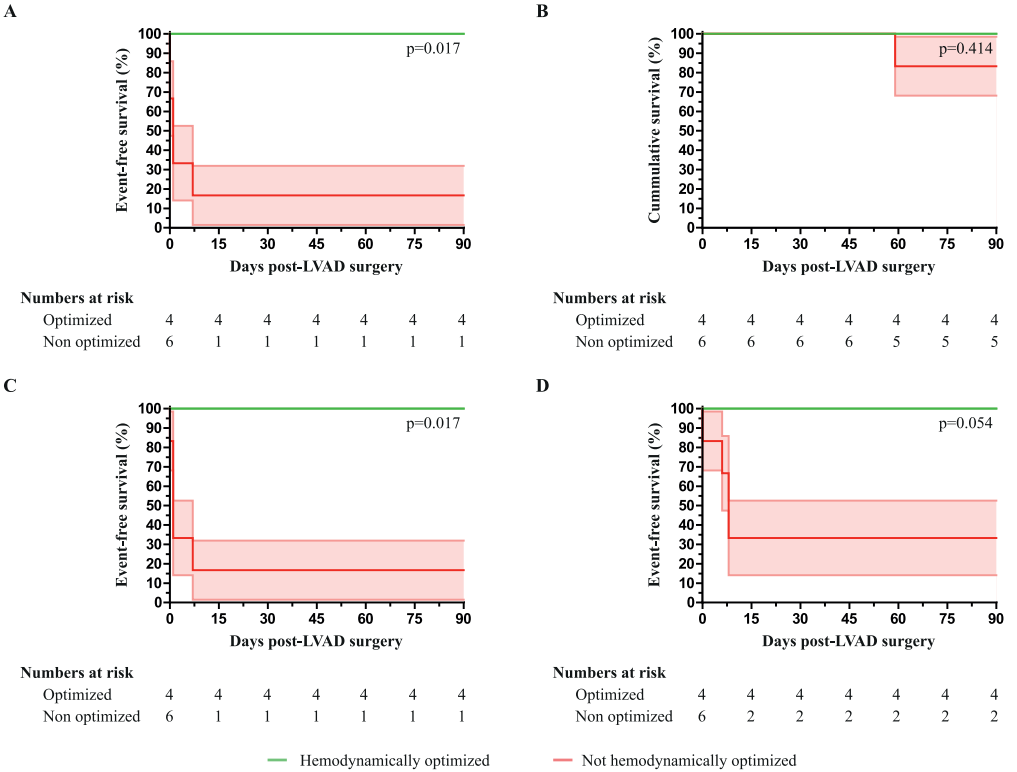

Figure 3. Kaplan-Meier plots of hemodynamically and not hemodynamically optimized patients post left ventricular assist device (LVAD) surgery. **A** the combined endpoint (all-cause mortality, acute kidney injury and/or renal replacement therapy, and right ventricular failure), **B** mortality, **C** acute kidney injury and/or renal replacement therapy, and **D** right ventricular failure

Colored area indicates ±1SE

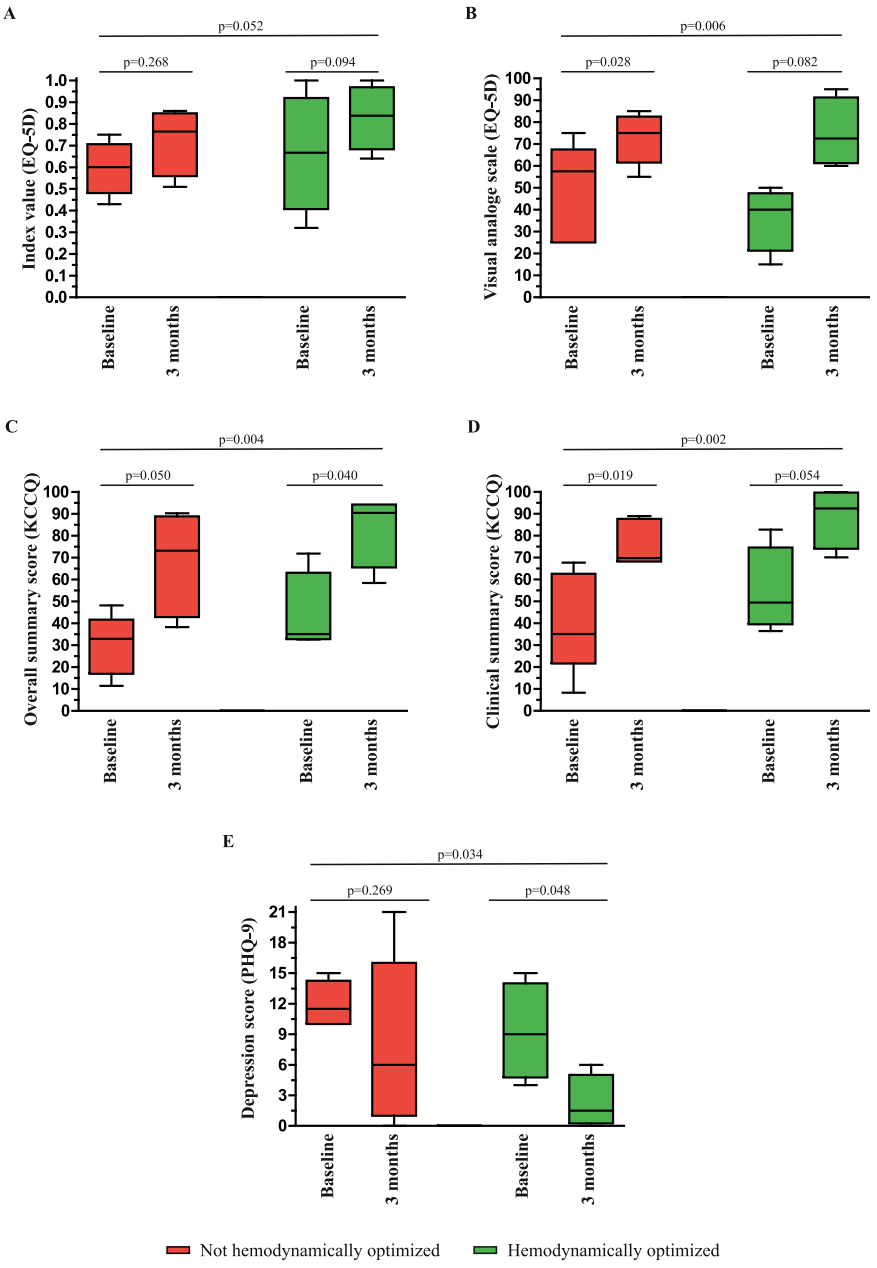

Figure 4. Changes in quality of life between baseline and 3 months post-LVAD surgery: **A** Index value (EQ-5D-5L) **B** Self-reported quality of life (EQ-5D-5L), **C** KCCQ overall summary score, **D** KCCQ clinical summary score and **E** PHQ-9 depression score

Lab values

The renal function, as well as the serum levels of NT-proBNP values and total bilirubin, improved in both patient groups, as shown in Supplementary Figure 2. The increase in serum creatinine levels increased the most in the CardioMEMS patients who were not hemodynamically optimized, and the least in the hemodynamically optimized CardioMEMS patients, as shown in Supplementary Figure 3.

Quality of life and functional performance

The self-reported quality of life in the CardioMEMS cohort improved during the first 3 months post-LVAD surgery for both patient groups, in all quality of life questionnaires (Figure 4A-E). In both CardioMEMS groups, a trend towards an improvement in the functional performance, measured by the 6-minute walking distance, between baseline and 3 months post-LVAD surgery was observed (Figure 5).

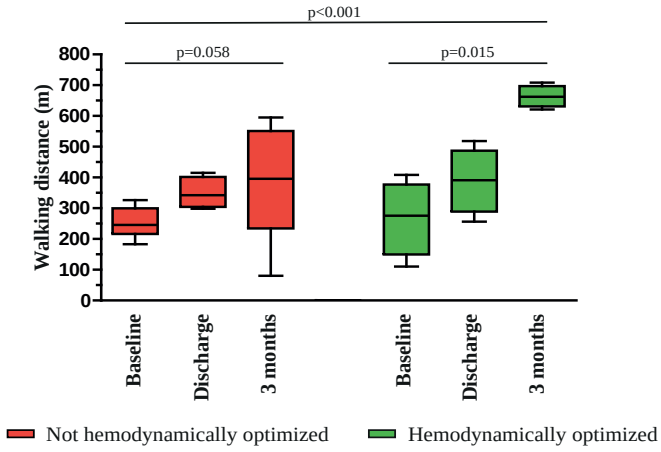

Figure 5. Changes in 6-minute walking distance at baseline, discharge and 3 months of follow-up in CardioMEMS patients

Discussion

The current pilot study showed that the concept of combining CardioMEMS before LVAD surgery is safe, feasible, and might improve patient management and outcome of LVAD patients. The hemodynamic feedback provided by CardioMEMS could be clinically useful and intuitive to identify a high-risk group of worse LVAD outcomes with no adequate response of PAP. The ability to adjust PAP before surgery with a

decongestion of the kidney and RV might identify a group with a good prognosis after elective LVAD surgery.

Using the hemodynamic feedback provided by the CardioMEMS pre-LVAD surgery leads to a tailored approach and true hemodynamic optimization of LVAD recipients. The current hybrid approach might serve as an important new risk marker or guide of therapy where the physician can be alerted to start RRT earlier or provide RV support at an early stage in anticipation of worse outcomes.

The overall survival of chronic HF patients supported with a continuous-flow LVAD has been extensively reported, with a 30-day survival rate between 89 and 98%[19, 20], and a one-year survival rate between 75 and 85%[19, 21-23]. Despite technological improvements, the short-term outcome is effected due to LVAD-related complications, such as RV-failure, renal failure, and post-operative bleedings[22]. Several risk factors for post-operative complications have been identified, including a higher age, LVAD surgery as DT, a worse kidney function, and a lower INTERMACS profile[2, 21-24]. Although it has been shown that improving the INTERMACS profile shortly prior to LVAD surgery improves outcomes[7], strategies to optimize the patient clinical status prior to LVAD surgery are still lacking. As our results demonstrate, using the hemodynamic feedback provided by the CardioMEMS device to hemodynamically optimize patients prior to LVAD surgery is safe, feasible and might improve the outcome of LVAD patients.

Patient selection, risk assessment, and timing of LVAD surgery remain significant challenges for treating physicians. In a small subgroup analysis of the CHAMPION trial and a small retrospective study, patients who received a CardioMEMS device and (naturally) progressed to end-stage HF needing LVAD showed a gradual increase in PAP till the moment of surgery[25, 26]. By using the hemodynamic information, clinicians could better identify chronic HF patients who did not respond to pharmacological therapies on top of standard care and could identify patients in need for LVAD surgery at an earlier stage[25]. However, both studies had a retrospective design, including a case series of studied patients already on LVAD therapy without a structured pre-operative approach using the sensor information going into surgery.

Based on physical examination and blood biomarkers, all patients included in the CardioMEMS cohort were deemed to be in an optimal state for surgery before CardioMEMS implantation. However, as indicated by the elevated PCWP at baseline, many patients were still in a hypervolemic state. Adding daily PAP monitoring on top

of standard care could help the HF-specialist to decongest the RV and kidneys truly, and achieve a better pre-operative condition. Normalization of the mPAP shortly prior to LVAD surgery might indicate an ideal optimization and could aid in improving the timing of LVAD surgery. Eventually, this might result in a lower incidence of AKI, RRT, and RV-failure post-LVAD surgery. Additionally, a very high-risk population for LVAD-related complications might be identified by the inability to normalize the mPAP pre-LVAD surgery.

Additionally, we observed a small increase in PAP in the first days after LVAD surgery, which could be caused by significant fluid infusion during surgery and at the ICU that may stress and impair the already vulnerable RV and kidney function in this period. PAP guidance could help to prevent aggressive fluid management, allowing relative hypotension in LVAD patients during the first days post-operatively (preventing unnecessarily stretching the RV). These findings are hypothesis-generating due to the small patient size, but clinically plausible.

Minimizing the risk of RV-failure and AKI post-LVAD

LVAD implantation affects the RV in multiple ways. LVAD support results in higher cardiac preload to the RV, resulting in a bigger venous return to the RV, potentially overloading the RV[27]. Also, LVAD support can cause an intraventricular septum shift, impairing the RV contraction[28]. These hemodynamic factors could contribute to the development of immediate RV-failure, that may occur in more than 20% of all LVAD implantations[2, 12]. Many risk factors for RV-failure post-LVAD surgery have been identified, including several patient characteristics, echocardiographic parameters and hemodynamic information, including higher PAP[12]. An elevated PAP might be used as an indicator of elevated preload and/or afterload of the RV, in addition to existing markers.

Recently, it has been proposed that concomitant implantation of a temporary transcutaneous RV assist device with LVAD surgery could improve LVAD patient's short term outcome [29]. However, identifying the appropriate patients remains challenging. Hemodynamic monitoring pre-LVAD surgery using the CardioMEMS could aid in identifying patients at high risk for RV-failure post-LVAD surgery. In these patients, concomitant implantation of a temporary transcutaneous RV assist device might be indicated.

A wide variation of the incidence of AKI post-LVAD surgery has been reported, ranging from 10-50%[30]. Additionally, AKI is strongly associated with a higher risk of mortality in

LVAD patients[31]. One of the risk factors for the development of AKI post-LVAD surgery venous congestion of the kidneys, indicated by an elevated CVP[12].

Hemodynamically guided medical optimization pre-LVAD surgery could result in a lower PAP prior to LVAD surgery. As a result of this, the RV afterload will be reduced, reducing the stress on the RV during and shortly after the LVAD implantation, and decongesting the kidneys, and hypothetically lowering the chance of RV-failure and AKI shortly after LVAD surgery.

Limitations

We acknowledge the small sample size of our pilot study, thereby limiting the results as hypothesis-generating in a pilot study. Additionally, the expected event rate in the hemodynamically optimized patients was very low, so observed differences might have been caused due to the small sample size. However, the results are clinically meaningful and promising, considering its shown significant findings and clinical plausibility/intuitiveness of the hybrid construction. Pilot studies need to be followed by a large scale pivotal study, which has currently started as a separate study in the US (NCT03247829). Much more hybrid construction can be tested in the near future of combining daily hemodynamic info with, for example CRT-D response and optimization, or diuretic management pre- and post-procedural of valvular interventions e.g., Mitraclip in a similar approach [32-34].

Conclusion

Remote monitoring using the CardioMEMS sensor in end-stage chronic HF patients pre- and post-LVAD surgery is a safe and feasible strategy positively testing the hypothesis that patient management and the outcome can be further improved when patients are hemodynamically optimized before surgery with the central concept of “better in, better out”. This novel combination of these two state-of-the-art techniques with direct hemodynamic feedback in LVAD patients warrants a large randomized controlled pivotal study.

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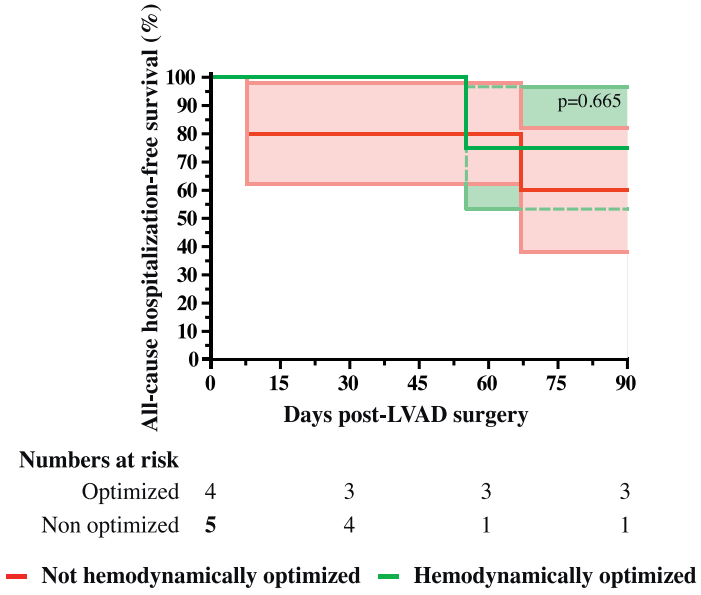
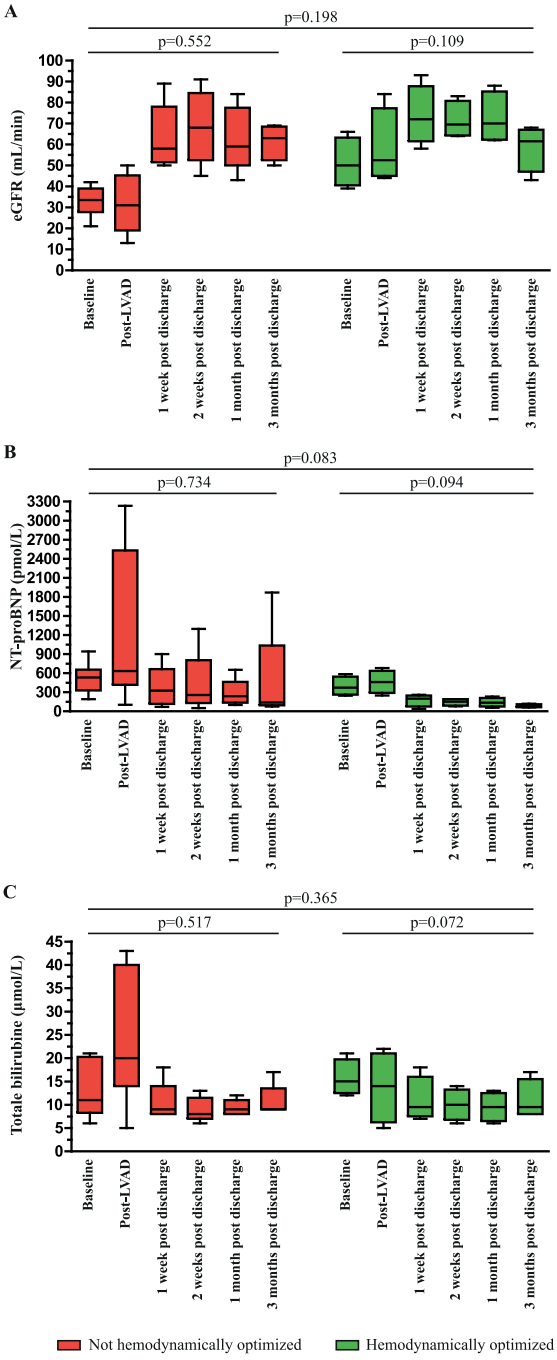
Supplementary data

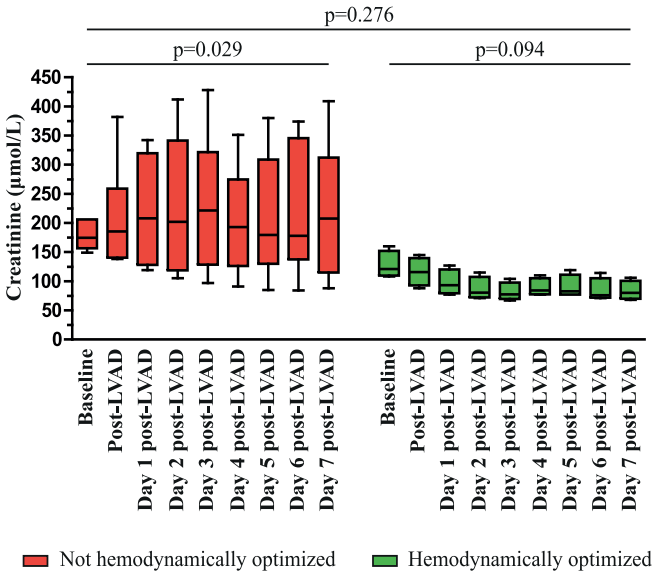


Supplementary Figure 1. Kaplan-Meier time event-free survival: freedom from all-cause hospitalization survival

Colored area indicates ±1SE



Supplementary Figure 2. Changes in laboratory results in CardioMEMS patients and historical controls: **A** changes in renal function (eGFR), **B** changes in NT-proBNP, **C** changes in total bilirubin



Supplementary Figure 3. Changes in serum creatinine levels shortly pre- and lost-LVAD surgery

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Safety and feasibility of a hybrid construction of hemodynamic guidance by pulmonary artery pressure monitoring and left ventricular assist device management: Main findings of the proof of concept HEMO-VAD study

Veenis JF, Radhoe SP, Van Mieghem NM, Manintveld OC, Bekkers JA, Caliskan K, Brugts JJ

Under embargo

Submitted

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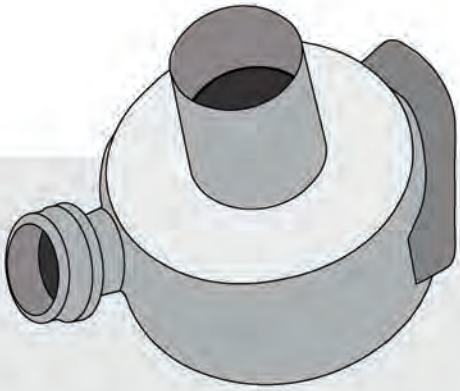

Optimizing left ventricular assist device management

Chapter 19
Cardiac implantable electronic devices with a defibrillator component and all-cause mortality in left ventricular assist device carriers: results from the PCHF-VAD Registry

Chapter 20
How does age affect the clinical course after left ventricular assist device implantation: results from the PCHF-VAD

Chapter 21
Underutilization of left ventricular assist devices in women at similar survival outcomes compated to men

Chapter 22
Survival following concomitant aortic valve procedure during left ventricular assist device surgery: an ISHLT Mechanically Assisted Circulatory Support (IMACS) Registry

Chapter 23
Rate of thromboembolic and bleeding events in patients with concomitant aortic valve surgery and left ventricular assist device implantation: an analysis of the IMACS dataset

Chapter 24
Prevalence of iron deficiency and iron administration in LVAD and heart transplantation patients

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Cardiac implantable electronic devices with a defibrillator component and all-cause mortality in left ventricular assist device carries: results from the PCHF-VAD Registry

Cikes M, Jakus N, Claggett B, Brugts JJ, Timmermans P, Pouleur AC, Rubis P, Van Craenenbroeck EM, Gaizauskas E, Grundmann S, Paolillo S, Brage-Caballero E, D'Amario D, Gkouziouta A, Planic I, Veenis JF, Jacquet LM, Houard L, Holcman K, Gigase A, Rega F, Rucinskas K, Adamopoulos S, Agostoni P, Biocina B, Gasparovic H, Lund LH, Flammer AJ, Metra M, Milicic D, Ruschitzka F

Eur J Heart Fail. 2019 Sep;21(9):1129-1141

Abstract

Aims: To compare characteristics of left ventricular assist device (LVAD) recipients receiving a cardiac implantable electronic device (CIED) with a defibrillator component (implantable cardioverter-defibrillator and cardiac resynchronization therapy with defibrillation, CIED-D) vs. those without one, and to assess whether carrying such a device contiguously with an LVAD is associated with outcomes.

Methods and results: Overall, 448 patients were analysed (mean age 52±13 years, 82% male) in the multicentre European PCHF-VAD registry. To account for all active CIED-Ds during ongoing LVAD treatment, outcome analyses were performed by a time-varying analysis with active CIED-D status post-LVAD as the time-varying covariate. At the time of LVAD implantation, 235 patients (52%) had an active CIED-D. Median time on LVAD support was 1.1 years (interquartile range 0.5–2.0 years). A reduction of 36% in the risk of all-cause mortality was observed in patients with an active CIED-D [hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.46–0.91; P = 0.012), increasing to 41% after adjustment for baseline covariates (HR 0.59, 95% CI 0.40–0.87; P = 0.008) and 39% after propensity score adjustment (HR 0.61, 95% CI 0.39–0.94; P = 0.027). Other than CIED-D, age, LVAD implant as redo surgery, number of ventricular arrhythmia episodes and use of vasopressors pre-LVAD were remaining significant risk factors of all-cause mortality. Incident ventricular arrhythmias post-LVAD portended a 2.4-fold and 2.6-fold increased risk of all-cause and cardiovascular death, respectively; carrying an active CIED-D remained associated with a 47% and 43% reduction in these events, respectively.

Conclusions: In an analysis accounting for all active CIED-Ds, including those implanted during LVAD support, carrying such a device was associated with significantly better survival during LVAD support.

Introduction

It is estimated that patients with advanced heart failure (HF) comprise 1–10% of the entire population of patients with HF, with increasing prevalence paralleling the growth of the HF population and the improvements in available treatments, prolonging survival.[1] Advances in long-term mechanical circulatory support with left ventricular assist devices (LVADs) have significantly improved outcomes in this rapidly expanding population.[2,3] However, several challenges in the clinical management of LVAD recipients remain and several opportunities exist to further optimize patient benefits,[4–6] including combined device therapy with cardiac implantable electronic devices (CIEDs).

Therapies for advanced HF are indicated with progression of the disease beyond adequate symptom management or adequate preservation of end-organ function, despite ongoing and optimized guideline-directed medical and device therapies.[1] For patients with HF with reduced ejection fraction (HFrEF), the guidelines mandate the use of implantable cardioverter-defibrillators (ICD) and, in selected patients, cardiac resynchronization therapy (CRT) devices.[7] Given the progressive nature of the disease, a certain amount of overlap of device-based treatment modalities is encountered – according to the INTERMACS database, 80% of LVAD recipients already have an ICD device in situ.[8] On the other hand, patients may receive an LVAD without having a CIED when the LVAD is indicated for an acute HF episode. Although the existing literature on patient outcomes with combined device therapy is growing, the results are conflicting; the majority of the studies were conducted in single-centre patient populations, with few exceptions.[8–15] Importantly, a perspective on the European landscape of combined device therapy in advanced HF is still lacking. The current International Society for Heart and Lung Transplantation (ISHLT) guidelines for mechanical circulatory support provide a class I recommendation for the reactivation of an ICD after LVAD surgery and a class IIa recommendation for ICD placement after LVAD for those without one.[16] However, more conservative strategies have recently been advocated.[17]

We compared characteristics among patients receiving a CIED with a defibrillator component (ICD and CRT-D devices) and those without one in a multicentre European registry of LVAD recipients to assess whether carrying a defibrillator component contiguously with an LVAD, including CIEDs implanted post-LVAD, was associated with improved outcomes.

Methods

Study population

This observational study enrolled patients through a network of 12 European HF tertiary referral centres, stemming from participants and alumni of the Postgraduate Course in Heart Failure (PCHF) of the Heart Failure Association of the European Society of Cardiology and the European Heart Academy, forming the PCHF-VAD registry. Each participating centre acquired the approval of their local institutional/ethics review board for the study protocol and retrospective acquisition of patient data, predominantly with a waiver of informed consent.

Currently, the registry consists of 488 patients who underwent durable ventricular assist device (VAD) implantation for advanced HF and are in regular follow-up by the participating centres. The variables collected in the registry include baseline demographic patient information, baseline device (VAD, ICD, CRT) information, patient physical status and functional class, electrocardiographic and echocardiography data, laboratory findings, right heart catheterisation data, data on medications and therapies as well as VAD and CIED parameters – except for baseline data, all other variables were collected at three time points: prior to VAD implantation, at discharge from VAD implantation, and 6 months after the last device implantation. In order to represent the currently most utilised form of durable mechanical circulatory support and to retain homogeneity of the studied cohort, data were analysed for patients implanted with a continuous-flow LVAD (cf-LVAD) – patients with pulsatile LVADs, right VADs and biventricular assist devices, as well as those with missing ICD/CRT carrier status (including missing implantation/potential inactivation dates) were excluded from the analysis. All cf-LVADs were implanted between 1 December 2006 and 15 April 2018. All-cause death was defined as the primary outcome. The secondary outcomes were cardiovascular mortality, hospitalisation for HF, the occurrence of clinically significant ventricular arrhythmias (VAs) after LVAD implantation (defined as symptomatic arrhythmias and/or arrhythmias leading to CIED therapy delivery, and/or arrhythmias requiring medical intervention), device-related (both LVAD and CIED) infections requiring antibiotic treatment, intracranial bleeding and non-cerebral bleeding events. The adjudication of outcomes was performed by the teams of the registry centres.

The patient data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools – a secure, web-based application,18 hosted at the University of Zagreb, School of Medicine, which served as the data coordinating centre.

Statistical analysis

Baseline characteristics are expressed as counts and percentages for categorical variables or as mean±standard deviation [alternatively, median (25th–75th percentile) for those non-normally distributed] for continuous variables. At baseline, the inter-group differences were based on CIED with an active defibrillator component (CIED-D) carrier status before LVAD implantation and were assessed using the chi-square test or ANOVA (or Kruskal–Wallis test for non-normally distributed variables) for categorical and continuous variables, respectively.

Outcome analyses were performed using the primary endpoint of all-cause death as well as the secondary outcomes. For survival analyses, the time of LVAD implantation was considered as the index date; the time of follow-up was defined as time to last contact, heart transplant, weaning from LVAD or death (whichever came first). In order to include in the analysis all active ICD and CRT-D devices during the time of ongoing LVAD treatment (including those implanted and excluding those inactivated during LVAD support), outcome analyses were performed by a time-varying analysis with active CIED-D carrier status following LVAD implantation as the time-varying covariate to assess the association between active CIED-D carrier status post-LVAD and the occurrence and time course of the primary outcome. The incidence rate was estimated for the primary and secondary endpoints based on the time-varying covariate (active CIED-D carrier post-LVAD), and the hazard ratios (HR) were estimated using the Cox proportional hazards model with the group of patients with no active CIED-D post-LVAD serving as the referent group. A Cox regression model based on a forward stepwise selection process with a significance level of 0.05 and 0.10 for entry and removal thresholds, respectively, was used to test the association of active CIED-D carrier status with 25 baseline covariates (online supplementary Methods S1) that significantly differed between the two patient groups at baseline and had less than 30% missing data: age, gender, CIED-D status, heart rate, LVAD type, LVAD intention, INTERMACS class, aetiology of HF, known history of: chronic kidney disease, atrial fibrillation/flutter, VAs; significant VAs pre-LVAD, prior cardiac surgery, concomitant procedure with LVAD implant, type of life support prior to LVAD, diuretic use, beta-blocker use, ivabradine use, mineralocorticoid receptor antagonist use, vasopressor use, ultrafiltration, type of mechanical ventilation, creatinine values, left ventricular internal dimension at end-diastole, and LVAD implant date quartile (Table 1).

Table 1. Baseline characteristics of the studied patients by CIED-D carrier status prior to left ventricular assist device implantation

	Overall average	No CIED-D pre-LVAD (n=208)	CIED-D pre-LVAD (n=240)	P-value
Age, years	52±13	50±14	54±12	<0.001
Female sex	81 (18.1)	46 (22.1)	35 (14.6)	0.039
Geographical area				
Northwest Europe (The Netherlands, Belgium, Germany)	303 (76.6)	148 (71.2) (48.8% of region)	155 (64.6) 51.2% of region)	0.14
Southeast Europe (Croatia, Poland, Lithuania, Italy, Spain, Greece)	145 (32.4)	60 (28.8) (41.4% of region)	85 (35.4) (58.6% of region)	
Quartiles of date of LVAD implant				
1st quartile (6 Dec 2006 – 2 Jan 2012)	112 (25)	72 (34.6)	40 (16.7)	<0.001
2nd quartile (3 Jan 2012 – 8 Dec 2014)	112 (25)	62 (29.8)	50 (20.8)	
3rd quartile (9 Dec 2014 – 20 Jul 2016)	113 (25.2)	48 (23.1)	65 (27.1)	
4th quartile (21 Jul 2016 – 04 Apr 2018)	111 (24.8)	26 (12.5)	85 (35.4)	
ICD status				
No ICD	238 (53.1)	188 (90.4)	50 (20.8)	<0.001
Primary prevention	153 (34.2)	15 (7.2)	138 (57.5)	
Secundary prevention	57 (12.7)	5 (2.4)	52 (21.7)	
CRT status				
No CRT	345 (77.0)	188 (90.4)	157 (65.4)	<0.001
CRT-P carrier	16 (3.6)	16 (7.7)	0 (0.0)	
CRT-D carrier	87 (19.4)	4 (1.9)	83 (34.6)	
Heart rate, b.p.m.	85±20	93±21	80±17	<0.001
SBP, mmHg	100±15	101±16	100±14	0.71
DBP, mmHg	65±11	65±12	65±10	0.91
BMI, kg/m^2	25.8±4.6	25.3±4.4	26.2±4.8	0.050
NYHA class				
II	15 (3.8)	5 (2.9)	10 (4.5)	0.06
IIIa	132 (33.4)	58 (33.3)	74 (33.5)	
IIIb	105 (26.6)	37 (21.3)	68 (30.8)	
IV	143 (36.2)	74 (42.5)	69 (31.2)	

Table 1. *(continued)*

	Overall average	No CIED-D pre-LVAD (n=208)	CIED-D pre-LVAD (n=240)	P-value
LVAD type				
Heart Mate II	246 (54.9)	144 (69.2)	102 (42.5)	<0.001
HeartWare HVAD	94 (21.0)	36 (17.3)	58 (24.2)	
Heart Mate 3	87 (19.4)	22 (10.6)	65 (27.1)	
Other	21 (4.7)	6 (2.9)	15 (6.2)	
LVAD Intention				
BTT	305 (71.1)	137 (68.8)	168 (73.0)	<0.001
BTD	68 (15.9)	47 (23.6)	21 (9.1)	
DT	56 (13.1)	15 (7.5)	41 (17.8)	
INTERMACS class				
1	73 (16.7)	55 (27.4)	18 (7.6)	<0.001
2	121 (27.7)	63 (31.3)	58 (24.6)	
3	139 (31.8)	47 (23.4)	92 (39.0)	
4-7	104 (23.8)	36 (17.9)	68 (28.8)	
Aetiology of heart failure				
Dilated cardiomyopathy	190 (42.4)	68 (32.7)	122 (50.8)	<0.001
Ischaemic cardiomyopathy	206 (46.0)	104 (50.0)	102 (42.5)	
Other	52 (11.6)	36 (17.3)	16 (6.7)	
Co-morbidities				
Arterial hypertension	102 (22.8)	47 (22.6)	55 (22.9)	0.94
Diabetes mellitus	90 (20.1)	37 (17.8)	53 (22.1)	0.26
Chronic kidney disease	102 (22.8)	31 (14.9)	71 (29.6)	<0.001
Coronary artery disease	111 (24.8)	52 (25.0)	59 (24.6)	0.92
Prior MI	168 (37.5)	87 (41.8)	81 (33.8)	0.08
Prior coronary revascularization	132 (29.5)	66 (31.7)	66 (27.5)	0.33
COPD	42 (9.4)	14 (6.7)	28 (11.7)	0.07
Atrial fibrillation/flutter	128 (28.6)	31 (14.9)	97 (40.4)	<0.001
Ventricular arrhythmias	102 (22.8)	30 (14.4)	72 (30.0)	<0.001
Cerebrovascular events	33 (7.4)	12 (5.8)	21 (8.8)	0.23
Significant ventricular arrhythmias prior to LVAD implant				
None	245 (66.9)	120 (83.3)	125 (56.3)	<0.001
1 episode	58 (15.8)	14 (9.7)	44 (19.8)	
2 episodes	25 (6.8)	5 (3.5)	20 (9.0)	
3 episodes	21 (5.7)	2 (1.4)	19 (8.6)	
≥4 episodes	17 (4.6)	3 (2.1)	14 (6.3)	
Prior cardiac surgery	55 (12.3)	33 (15.9)	22 (9.2)	0.031

Table 1. *(continued)*

	Overall average	No CIED-D pre-LVAD (n=208)	CIED-D pre-LVAD (n=240)	P-value
Concomitant procedure with LVAD implant	79 (17.6)	50 (24.0)	29 (12.1)	<0.001
Life support prior to LVAD implant				
None	318 (73.6)	112 (56.0)	206 (88.8)	<0.001
ECMO	35 (8.1)	30 (15.0)	5 (2.2)	
Temporary LVAD	4 (0.9)	4 (2.0)	0 (0.0)	
Temporary BiVAD	1 (0.2)	1 (0.5)	0 (0.0)	
IABP	55 (12.7)	35 (17.5)	20 (8.6)	
Other	19 (4.4)	18 (9.0)	1 (0.4)	
Medications				
Diuretic	349 (90.6)	130 (79.3)	219 (99.1)	<0.001
Beta blocker	230 (64.1)	64 (43.5)	166 (78.3)	<0.001
ACEI/ARB	183 (49.5)	78 (49.7)	105 (49.3)	0.94
MRA	243 (72.8)	76 (55.9)	167 (84.3)	<0.001
Ivabradine	36 (11.6)	9 (7.1)	27 (14.7)	0.042
Inotrope	232 (65.5)	104 (68.9)	128 (63.1)	0.25
Vasopressor	36 (10.8)	23 (16.8)	13 (6.6)	0.003
Ultradiltration	12 (3.6)	10 (7.4)	2 (1.0)	0.003
Mechanical ventilation				
None	310 (92.3)	116 (84.1)	194 (98.0)	<0.001
NIV/cPAP	2 (0.6)	2 (1.4)	0 (0.0)	
Intubation	24 (7.1)	20 (14.5)	4 (2.0)	
Laboratory valuese				
Creatinine, umol/L	126±57	117±57	133±56	0.004
Bilirubin, umol/l	19.0 (12.0-30.8)	19.8 (12.0-34.0)	18.8 (12.0-28.0)	0.019
Echocardiographic data				
LVIDd, mm	70.4±12.8	67.4±13.1	72.5±12.2	<0.001
LVEF, %	19±7	19±8	20±7	0.46

Values expressed as mean±standard deviation, number (%), or median (interquartile range).
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BiVAD, biventricular assist device; BMI, body mass index; BTD, bridge to decision; BTT, bridge to transplantation; CIED-D, cardiac implantable electronic device with a defibrillator component; COPD, chronic obstructive pulmonary disease; cPAP, continuous positive airway pressure; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with a defibrillator component; CRT-P, cardiac resynchronization therapy with a pacemaker component; DBP, diastolic blood pressure; DT, destination therapy; ECMO, extracorporeal membrane oxygenation; FAC, fractional area change; IABP, intra-aortic balloon pump; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; LVIDd, left ventricular intraventricular dimension in end-diastole;MI,myocardial infarction;MRA,mineralocorticoid receptor antagonist;NIV, non-invasive ventilation;NYHA, New York Heart Association; RVIDd, right ventricular intraventricular dimension in end-diastole; SBP, systolic blood pressure; VAD, ventricular assist device.

Additional sensitivity analyses were performed to determine the consistency of the results. A multiple imputation was performed whereby missing data were managed using multiple imputation by chained equations (STATA mi impute chained). Imputation was performed for each variable with 1–30% of missing data; it was based on linear regression using 20 baseline clinical variables and 18 predictor variables and estimated over 30 imputations.[19] Furthermore, in order to additionally adjust for the differences between the patients grouped by CIED-D carrier status prior to LVAD implantation (Table 1), we created a propensity score to determine the possibility of having a CIED-D pre-LVAD. The propensity score was calculated using a multivariable logistic regression model including the following variables: ICD/CRT carrier status, age, gender, previous history of hypertension, diabetes, chronic kidney disease, coronary artery disease, myocardial infarction, cerebrovascular accident, atrial fibrillation and VAs; type of LVAD, intention of LVAD treatment, INTERMACS score, LVAD implant as redo surgery and concomitant surgical procedures. This was followed by a propensity score adjusted analysis to assess the relation of CIED-D carrier status and the occurrence of the primary and secondary outcomes. Finally, to control for immediate perioperative deaths, we have utilised the time-varying coefficient to test the interaction between the duration of follow-up and the CIED-D treatment effect at 30 and 90 days following LVAD implantation.

A P-value of <0.05 was considered statistically significant. The statistical analyses were performed in Stata version 14 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics

After excluding data from 14 patients with pulsatile LVADs and biventricular assist devices, as well as 26 patients with missing ICD/CRT carrier status (including missing implantation and potential inactivation dates), the analysed population consisted of 448 patients (Figure 1). The baseline clinical characteristics were collected prior to LVAD implantation; the patients were thus divided into two groups according to CIED-D status before LVAD implantation: 240 patients (54%) were an CIED-D carrier pre-LVAD, while the remaining 208 patients (46%) did not carry any of these devices pre-LVAD (of note, the discrepancies such as the 20 ICD patients in the non-CIED-D group are those that cross-over during the course of LVAD treatment) (Figure 1). Baseline characteristics of the patient population according to CIED-D status pre-LVAD are provided in Table 1 and in the online supplementary Table S1. CIED-D carriers were older and more frequently

male compared to those without CIED-D pre-LVAD. Of the patients receiving a CIED-D pre-LVAD, the majority were those implanted with an LVAD in the last quartile of LVAD implantation dates, i.e. from 21 July 2016 onwards (online supplementary Figure S1). The predominant disease aetiology was dilated cardiomyopathy in those with CIED-D, while ischaemic cardiomyopathy was more common in the other group. While chronic kidney disease was more represented in CIED-D carriers, other co-morbidities such as hypertension, diabetesmellitus, coronary artery disease, chronic obstructive pulmonary disease and prior cerebrovascular accident did not differ significantly between the two groups. Known atrial fibrillation and previous VAs (defined as those requiring ICD therapy or external defibrillation prior to LVAD implantation verified in ICD memory or during patient monitoring) were more frequent in the CIED-D pre-LVAD group. Although left ventricular ejection fraction did not differ significantly between groups, patients with CIED-D pre-LVAD had larger left ventricles. Haemodynamic measurements did not reveal a significant difference between groups, nor did their blood pressure values. However, heart rate was significantly higher in those without CIED-D pre-LVAD.

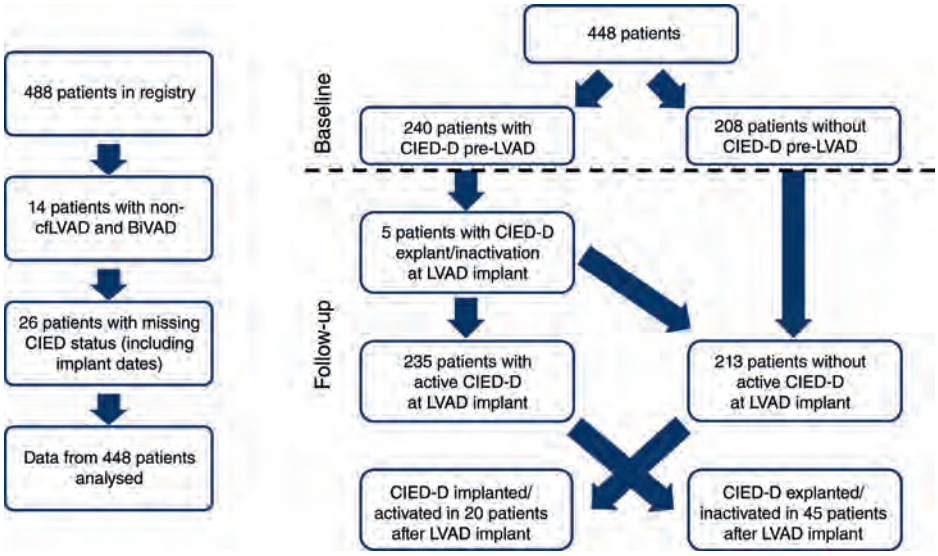

Figure 1. (*Left*) Selection of the study population from the PCHF-VAD registry. (*Right*) Patient flow during the follow-up period in respect to a cardiac implantable electronic device (CIED) with a defibrillator component (CIED-D). BiVAD, biventricular assist device; cfLVAD, continuous-flow left ventricular assist device; LVAD, left ventricular assist device.

The distribution of LVAD types differed significantly: those with CIED-D were more frequently carriers of HeartWare HVAD and HeartMate 3 devices than patients in the

other subgroup, where HeartMate II was more common. The proportion with an LVAD as a bridge to decision was higher in those without a CIED-D; these patients were also more frequently in INTERMACS classes 1 and 2, while no significant difference in New York Heart Association (NYHA) class was noted. The proportion of patients on diuretics, beta-blockers and mineralocorticoid receptor antagonists was higher in those with a CIED-D pre-LVAD. A higher proportion of patients without a CIED-D pre-LVAD was treated with vasopressor medications (but not inotropes) and was on life support, predominantly intra-aortic balloon pump and extracorporeal membrane oxygenation. LVAD implantation as redo surgery as well as concomitant surgical procedures were more frequent in this group as well. In the group with CIED-D pre-LVAD, 58% of the patients carrying an ICD received it for primary prevention; 44% of the patients without a CIED-D pre-LVAD and 34% of those with such a device were transplanted (39% of the entire cohort).

Twenty patients received a CIED-D post-LVAD (9.6% of those without a CIED-D pre-VAD), at a median time to CIED-D implant of 57 days [interquartile range (IQR) 29.5–243.5 days, range 0–1068 days]. Forty-five patients (19% of those with a CIED-D pre-VAD) had their ICD or CRT-D device deactivated post-LVAD at a median time of deactivation of 252 days (IQR 77–379 days, range 0–981 days). Of these deactivations, 11 occurred during active LVAD support (median time to deactivation 40 days; IQR 0–368 days, range 0–664 days), while in the remaining 34 patients the deactivation occurred due to heart transplantation, i.e. on the day of transplantation (Figure 1 and online supplementary Figure S2).

All-cause mortality and active CIED-D carrier status following left ventricular assist device implantation

The median time on LVAD support was 1.1 years (IQR 0.5–2.0 years) starting at the time of LVAD implantation (online supplementary Figure S3), which was similar in those with active CIED-D carrier status during LVAD support and those without one (median 1.1 years, IQR 0.5–2.0 years; and 1.1 years, IQR 0.4–2.0 years, respectively). At the time of LVAD implantation, 213 patients (48%) did not have a CIED-D and 235 patients (52%) had such a CIED in situ and activated (Figure 1). The primary outcome of all-cause death occurred in a total of 134 patients (30% of the overall study population). A total of 68 patients remained in the non-CIED-D group and 55 remained in the CIED-D group and suffered from all-cause death. Five patients had the CIED-D deactivated and six entered the CIED-D group before the event. The incidence rates for all-cause death were 28 events per 100 patient-years [95% confidence interval (CI) 22–36 events] and 18 events

per 100 patient-years (95% CI 14–23 events) for those without and with a CIED-D after LVAD implant, respectively (Table 2). One-year survival in the overall cohort was 80.1%. The rate of all-cause death was the greatest in the first 30 days post-LVAD implant (event rate 7.3% per month; 95% CI 5.2–10.4%), declined between 30 and 90 days (event rate 3.0% per month; 95% CI 2.0–4.5%) and between 90 days and 1 year (event rate 1.3% per month; 95% CI 0.9–1.8%), remaining stable after 1 year (event rate 1.4% per month; 95% CI 1.0–1.9%). In a time-varying analysis, the unadjusted HR demonstrated a 36% reduction in the risk of all-cause mortality in patients with an active CIED-D following LVAD implantation (HR 0.64; 95% CI 0.46–0.91, P = 0.012) (Figure 2 and Table 2). No significant alteration in the treatment effect after 30 or 90 days following LVAD implantation was found (interaction P =0.68 and P =0.07, respectively).

Table 2. Incidence rates and hazard ratios for the primary endpoint (all-cause death), cardiovascular mortality, heart failure hospitalisation, ventricular arrhythmias post-left ventricular assist device (LVAD), device-related infection requiring systemic antibiotics, non-cerebral and intracranial bleeding by time-updated CIED-D carrier status following LVAD implantation

	No CIED-D at LVAD implant (n=213)	CIED-D at LVAD implant (n=235)	HR (95% CI)	
			Unadjusted	Adjusted[a]
All-cause mortality (n of events=134)	28.2 (22.4-35.5)	18.1 (14.1-23.2)	0.64 (0.46-0.91) P=0.012	0.59 (0.40-0.87) P=0.008
Cardiovasucalr mortality (n of events = 83)	16.7 (12.4-22.5)	11.9 (8.7-16.2)	0.72 (0.46-1.11) P=0.13	0.65 (0.39-1.07) P=0.09
Heart failure hospitalization (n of event = 80)	11.9 (8.3-17.1)	17.8 (13.5-23.4)	1.50 (0.96-2.38) P=0.08	0.92 (0.56-1.51) P=0.74
Ventricular arrhythmias post-LVAD (n of events = 107)	14.0 (9.9-19.8)	31.3 (24.9-39.2)	2.20 (1.46-3.34) P<0.001	1.57 (0.98-2.52) P=0.06
Device-related infection requiring systemic antibiotics (n of events = 149)	39.1 (31.1-49.2)	28.1 (22.4-35.2)	0.76 (0.55-1.05) P=0.09	0.96 (0.66-1.40) P=0.84
Non-cerebral bleeding (n of events = 88)	19.5 (14.5-26.3)	15.5 (11.5-20.8)	0.79 (0.52-1.20) P=0.27	0.64 (0.40-1.03) P=0.07
Intracranial bleeding (n of events = 32)	6.3 (3.9-10.3)	4.8 (3.0-7.9)	0.75 (0.37-1.52) P=0.42	0.55 (0.24-1.26) P=0.16

The incidence rates are presented as number of events per 100 patient-years (95% CI).
CI, confidence interval; CIED-D, cardiac implantable electronic device with a defibrillator component; HR, hazard ratio.
[a]Adjusted for age, number of ventricular arrhythmia episodes before LVAD implantation, use of vasopressors prior to LVAD implantation, LVAD type and LVAD implant as a redo surgical procedure.

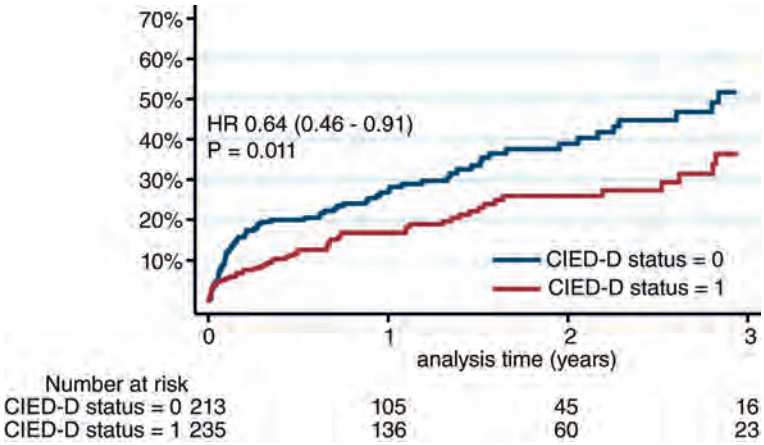

Figure 2. Kaplan–Meier plot of time to all-cause mortality, according to CIED-D carrier status following left ventricular assist device (LVAD) implantation. The analysis time begins at the time of LVAD implantation. CIED-D status 0 stands for no CIED-D present post-LVAD, CIED-D status 1 stands for CIED-D present post-LVAD. CIED-D, cardiac implantable electronic device with a defibrillator component; HR, hazard ratio.

Using stepwise regression, CIED-D carrier status, age, number of VA episodes before LVAD implantation, use of vasopressors prior to LVAD implantation, LVAD type and LVAD implant as a redo surgical procedure were identified as independently significant of all-cause mortality. After adjustment for these variables, the HR for CIED-D post-LVAD status remained significant (0.59, 95% CI 0.40–0.87; P = 0.008). Age, LVAD implant as redo surgery, number of VA episodes pre-LVAD and vasopressor use were the remaining significant predictors of the primary outcome (Table 3). Active CIED-D carrier status after LVAD implant remained significant after adding active CRT with a pacemaker component (CRT-P) carrier status post-LVAD implant to the model (HR 0.57, 95% CI 0.38–0.84; P = 0.005) (Table 3). Furthermore, the benefit of CIED-D treatment on all-cause mortality remained significant even after excluding patients with a CIED-D placed or deactivated/removed following LVAD implantation, both in unadjusted (HR 0.71, 95% CI 0.50–1.00; P = 0.048) and adjusted analysis (HR 0.63, 95% CI 0.41–0.96; P = 0.030). In a subgroup analysis, the effect of treatment with a CIED-D following LVAD implantation was consistent across various categorical subgroups at baseline (Figure 3). Of note, exposure to ultrafiltration at baseline was associated with a significant interaction P-value (0.0044), suggesting a possible interaction effect: CIED-D therapy post-LVAD was associated with a larger benefit in those not undergoing ultrafiltration pre-LVAD implant (HR 0.63, 95% CI 0.42–0.94) compared to those undergoing ultrafiltration (HR 7.76, 95% CI 1.07–56.0), however only five patients in the latter subgroup died during follow-up (hence not shown in the forest plot).

Table 3. Multivariate Cox regression models of risk factors for all-cause death by time-updated CIED-D carrier status following left ventricular assist device implantation

Variable	HR (95% CI)	P-value
CIED-D post-LVAD	0.59 (0.40-0.87)	0.008
Age	1.03 (1.02-1.05)	<0.0001
LVAD implant as redo surgery	1.69 (1.09-2.61)	0.019
LVAD type		
Heart Mate II	Referent	0.35
Heart Ware	1.28 (0.81-2.02)	
Heart Mate 3	0.73 (0.39-1.36)	
Other	0.76 (0.33-1.72)	
No. of VA episodes pre-LVAD		
≥4	Referent	0.011
None	0.51 (0.23-1.14)	
1	0.29 (0.11-0.79)	
2	0.75 (0.28-1.97)	
3	0.44 (0.14-1.38)	
Unknown	0.21 (0.08-0.58)	
Vasopressor use in pre-LVAD		
Yes	Referent	0.008
No	0.49 (0.28-0.86)	
Unknown	0.89 (0.47-1.70)	
CIED-D post-LVAD	0.57 (0.38-0.84)	0.005
CRT-P post-LVAD	0.62 (0.25-1.59)	0.322
Age	1.03 (1.01-1.05)	<0.0001
LVAD implant as redo surgery	1.74 (1.12-2.71)	0.014
LVAD type		
Heart Mate II	Referent	0.349
Heart Ware	1.27 (0.80-2.00)	
Heart Mate 3	0.73 (0.39-1.36)	
Other	0.73 (0.32-1.66)	
No. of VA episodes pre-LVAD		
≥4	Referent	0.011
None	0.51 (0.23-1.16)	
1	0.29 (0.11-0.79)	
2	0.75 (0.28-1.97)	
3	0.48 (0.15-1.50)	
Unknown	0.21 (0.08-0.58)	
Vasopressore use in pre-LVAD		
Yes	Referent	0.007
No	0.48 (0.27-0.84)	
Unknown	0.85 (0.45-1.64)	

CI, confidence interval; CIED-D, cardiac implantable electronic device with a defibrillator component; CRT-P, cardiac resynchronization therapy with a pacemaker component; HR, hazard ratio; LVAD, left ventricular assist device; VA, ventricular arrhythmia; VAD, ventricular assist device.

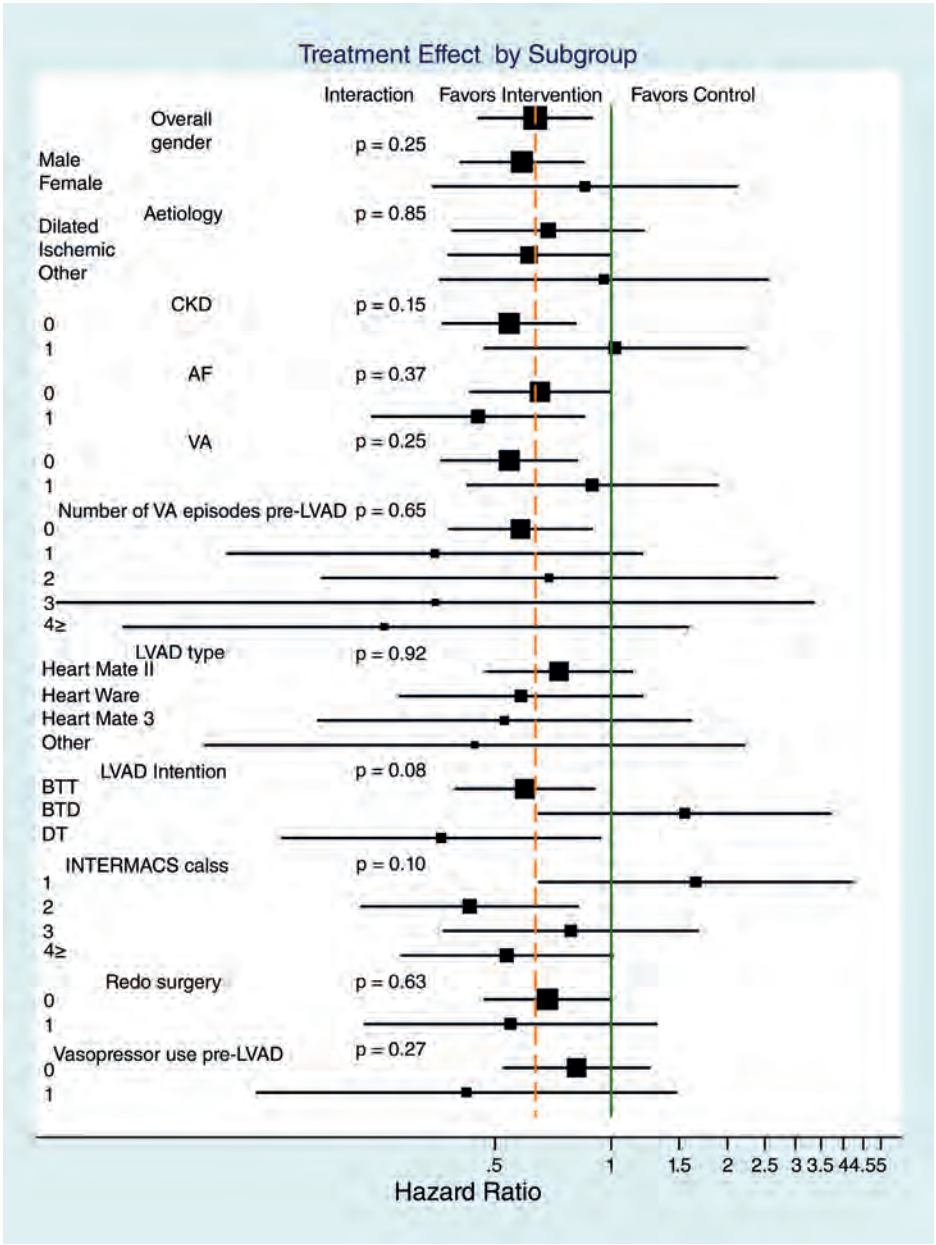

Figure 3. The effect of treatment with a cardiac implantable electronic device with a defibrillator component following left ventricular assist device (LVAD) implantation on all all-cause mortality for individual patient subgroups. 0 stands for absent, 1 for present. AF, atrial fibrillation; BTD, bridge to decision; BTT, bridge to transplant; CKD, chronic kidney disease; DT, destination therapy; VA, ventricular arrhythmia.

Secondary outcomes and active ICD/CRT-D carrier status following left ventricular assist device implantation

The occurrence of one or more episodes of symptomatic VAs or those requiring intervention was noted in 24% of the entire cohort (107 patients): 30 patients remained in the non-CIED-D group and 73 remained in the CIED-D group and suffered from new-onset VAs, while two patients transitioned from the CIED-D group and two entered the CIED-D group before their event (the incidence rates are provided in Table 2). In patients with a CIED-D, a VA episode requiring anti-tachycardia pacing (ATP) occurred in 25 patients (median time to first ATP 231 days; IQR 25–495 days), while 42 patients received a shock (median time to first shock 121 days; IQR 7–231 days); 29% of the CIED-D cohort received at least one of these therapies. None of these patients died on the day of therapy delivery. Patients with a CIED-D post-LVAD had a nominally significant crude increased risk of post-LVAD VAs which was no longer significant after adjusting for the relevant baseline characteristics (HR 1.57, 95% CI 0.98–2.52, P = 0.06, adjusted by variable selection for the primary outcome; Table 2 and online supplementary Tables S2 and S3). We further used stepwise regression to detect variables that are independently significant of the occurrence of VAs post-LVAD. After additional adjustment for these variables, active CIED-D post-LVAD status remained unrelated to the occurrence of this secondary endpoint (online supplementary Table S2). An additional analysis of incident VAs post-LVAD as a time-varying covariate demonstrated that the occurrence of such arrhythmias portended a 2.4-fold increased risk of all-cause death and a 2.6-fold increased risk of cardiovascular death, while carrying an active CIED-D remained associated with a significant 47% reduction in all-cause death and 43% reduction in cardiovascular death. LVAD implant as redo surgery, vasopressor use prior to LVAD implant and increasing patient age were significantly associated with both of these outcomes, while the occurrence of VAs pre-LVAD was identified as an additional risk factor for all-cause death (online supplementary Table S4).

The incidence rates for cardiovascular mortality, HF hospitalisation, device-related infection requiring systemic antibiotics, as well as extracranial and intracranial bleeding events are presented in Table 2. Cardiovascular death occurred in 83 patients: 40 remained in the non-CIED-D group and 36 remained in the CIED-D group and suffered from cardiovascular death, while three patients transitioned from the CIED-D group and four entered the CIED-D group before death from cardiovascular cause. The crude risk for cardiovascular mortality was not modified by CIED-D status, while in the adjusted analysis there was a trend towards a reduction in the risk of cardiovascular death with active CIED-D status (HR 0.65, 95% CI 0.39–1.07; P = 0.09) (online supplementary Tables

S3 and S4). Both the crude and adjusted risks for the remaining outcomes were not significantly modified by CIED-D post-LVAD (Table 2 and online supplementary Table S3; the full results of the multivariable regression models for the remaining outcomes are provided in the online supplementary Tables S5 and S6).

Sensitivity analyses

In addition to a forward variable selection procedure, we have also performed a backwards selection, according to which CIED-D carrier status, age, disease aetiology, number of VA episodes before LVAD, LVAD type, intention of LVAD therapy, use of vasopressors, use of beta-blockers, type of mechanical ventilation implantation and intention of LVAD therapy were identified as independently significant of all-cause mortality. After adjustment for these variables, the results remained consistent with the primary analysis (HR 0.61, 95% CI 0.40–0.94; P = 0.024); the remaining significant predictors of the primary outcome were age (HR per 1 year change in age: 1.04, 95% CI 1.02–1.06; P <0.0001), vasopressor use pre-LVAD (P = 0.0007), type of mechanical ventilation pre-LVAD (P = 0.025) and number of episodes of VAs pre-LVAD (P = 0.028) (online supplementary Table S7).

Given the significant differences in the baseline characteristics between the two patient groups, we have additionally performed a propensity score adjustment, following which the relative risk of all-cause death remained significantly reduced in the CIED-D carriers (HR 0.60, 95% CI 0.39–0.94; P = 0.024), while the propensity score itself was not significantly related to all-cause death. Strong predictors of CIED-D carrier status included having a history of atrial fibrillation [odds ratio (OR) 2.9] or VAs (OR 2.0), while having a prior myocardial infarction and a concomitant procedure with LVAD implant reduced the odds of carrying a CIED-D (OR 0.5 and 0.4, respectively). LVAD type, LVAD intention and INTERMACS class were additional predictors of CIED-D carrier status (all P <0.05) (online supplementary Table S8).

In order to account for missing data, additional sensitivity analyses were performed by multiple imputation of missing values. The results were consistent with the original analyses – when adjusting by variable selection for the primary outcome, time-updated active CIED-D carrier status, patient age and LVAD implantation as a redo surgical procedure remained the only significant predictors of all-cause mortality (online supplementary Table S9). In an additional stepwise multiple regression model obtained from the multiple imputation dataset, age and LVAD implantation as redo

surgery remained additional predictors of all-cause mortality, in addition to active CIED-D status post-LVAD (online supplementary Table S10).

In an additional analysis of ICD-only carriers (excluding those with a CRT-D device) contiguously with an LVAD, the crude HR showed a trend towards a reduction in all-cause mortality (HR 0.73, 95% CI 0.51–1.04; P = 0.077). However, in adjusted analysis, carrying an ICD-only reached a significant reduction in all-cause mortality (HR 0.60, 95% CI 0.39–0.92; P = 0.019, online supplementary Table S11). After multiple imputation, the adjusted HR remained consistent, suggesting a 35% reduction in all-cause death in active ICD-only carriers during LVAD support (online supplementary Table S11).

Discussion

In this analysis of the PCHF-VAD registry, we have described the baseline characteristics and outcomes of 448 cf-LVAD carriers from 12 European academic centres in relation to carrying a CIED with an active defibrillator component (either in an ICD or CRT-D device) during the course of LVAD support. In patients enrolled in the registry, carrying an active defibrillator component during LVAD support was associated with a reduced crude and adjusted risk of all-cause mortality, compared to the patients without an active defibrillator component. This finding was consistent in several sensitivity analyses, including a propensity score adjusted analysis. Higher patient age, LVAD implantation as a redo surgical procedure, number of clinically significant VA episodes pre-LVAD and use of vasopressors recognized as other significant predictors of all-cause mortality.

The prevalence of either ICD or CRT-D carriers prior to LVAD implantation of 54% in this cohort is notably lower than that of >80% of LVAD carriers with an ICD in recent analyses of the INTERMACS and UNOS registries,[8,9] while it is more comparable to the EUROMACS population in which 58% carry an ICD.[20] This points out an important difference between LVAD carriers in Europe and the United States, while the currently available data predominantly originate from US centres. The source of this discrepancy is unclear but might be reflective of nearly four-fold higher ICD implantation rates in the United States, compared to Europe.[21] The clinical profile of CIED-D carriers pre-LVAD in our registry suggests a more chronic course of HF prior to the initiation of LVAD support – these patients were in higher INTERMACS classes with less need for life support therapies (vasopressors, ultrafiltration or mechanical ventilation) prior to LVAD; they had more remodelled left ventricles and a higher use of guideline-mandated HF therapies, including beta-blockers that may supress ventricular ectopy, compared

to patients without an CIED-D pre-LVAD. A more chronic profile corresponds to ICD carriers described in other LVAD cohorts.[10,11,13–15] However, compared to several other analyses, the use of LVADs as bridge to transplantation was much more frequent in our cohort.[9,10] Furthermore, patients implanted with an LVADmore recently were more likely to have received an CIED-D, as well as those with a higher number of VAs pre-LVAD.

While the survival benefit of ICDs is well established in symptomatic HFrEF patients,[7] the data on the utility of defibrillators in LVAD carriers are still conflicting. Traditionally, LVAD patients are considered to tolerate life-threatening VAs,[22] possibly due to the Fontan-like circulation that occurs when the fibrillating right ventricle becomes a passive conduit.[17] Conversely, in some patients VAs may cause progressive right ventricular failure or lead to more gradual HF and death. 'Routine' implantation of ICDs post-LVAD is still debated and predominantly hindered by increased risk of bleeding and infection in this high-risk population.[23–25] Notwithstanding this, the replacement of exhausted generators of defibrillators implanted prior to onset of LVAD therapy is increasingly supported.[16,17]

While a meta-analysis of six observational studies assessing the impact of ICDs on survival of LVAD patients reported a significant reduction in mortality associated with ICD use, this finding was not significant when confined to the cf-LVAD population.[22] The results of one of these studies suggested that only patients who suffered potentially life-threatening VAs prior to LVAD implantation had recurring arrhythmias after LVAD implantation, thus benefiting from ICD therapy.[10] However, the rate of all-cause death in our multicentre cohort, and in particular the subgroup without CIED-D post-LVAD, was notably higher in comparison to this single-centre study, yet lower than reported from the EUROMACS data, and similar to the INTERMACS report.[8,10,26] In an analysis of the UNOS registry, the presence of ICDs at listing in durable LVAD recipients was not associated with lower waitlist mortality; however, numerically fewer arrhythmic deaths were noted in the ICD group.[27] As mentioned, the penetration of ICDs in this cohort is notably greater than in our European cohort which may portend differences among the populations. In the largest currently available analysis from the INTERMACS database, no survival benefit was associated with ICD in VAD carriers: in the primary analysis, ICD implantation was associated with increased mortality of unexpected death, which had not met significance levels in additional sensitivity analyses.[8] While we can only speculate on the aggregate causes of the discrepant results between our and the INTERMACS registry, several features clearly differ between these cohorts: the INTERMACS cohort was dominated by patients in NYHA class IV (around 83% of patients in the propensity score-matched cohort, as opposed to 36% of our cohort), a much

larger proportion of destination therapy patients (40%, as opposed to only 13% of our population) and those with prior cardiac surgery (68% in INTERMACS compared to 12% in PCHF-VAD). Despite the fact that both studies identify clear differences in outcomes between those with and without an ICD, it is unclear whether the patient characteristics more typical for the INTERMACS registry portended potentially harmful effects of ICD therapy in that cohort. Importantly, in addition to a much larger penetration of ICDs within the LVAD population compared to our European registry, the INTERMACS analysis excluded patients with de-novo ICDs after LVAD implantation. As such, possible 'crossover', i.e. initiation and/or termination of CIED therapy during active LVAD support warrants to be accounted for.

We have thus utilised a time-varying analysis that has provided consistent results: in an unadjusted analysis, carrying an active CIED with a defibrillator component was associated with a 36% reduction in all-cause death, which remained significant and comparable after adjustment for the relevant baseline covariates (41% reduction in all-cause death), after propensity score adjustment (40% reduction), after adjustment for the occurrence of VAs post-LVAD (47% reduction) and by utilising multiple imputation to compensate for the missing data (37% reduction). Our analysis was expanded to carriers of both ICD and CRT-D devices to include the effect of the defibrillator component in either type of CIED. After additional adjustment for CRT-P carrier status, the reduction in the risk of all cause-death remained significant and reached 43%. Furthermore, in a sub-analysis of the ICD-only subgroup, the crude HR suggested a trend towards reduced all-cause death, while the adjusted analysis confirmed a 40% reduction in all-cause death in active ICD-only carriers during LVAD support. The benefit of active CIED-D therapy with an LVAD remained consistent in subgroup analyses as well as with additional sensitivity analyses.

Ventricular arrhythmias post-LVAD occurred in 24% of our cohort, which is within the reported range of 22–52%.[8] In the MOMENTUM 3 trial, sustained ventricular tachyarrhythmias occurred relatively frequently (18% in centrifugal-flow VADs, 20% in axial-flow VADs), but rarely resulted in death.[3] While our data suggested a nominally increased crude risk of developing clinically significant VAs post-LVAD in CIED-D carriers (Table 2), this did not remain significant in adjusted analyses and was likely an effect of enhanced arrhythmia monitoring provided by the CIED. While we cannot infer causality between the delivery of defibrillator-driven therapies and reduction in mortality, we have noted that nearly one third of the CIED-D carriers received at least one of these therapies on at least one occasion, with a median time to first ATP or shock well beyond

the arrhythmically fragile early post-surgical period. Moreover, in an analysis of incident VAs post-LVAD as a time-varying covariate, the occurrence of the arrhythmia was a strong predictor of all-cause and cardiovascular mortality as was increasing patient age, LVAD implant as redo surgery and vasopressor use prior to LVAD, while the presence of an active CIED-D device remained associated with a reduction in the risk of all-cause death. Whether the optimal timing of CIED-D implantation is before or after LVAD remains to be explored.

Limitations

Our analysis was limited by typical features of retrospective registry studies: incompleteness of the dataset which we aimed to account for by multiple imputation methods, possible selection bias and misclassification of events. Furthermore, the study was limited by lack of data on arrhythmic events in non-CIED-D carriers. We acknowledge the limited possibility of determining causality with a retrospective analysis, as well as the ability to adequately adjudicate the endpoints which also limits the possibility of determining the mitigation of risk of arrhythmic deaths by a CIED-D. Finally, this type of study design does not allow optimal control for multiple potential confounders, however extensive adjustments have confirmed the robustness of our results in terms of reduced all-cause mortality with CIED-D post-LVAD, whereby all adjusted models for all-cause death show a stronger treatment effect of CIED-D. However, only a randomised prospective trial, which we believe is warranted, would be able to adequately address this clinically relevant topic.

Conclusion

In an LVAD cohort with granularly described baseline data stemming from a multicentre European registry, we report a significant reduction in the crude and adjusted risk of all-cause death in patients carrying a CIED with an active defibrillator component during LVAD support, which was consistent across sensitivity analyses. Higher patient age, number of clinically significant VAs pre-LVAD, use of vasopressors and LVAD implantation as redo surgery were recognized as other significant predictors of all-cause mortality.

Finally, an analysis of incident VAs post-LVAD confirmed its occurrence as a strong predictor of all-cause and cardiovascular mortality, while in this analysis the presence

of an active CIED-D remained associated with a reduction in the risk of all-cause and cardiovascular death.

Unambiguous disparities in CIED-D usage in LVAD recipients as well as its impact on outcomes exist between European and US cohorts. Further insight in the comparison of these populations should improve the understanding of (non-)response to CIEDs, while evidence from a randomised controlled trial would be anticipated to inform decisions on contiguous device usage in this growing patient population.

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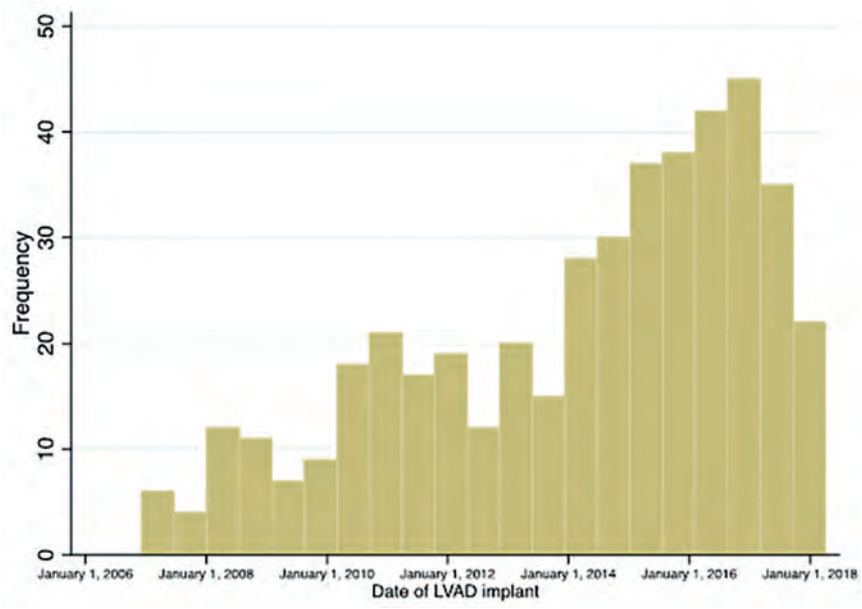
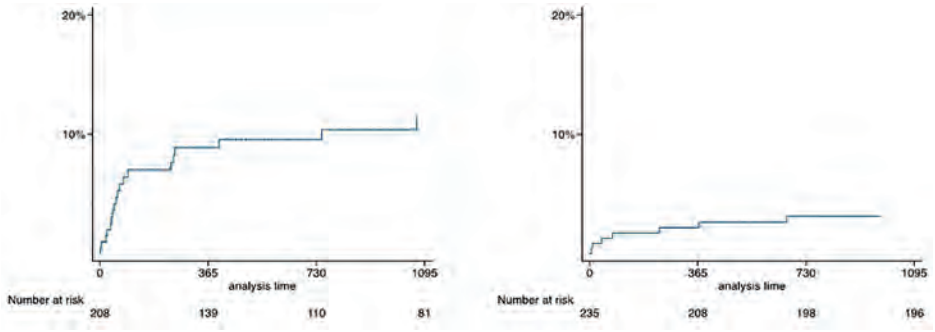
Supplementary content

Supplemental methods:

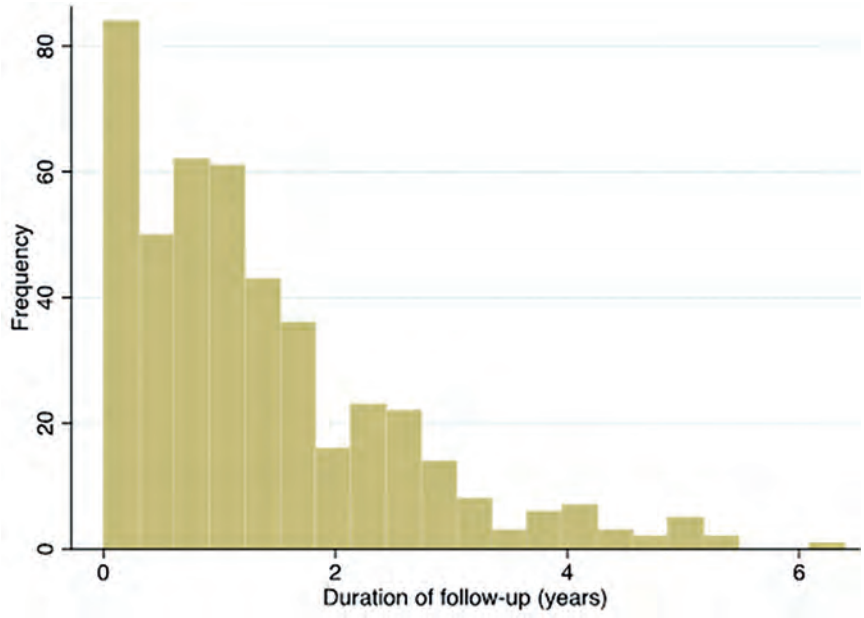
We have used 25 variables for the current stepwise selection process; the data were complete for 11 of these variables. The forward stepwise procedure considered only complete cases and was ultimately based on 333 subjects – for categorical variables with >5% of unreported values, we treated the unreported values as an additional category which increased the number of subjects from 249 to the final 333 subjects. In order to address the issue with missingness from an additional approach, we have also performed a multiple imputation analysis which has provided comparable results (adjusted analysis for the primary outcome: HR 0.59, 95% CI: 0.40-0.87; p=0.008, adjusted analysis for the primary outcome including multiple imputation: HR 0.63, 95% CI 0.43-0.93, p=0.019).



Supplemental Figure 1. The dates of LVAD implantation.



Supplemental Figure 2: Left panel: Kaplan-Meier plot of time to CIED-D implantation following LVAD implantation (during active LVAD support). Right panel: Kaplan-Meier plot of time to CIED-D deactivation following LVAD implantation (during active LVAD support).



Supplemental Figure 3. The duration of follow-up. The median time on LVAD support was 1.1 years (IQR 0.5-2.0 years) starting at the time of LVAD implantation.

Supplemental Table 1. Baseline characteristics of the studied patients by CIED-D carrier status prior to LVAD implantation – additional variables with more than 30% missing data

	Overall average	No CIED-D pre-LVAD (n=208)	CIED-D pre-LVAD (n=240)	P value
Medications, n (%)				
ARNI	3 (1.0)	1 (0.8)	2 (1.1)	0.80
Calcium channel blocker	1 (0.3)	1 (0.8)	0 (0.0)	0.23
Laboratory values				
Total cholesterol, mmol/L	3.6±1.2	3.5±1.1	3.7±1.2	0.25
NT-proBNP, pg/mL	4446 (2663- 8904)	3968 (2538- 8904)	4673 (2850-8950)	0.28
BNP, pg/mL	1750 (944-3174)	2219 (1335-4015)	1487 (682-2282)	0.05
Echocardiographic data				
RVIDd, mm	42.3±8.2	40.8±7.8	43.4±8.4	0.15
FAC, %	28±10	28±9	28±10	0.97
Right heart catheterization data				
sPAP, mmHg	51±17	52±17	51±18	0.41
mPAP, mmHg	34±12	35±11	34±13	0.38
dPAP, mmHg	27±11	29±10	27±11	0.13
CVP, mmHg	10 (6-14)	11 (7-15)	10 (5-14)	0.037
PCWP, mmHg	24.7±8.9	25.9±8.5	24.1±9.0	0.08
TPG, mmHg	11.7±6.7	11.2±7.1	12.1±6.4	0.40
PVR, Wood Units	3.0 (2.0-4.5)	3.0 (2.2-4.9)	3.0 (1.9-4.3)	0.32
CO, L/min	3.8±1.1	3.7±1.0	3.8±1.1	0.25
CI, L/min/m^2	1.9±0.5	1.9±0.5	2.0±0.6	0.22

Values expressed as mean ± standard deviation or median (interquartile range).
ARNI – angiotensin receptor-neprilysin inhibitor; BNP – B-type natriuretic peptide; NT-proBNP – N-terminal pro hormone BNP; RVIDd - right ventricular intraventricular dimension in end-diastole; FAC – fractional area change; TAPSE - tricuspid annular plane systolic excursion; sPAP – systolic pulmonary artery pressure; mPAP – mean pulmonary artery pressure; dPAP – diastolic pulmonary artery pressure; CVP – central venous pressure; PCWP – pulmonary capillary wedge pressure; TPG – transpulmonary gradient; PVR – pulmonary vascular resistance; CO – cardiac output; CI – cardiac index.

Supplemental table 2a. Multivariate Cox regression model of risk factors for the secondary outcome of the occurrence of ventricular arrhythmias post-LVAD implantation from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by variable selection per the primary outcome

Variable	HR	95% CI	P value
CIED-D post-LVAD	1.57	0.98-2.52	0.06
Age	0.99	0.98-1.01	0.30
LVAD implant as redo surgery	0.74	0.35-1.54	0.42
LVAD type			
Heart Mate II	Referent		
Heart Ware	0.90	0.54-1.50	0.80
Heart Mate 3	1.03	0.61-1.74	
Other	0.64	0.24-1.69	
Number of VA episodes pre-VAD			
Four or more	Referent		
None	0.45	0.19-1.08	
One	0.87	0.34-2.19	<0.0001
Two	2.05	0.80-5.29	
Three	1.59	0.58-4.39	
Unknown	0.27	0.08-0.88	
Vasopressor use pre-LVAD			
Yes	Referent		
No	0.54	0.28-1.02	0.12
Unknown	0.45	0.19-1.04	

Supplemental table 2b. Multivariate Cox regression model of risk factors for the secondary outcome of the occurrence of ventricular arrhythmias post-LVAD implantation from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by outcome-specific variable selection

Variable	HR	95% CI	P value
CIED-D post-LVAD	1.52	0.94-2.46	0.09
Female gender	0.38	0.18-0.80	0.011
Age	0.98	0.97-1.00	0.055
Aetiology			
Nonischaemic cardiomyopathy	Referent		
Ischaemic cardiomyopathy	1.78	1.15-2.76	0.02
Other	0.96	0.44-2.11	
Number of VA episodes pre-VAD			
Four or more	Referent		
None	0.62	0.26-1.49	
One	1.01	0.39-2.61	0.0001
Two	2.22	0.85-5.79	
Three	1.85	0.67-5.10	
Unknown	0.26	0.08-0.86	

Supplemental table 2b. *(Continued)*

Variable	HR	95% CI	P value
Vasopressor use pre-LVAD			
Yes	Referent		
No	0.50	0.25-1.03	0.16
Unknown	0.44	0.05-3.81	
Beta blocker use pre-LVAD			
Yes	Referent		
No	0.49	0.27-0.86	0.009
Unknown	1.62	0.76-3.42	
Mechanical ventilation use pre-LVAD			
Invasive ventilation	Referent		
None	0.66	0.25-1.76	0.64
Non-invasive ventilation	0.00		
Unknown	0.47	0.05-4.47	

Supplemental Table 3. Unadjusted and adjusted hazard ratios for the primary endpoint (all-cause death) and secondary endpoints by time-updated CIED-D carrier status following LVAD implantation.

	Hazard Ratio 95% confidence interval p-value			
	Unadjusted	Adjusted by variable selection for the primary outcome	Adjusted by outcome-specific variable selection	Propensity score adjusted model
All-cause mortality (n=134)	0.64 0.46-0.91 p=0.012	0.59* 0.40-0.87 p=0.008	0.59* 0.40-0.87 p=0.008	0.60 0.39-0.94 p=0.024
Cardiovascular mortality (n=83)	0.72 0.46-1.11 p=0.13	0.65* 0.39-1.07 p=0.09	0.79† 0.50-1.24 p=0.30	0.73 0.42-1.28 p=0.27
Heart failure hospitalization (n=80)	1.50 0.96-2.38 p=0.08	0.92* 0.56-1.51 p=0.74	0.93‡ 0.57- 1.51 p=0.76	1.10 0.62-1.95 p=0.76
Ventricular arrhythmias post-LVAD (n=107)	2.20 1.46-3.34 p<0.0001	1.57* 0.98-2.52 p=0.06	1.52§ 0.94-2.46 p=0.09	1.68 1.00-2.81 P=0.049
Device-related infection requiring systemic antibiotics (n=149)	0.76 0.55-1.05 p=0.09	0.96* 0.66-1.40 p=0.84	0.96‖ 0.65-1.41 p=0.82	0.96 0.64-1.45 P=0.85
Non-cerebral bleeding (n=88)	0.79 0.52-1.20 p=0.27	0.64* 0.40-1.03 p=0.07	0.82¶ 0.52-1.28 p=0.37	0.67 0.39-1.17 p=0.16

Supplemental Table 3. *(Continued)*

	Hazard Ratio 95% confidence interval p-value			
	Unadjusted	**Adjusted by variable selection for the primary outcome**	**Adjusted by outcome-specific variable selection**	**Propensity score adjusted model**
Intracranial bleeding (n=32)	0.75 0.37-1.52 p=0.42	0.55* 0.24-1.26 p=0.16	0.70# 0.34-1.46 p=0.34	0.51 0.20-1.28 p=0.15

* Adjusted for age, number of ventricular arrhythmia episodes before LVAD implantation, use of vasopressors prior to LVAD implantation, LVAD type and LVAD implant as a redo surgical procedure.
† Adjusted for: LVAD type and LVAD implant as a redo surgical procedure.
‡ Adjusted for: LVAD type, number of VA episodes pre LVAD.
§ Adjusted for: gender, age, aetiology, number of VA episodes pre LVAD, use of vasopressors, beta-blockers and type of mechanical ventilation pre-LVAD.
ǁ Adjusted for: age, LVAD type, number of VA episodes pre LVAD, use of ivabradine and beta-blockers and pre-LVAD.
¶ Adjusted for: aetiology, quartile of date of LVAD implant.
# Adjusted for: LVAD type.

Supplemental table 4a. Multivariate Cox regression model of risk factors for the primary outcome of all-cause death, using post-LVAD VAs as a time-varying covariate.

Variable	**HR**	**95% CI**	**P value**
CIED-D post-LVAD	0.53	0.36-0.79	0.002
Incident VA post-LVAD	2.42	1.58-3.69	<0.0001
LVAD implant as redo surgery	1.75	1.12-2.73	0.013
Age	1.03	1.02-1.05	<0.0001
LVAD type			
Heart Mate II	Referent		
Heart Ware	1.34	0.85-2.13	0.29
Heart Mate 3	0.72	0.39-1.34	
Other	0.82	0.36-1.88	
Number of VA episodes pre-VAD			
Four or more	Referent		
None	0.58	0.25-1.31	
One	0.28	0.10-0.76	0.015
Two	0.64	0.24-1.70	
Three	0.43	0.14-1.34	
Unknown	0.24	0.09-0.68	
Vasopressor use			
Yes	Referent		
No	0.49	0.28-0.86	0.006
Unknown	0.90	0.47-1.73	

Supplemental table 4b. Multivariate Cox regression model of risk factors for the secondary outcome of cardiovascular death, using post-LVAD VAs as a time-varying covariate.

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.57	0.34-0.95	0.031
Incident VA post-LVAD	2.60	1.53-4.43	<0.0001
LVAD implant as redo surgery	2.29	1.32-3.97	0.003
Age	1.03	1.01-1.05	0.01
LVAD type			
Heart Mate II	Referent		
Heart Ware	1.41	0.80-2.49	0.23
Heart Mate 3	0.74	0.35-1.58	
Other	0.47	0.13-1.62	
Number of VA episodes pre-VAD			
Four or more	Referent		
None	0.75	0.26-2.21	
One	0.38	0.11-1.34	0.19
Two	0.90	0.26-3.11	
Three	0.74	0.18-2.97	
Unknown	0.29	0.07-1.20	
Vasopressor use			
Yes	Referent		
No	0.40	0.21-0.77	0.022
Unknown	0.50	0.22-1.13	

Supplemental Table 5a. Multivariate Cox regression model of risk factors for secondary outcome of cardiovascular death. from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by variable selection per the primary outcome

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.65	0.39-1.07	0.09
Age	1.03	1.00-1.05	0.018
LVAD as redo surgery	2.14	1.25-3.67	0.006
LVAD type			
Heart Mate II	Referent		
Heart Ware	1.32	0.75-2.31	0.30
Heart Mate 3	0.76	0.36-1.61	
Other	0.46	0.13-1.55	
Number of VA episodes pre-VAD			

Supplemental Table 5a. *(Continued)*

Variable	HR	95% CI	P value
Four or more	Referent		
None	0.63	0.22-1.83	
One	0.38	0.11-1.34	0.14
Two	1.03	0.30-3.49	
Three	0.72	0.18-2.87	
Unknown	0.25	0.06-0.98	
Vasopressor use pre-LVAD			
Yes	Referent		
No	0.41	0.21-0.78	0.024
Unknown	0.49	0.22-1.10	

Supplemental table 5b. Multivariate Cox regression model of risk factors for secondary outcome of cardiovascular death. from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by outcome-specific variable selection

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.79	0.50-1.24	0.30
LVAD implant as redo surgery	2.16	1.27-3.66	0.004
LVAD type			
Heart Mate II	Referent		
Heart Ware	1.26	0.75-2.13	0.41
Heart Mate 3	0.76	0.36-1.58	
Other	0.54	0.17-1.76	

Supplemental Table 6a. Multivariate Cox regression model of risk factors for secondary outcome of heart failure hospitalisation from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by variable selection per the primary outcome

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.92	0.56-1.51	0.74
Age	1.01	0.99-1.03	0.60
LVAD as redo surgery	0.88	0.40-1.96	0.76
LVAD type			
Heart Mate II	Referent		
Heart Ware	3.02	1.74-5.24	0.0009
Heart Mate 3	2.23	1.20-4.14	
Other	1.33	0.49-3.59	
Number of VA episodes pre-VAD			

Supplemental Table 6a. *(Continued)*

Variable	HR	95% CI	P value
Four or more	Referent		
None	0.33	0.13-0.81	0.0177
One	0.38	0.14-1.05	
Two	0.36	0.11-1.14	
Three	0.58	0.18-1.90	
Unknown	0.07	0.02-0.31	
Vasopressor use pre-LVAD			
Yes	Referent		
No	0.85	0.37-1.92	0.92
Unknown	0.84	0.28-2.48	

Supplemental table 6b. Multivariate Cox regression model of risk factors for secondary outcome of heart failure hospitalisation from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by outcome-specific variable selection

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.93	0.57-1.51	0.76
LVAD type			
Heart Mate 2	Referent		
Heart Ware	3.05	1.79-5.21	0.0005
Heart Mate 3	2.25	1.23-4.13	
Other	1.39	0.53-3.62	
Number of VA episodes pre-VAD			
Four or more	Referent		
None	0.35	0.14-0.83	0.0085
One	0.40	0.15-1.08	
Two	0.38	0.12-1.18	
Three	0.63	0.20-2.01	
Unknown	0.07	0.02-0.28	

Supplemental Table 6c. Multivariate Cox regression model of risk factors for secondary outcome of device-related infection requiring systemic antibiotics from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by variable selection per the primary outcome

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.96	0.66-1.40	0.84
Age	1.00	0.98-1.01	0.64
LVAD as redo surgery	1.50	0.95-2.39	0.09
LVAD type			
Heart Mate II	Referent		
Heart Ware	1.72	1.16-2.55	0.0008
Heart Mate 3	0.57	0.32-1.03	
Other	0.47	0.17-1.33	
Number of VA episodes pre-VAD			
Four or more	Referent		
None	0.63	0.28-1.42	
One	0.42	0.16-1.09	0.49
Two	0.68	0.24-1.89	
Three	0.63	0.20-1.95	
Unknown	0.82	0.33-2.02	
Vasopressor use pre-LVAD			
Yes	Referent		
No	1.33	0.61-2.92	0.26
Unknown	1.81	0.78-4.19	

Supplemental table 6d. Multivariate Cox regression model of risk factors for secondary outcome of device-related infection requiring systemic antibiotics from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by outcome-specific variable selection

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.96	0.65-1.41	0.82
Age	1.00	0.99-1.01	0.89
LVAD type			
Heart Mate II	Referent		
Heart Ware	1.88	1.25-2.83	0.0005
Heart Mate 3	0.59	0.33-1.07	
Other	0.57	0.20-1.62	
Number of VA episodes pre-VAD			
Four or more	Referent		
None	0.54	0.24-1.21	
One	0.37	0.14-0.97	0.39
Two	0.67	0.24-1.87	
Three	0.57	0.18-1.75	
Unknown	0.70	0.29-1.69	
Ivabradine use pre-LVAD			

Supplemental table 6d. *(Continued)*

Variable	HR	95% CI	P value
Yes	Referent		
No	1.17	0.58-2.36	0.0016
Unknown	2.74	1.24-6.04	
Beta blocker use pre-LVAD			
Yes	Referent		
No	1.11	0.73-1.69	0.17
Unknown	0.65	0.37-1.11	

Supplemental Table 6e. Multivariate Cox regression model of risk factors for secondary outcome of non-cerebral bleeding from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by variable selection per the primary outcome

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.64	0.40-1.03	0.07
Age	1.02	1.00-1.04	0.07
LVAD as redo surgery	1.42	0.77-2.61	0.26
LVAD type			
Heart Mate II	Referent		
Heart Ware	1.03	0.58-1.83	0.90
Heart Mate 3	0.81	0.43-1.54	
Other	0.85	0.37-1.96	
Number of VA episodes pre-VAD			
Four or more	Referent		
None	1.57	0.37-6.62	
One	1.69	0.38-7.55	0.15
Two	0.51	0.07-3.65	
Three	1.86	0.36-9.63	
Unknown	0.50	0.09-2.77	
Vasopressor use pre-LVAD			
Yes	Referent		
No	0.85	0.40-1.82	0.43
Unknown	0.56	0.21-1.47	

Supplemental table 6f. Multivariate Cox regression model of risk factors for secondary outcome of non-cerebral bleeding from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by outcome-specific variable selection

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.82	0.52-1.28	0.37
Aetiology			
Nonischaemic cardiomyopathy	Referent		
Ischaemic cardiomyopathy	1.23	0.77-1.94	0.10
Other	2.02	1.06-3.86	
LVAD implant date quartile			
Q1	Referent		
Q2	0.55	0.30-1.03	0.17
Q3	1.05	0.59-1.86	
Q4	0.94	0.50-1.77	

Supplemental Table 6g. Multivariate Cox regression model of risk factors for secondary outcome of intracranial bleeding from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by variable selection per the primary outcome

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.55	0.24-1.26	0.16
Age	1.05	1.01-1.09	0.01
LVAD as redo surgery	1.11	0.38-3.21	0.85
LVAD type			
Heart Mate II	Referent		
Heart Ware	2.63	1.07-6.47	0.18
Heart Mate 3	1.20	0.36-4.01	
Other	0.98	0.20-4.76	
Number of VA episodes pre-VAD			
Four or more	Referent		
None	1.02	0.13-7.99	
One	0.20	0.01-3.35	0.42
Two	1.83	0.20-16.64	
Three	1.15	0.10-13.70	
Unknown	0.50	0.04-5.66	
Vasopressor use pre-LVAD			
Yes	Referent		
No	0.63	0.18-2.22	0.65
Unknown	0.92	0.20-4.18	

Supplemental table 6h. Multivariate Cox regression model of risk factors for secondary outcome of intracranial bleeding from the stepwise selection process by time-updated CIED-D carrier status following LVAD implantation, adjusted by outcome-specific variable selection

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.70	0.34-1.46	0.34
LVAD type			
Heart Mate II	Referent		
Heart Ware	2.07	0.92-4.65	0.35
Heart Mate 3	1.09	0.35-3.43	
Other	1.33	0.30-5.88	

Supplemental Table 7. Multivariate Cox regression model of risk factors for all-cause death based on a backward variable selection model, by time-updated CIED-D carrier status following LVAD implantation.

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.61	0.40-0.94	0.024
Age	1.04	1.02-1.06	<0.0001
Aetiology			
Nonischaemic	Referent		
Ischaemic	1.01	0.68-1.51	0.73
Other	1.25	0.70-2.24	
LVAD type			
Heart Mate II	Referent		
Heart Ware	1.19	0.74-1.92	0.43
Heart Mate 3	0.70	0.37-1.34	
Other	0.70	0.26-1.89	
LVAD intention			
Bridge to transplantation (BTT)	Referent		
Bridge to decision (BTD)	1.13	0.66-1.92	0.43
Destination therapy (DT)	0.70	0.38-1.30	
Beta blocker use			
No	Referent		
Yes	0.86	0.55-1.34	0.52
Unknown	0.67	0.33-1.38	
Vasopressor use			
No	Referent		
Yes	1.87	1.02-3.40	0.0007
Unknown	7.48	2.35-22.82	
Mechanical ventilation			
Intubated	Referent		
None	0.69	0.34-1.40	0.025
Non-invasive	1.80	0.17-19.30	
Unknown	0.18	0.05-0.68	
Number of VA episodes pre-VAD			

Supplemental Table 7. *(Continued).*

Variable	HR	95% CI	P value
Four or more	Referent		
None	0.43	0.19-0.99	0.028
One	0.26	0.09-0.72	
Two	0.72	0.27-1.93	
Three	0.41	0.13-1.29	
Unknown	0.23	0.08-0.65	

Supplemental table 8. Results of the propensity score model assessing the possibility of having a CIED-D pre-LVAD.

Variable	OR	95% CI	P value
Age	1.02	1.00-1.04	0.07
Female gender	0.76	0.40-1.45	0.41
Arterial hypertension	1.12	0.62-2.02	0.72
Diabetes mellitus	0.94	0.50-1.77	0.85
Chronic kidney disease	1.62	0.89-2.96	0.12
Coronary artery disease	0.69	0.35-1.38	0.30
Prior MI	0.45	0.21-0.96	0.04
Prior coronary revascularization	1.56	0.72-3.37	0.26
Cerebrovascular events	1.68	0.68-4.15	0.26
Atrial fibrillation/flutter	2.90	1.63-5.15	<0.0001
Ventricular arrhythmias	2.03	1.12-3.68	0.020
LVAD as redo surgery	0.59	0.28-1.23	0.16
Concomitant procedure with LVAD implant	0.39	0.21-0.73	0.003
LVAD type			
Heart Mate II	Referent		
Heart Ware	3.24	1.63-6.45	<0.0001
Heart Mate 3	5.88	2.90-11.91	
Other	3.91	1.04-14.75	
LVAD intention			
Bridge to transplantation	Referent		
Bridge to decision	0.24	0.11-0.50	0.0008
Destination therapy	0.65	0.27-1.57	
INTERMACS class			
1	Referent		
2	2.33	1.04-5.20	0.002
3	4.25	1.86-9.72	
4 or higher	4.31	1.94-10.11	

Supplemental table 9a. Sensitivity analyses performed through additional multivariate Cox regression models of risk factors for all-cause death by time-updated CIED-D carrier status following LVAD implantation estimated by multiple imputation procedures.

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.63	0.43-0.93	0.019
Age	1.03	1.02-1.05	<0.0001
LVAD as redo surgery	1.72	1.11-2.66	0.015
LVAD type			
Heart Mate II	Referent		
Heart Ware	1.13	0.73-1.76	0.36
Heart Mate 3	0.66	0.36-1.22	
Other	0.68	0.30-1.52	
Number of VA episodes pre-VAD			
None	Referent		
One	0.56	0.29-1.08	
Two	1.37	0.71-2.66	0.13
Three	0.79	0.33-1.88	
Four or more	1.87	0.81-4.29	
Vasopressor use pre-LVAD			
No	Referent		0.13
Yes	1.52	0.88-2.63	

Supplemental table 9b. Sensitivity analyses performed through additional multivariate Cox regression models of risk factors for all-cause death by time-updated CIED-D carrier status following LVAD implantation estimated by multiple imputation procedures.

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.61	0.41-0.90	0.013
CRT-P post-LVAD	0.65	0.25-1.66	0.37
Age	1.03	1.02-1.05	<0.0001
LVAD as redo surgery	1.78	1.15-2.78	0.01
LVAD type			
Heart Mate II	Referent		
Heart Ware	1.13	0.73-1.76	0.35
Heart Mate 3	0.66	0.36-1.22	
Other	0.66	0.29-1.48	
Number of VA episodes pre-VAD			
None	Referent		
One	0.56	0.29-1.07	
Two	1.35	0.70-2.63	0.14
Three	0.82	0.34-1.97	
Four or more	1.84	0.80-4.25	
Vasopressor use pre-LVAD			
No	Referent		0.11
Yes	1.56	0.90-2.70	

Supplemental Table 10. Sensitivity analysis performed through an additional multivariate Cox regression model obtained from the stepwise selection process of risk factors for all-cause mortality, based on multiple imputation methods.

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.58	0.41-0.82	0.002
Age	1.03	1.01-1.05	<0.0001
LVAD as redo surgery	1.71	1.11-2.64	0.014

Supplemental Table 11a. Multivariate Cox regression model of risk factors for all-cause mortality by time-updated ICD carrier status following LVAD implantation, adjusted by outcome-specific variable selection

Variable	HR	95% CI	P value
ICD status	0.60	0.39-0.92	0.019
Age	1.03	1.01-1.05	0.001
LVAD implant as redo surgery	2.02	1.24-3.31	0.005
LVAD type			
Heart Mate II	Referent		
Heart Ware	1.40	0.86-2.27	0.31
Heart Mate 3	0.76	0.41-1.41	
Other	0.86	0.37-2.00	
Number of VA episodes pre-LVAD			
Four or more	Referent		
None	0.37	0.16-0.86	
One	0.21	0.07-0.59	0.0095
Two	0.56	0.21-1.50	
Three	0.31	0.10-1.02	
Unknown	0.13	0.04-0.44	
Vasopressor use pre-LVAD			
Yes	Referent		
No	0.44	0.23-0.82	0.01
Unknown	0.79	0.36-1.73	
LVIDd pre-LVAD	0.98	0.97-1.00	0.064

Supplemental Table 11b. Multivariate Cox regression model of risk factors for all-cause mortality by time-updated ICD carrier status following LVAD implantation, adjusted by outcome-specific variable selection - sensitivity analysis based on multiple imputation.

Variable	HR	95% CI	P value
CIED-D post-LVAD	0.65	0.44-0.97	0.034
Age	1.03	1.02-1.05	<0.0001
LVAD as redo surgery	1.72	1.10-2.67	0.015
LVAD type			
Heart Mate II	Referent		
Heart Ware	1.13	0.72-1.76	0.27
Heart Mate 3	0.60	0.33-1.09	
Other	0.74	0.33-1.67	
Number of VA episodes pre-VAD			
None	Referent		
One	0.56	0.29-1.08	
Two	1.42	0.73-2.78	0.10
Three	0.72	0.30-1.74	
Four or more	1.97	0.84-4.62	
Vasopressor use pre-LVAD			
No	Referent		0.16
Yes	1.50	0.85-2.64	
LVIDd at LVAD implant	0.99	0.98-1.01	0.49

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How does age affect the clinical course after left ventricular assist device implantation: results from the PCHF-VAD registry

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* Equal contributions

Under embargo

Submitted

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Underutilization of left ventricular assist devices in women at similar survival outcomes compared to men

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Under embargo

Submitted

22

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

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Abstract

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

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

Patients who underwent concomitant AoV replacement (n=457) or AoV repair (n=328) had a significantly reduced late survival compared with patients without an AoV procedure (n=14,482) (56%, 61%, 62%, respectively p=0.001), although the biggest difference occurred in the early postoperative period. After adjustment for other significant predictors, concomitant AoV replacement remained an independent predictor for early (HR 1.226 [1.037-1.449]) and late mortality (HR 1.477 [1.154-1.890]).

Only, in patients with moderate or severe AoV regurgitation, no significant survival differences were observed between patients with concomitant AoV replacement, AoV repair and without an AoV procedure (58%, 61%, 59%, respectively, p=0.923).

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

Introduction

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

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

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

Methods

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

All adult patients (age ≥18 years) who underwent primary implantation of a continuous-flow LVAD from January 2013 through November 2017 were included in this analysis. Patients with a total artificial heart, isolated right ventricular assist device or with missing information on concomitant AoV procedure were excluded from this analysis (Supplementary Figure 1). The endpoint for this analysis was all-cause mortality post-LVAD surgery, device explantation or heart transplantation. The primary outcome was early (≤90 days post-LVAD surgery) survival. Secondary outcomes were late (survival during the entire follow-up period) and conditional survival (in patients who survived the first 90 days post-LVAD surgery), causes of early and late death post-LVAD surgery, device explantation and heart transplantation. The definitions of causes of death were defined earlier by the IMACS registry, by granular data on the causes of death were not available [9].

Statistical analysis

Patient characteristics are presented as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on the distribution of continuous data and counts and percentages (%) for categorical data. The one-way ANOVA test or Kruskal-Wallis test was used to compare data for categorical variables, depending on the distribution of the data, and the Chi-square test was used to compare data for categorical variables. All included LVAD patients were stratified into those without a concomitant AoV procedure or those with AoV intervention (replacement or concomitant AoV repair) at the of LVAD implant. Additional data on which type of AoV repair technique was used was not available.

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

Several subanalyzes have been performed, including a survival analysis in patients with documented moderate to severe AoV regurgitation, a survival analysis stratified to INTERMACS classification, device destination, presence of AoV regurgitation and a subanalysis without patients who proceeded towards heart transplantation.

Missing data in the baseline variables were imputed, using multiple imputation. If the missing variables showed a monotone pattern of missing values, the monotone method was used, otherwise, an iterative Markov chain Monte Carlo method was used with a number of 10 iterations. A total of five imputations was performed, and the pooled data were analyzed. Variables with less than 40% missing data in the entire population were accepted for multiple imputation [10]. The vast majority of variables had less than 5% missing data (Supplementary Table 3). The imputed data were only used in the Cox proportional hazard analysis.

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

The findings herein were reviewed and approved by the IMACS Steering Committee.

Results

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

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

	Overall population (n=15,267)	No AoV procedure (n=14,482)	AoV replacement (n=457)	AoV repair (n=328)	p-value
Demographics					
Age (years)	58.0 [49.0-66.0]	58.0 [48.0-66.0]	62.0 [53.0-69.0]	64.0 [57.0-69.0]	<0.001
Men	12,093 (79.3)	11,433 (79.1)	396 (87.0)	264 (80.5)	<0.001
BSA (m^2)	2.04 [1.85-2.25]	2.04 [1.86-2.25]	1.99 [1.83-2.18]	1.96 [1.81-2.16]	<0.001
BMI (kg/m^2)	27.4 [23.8-32.0]	27.5 [23.9-32.1]	26.1 [22.8-30.4]	25.1 [22.8-29.4]	<0.001
Ischemic etiology	5,721 (38.5)	5,451 (38.6)	147 (35.6)	123 (39.5)	0.437
Comorbidities					
CVA	655 (4.4)	621 (4.4)	21 (4.8)	13 (4.1)	0.877
DM	1,477 (9.9)	1,417 (10.0)	37 (8.3)	23 (7.0)	0.105
Current smoker	866 (5.9)	818 (5.9)	29 (6.9)	19 (5.8)	0.693
Dialysis	444 (2.9)	423 (2.9)	16 (3.5)	5 (1.5)	0.246
Current ICD therapy	10,392 (78.1)	9,860 (78.1)	279 (76.9)	253 (81.9)	0.393
History of CABG	2,544 (19.0)	2,415 (19.1)	68 (17.8)	61 (19.4)	0.814
Atrial fibrillation	1,408 (21.9)	1,309 (21.6)	58 (28.6)	41 (22.8)	0.058
NYHA-classification					
NYHA I/II	174 (1.2)	164 (1.2)	7 (1.6)	3 (1.0)	
NYHA III	2,690 (19.2)	2,558 (19.3)	79 (18.6)	53 (17.0)	0.761
NYHA IV	11,151 (79.6)	10,557 (79.5)	339 (79.8)	255 (82.0)	
INTERMACS classification					
INTERMACS 1	2,373 (15.6)	2,269 (15.8)	60 (13.3)	44 (13.4)	
INTERMACS 2	5,173 (34.1)	4,887 (34.0)	165 (36.5)	121 (36.9)	
INTERMACS 3	5,179 (34.1)	4,914 (34.1)	156 (34.5)	109 (33.2)	
INTERMACS 4	1,968 (13.0)	1,873 (13.0)	55 (12.2)	40 (12.2)	0.502
INTERMACS 5	315 (2.1)	296 (2.1)	9 (2.0)	10 (3.0)	
INTERMACS 6	95 (0.6)	86 (0.6)	6 (1.3)	3 (0.9)	
INTERMACS 7	68 (0.4)	66 (0.5)	1 (0.2)	1 (0.3)	

Table 1. *(continued)*

	Overall population (n=15,267)	No AoV procedure (n=14,482)	AoV replacement (n=457)	AoV repair (n=328)	p-value
IABP prior to LVAD surgery	4,302 (28.9)	4,109 (29.1)	105 (24.0)	88 (26.8)	0.049
ECMO prior to LVAD surgery	891 (6.0)	853 (6.0)	18 (4.1)	20 (6.1)	0.238
Ventilator prior to LVAD surgery	1,934 (12.7)	1,845 (12.8)	48 (10.5)	41 (12.5)	0.364
History of AoV replacement/repair	396 (3.0)	282 (2.2)	85 (22.3)	29 (9.2)	<0.001
Laboratory					
Creatinine, mg/dL	1.20 [0.98-1.50]	1.20 [0.97-1.50]	1.27 [1.05-1.57]	1.20 [1.00-1.50]	0.003
BUN, mg/dL	25.0 [18.0-37.3]	25.0 [18.0-37.0]	29.0 [21.0-40.0]	26.0 [18.0-36.0]	<0.001
AST, U/L	29.0 [21.0-44.0]	29.0 [21.0-44.0]	30.0 [22.0-46.0]	30.0 [21.5-42.0]	0.226
ALT, U/L	29.0 [19.0-49.0]	29.0 [19.0-49.0]	28.5 [18.8-46.3]	29.0 [20.0-52.0]	0.782
LDH, (U/L)	279.0 [220.0-391.0]	279.0 [220.0-391.0]	289.5 [222.8-390.3]	276.5 [216.3-395.0]	0.753
Total bilirubin, mg/dL	1.0 [0.6-1.6]	1.0 [0.6-1.6]	1.1 [0.7-1.7]	1.1 [0.7-1.7]	0.010
WBC, $x10^9$/L	7.9 [6.3-10.2]	7.9 [6.3-10.2]	7.8 [6.2-9.8]	7.5 [6.0-10.4]	0.167
Platelets, $x10^9$/L	188.0 [142.0-242.0]	188.0 [142.0-242.0]	187.0 [132.0-232.0]	176.5 [131.3-226.0]	0.001
INR	1.2 [1.1-1.4]	1.2 [1.1-1.4]	1.3 [1.1-1.5]	1.2 [1.1-1.4]	<0.001
Albumin, g/dL	3.5 [3.0-3.8]	3.5 [3.0-3.8]	3.4 [3.0-3.8]	3.4 [3.0-3.8]	0.552
Hemoglobin, g/dL	11.3 [9.8-12.8]	11.3 [9.8-12.8]	11.2 [9.9-12.6]	11.2 [9.7-12.5]	0.539
Hemodynamics					
RA pressure, mmHg	11.0 [7.0-16.0]	11.0 [7.0-16.0]	11.0 [7.0-17.0]	10.5 [7.0-15.0]	0.295
PCWP, mmHg	25.0 [19.0-31.0]	25.0 [19.0-31.0]	25.0 [20.0-31.0]	25.0 [19.0-32.0]	0.551
Systolic PAP, mmHg	50.0 [40.0-60.0]	50.0 [40.0-60.0]	51.0 [41.0-63.0]	50.0 [40.0-60.0]	0.012
Diastolic PAP, mmHg	25.0 [19.0-30.0]	25.0 [19.0-30.0]	25.0 [20.0-32.0]	24.0 [18.0-29.0]	0.026
Cardiac output, L/min	3.93 [3.14-4.80]	3.96 [3.15-4.80]	3.90 [3.20-4.71]	3.79 [3.00-4.55]	0.077

Table 1. *(continued)*

	Overall population (n=15,267)	No AoV procedure (n=14,482)	AoV replacement (n=457)	AoV repair (n=328)	p-value
Echocardiographic					
LVEF					
≥40%	347 (8.5)	327 (8.5)	18 (14.4)	2 (1.8)	
30-39%	484 (11.8)	460 (11.9)	12 (9.6)	2 (10.7)	0.012
20-29%	3,260 (79.7)	3,067 (79.6)	95 (76.0)	98 (87.5)	
RVEF					
Normal	2,941 (26.0)	2,790 (26.1)	73 (22.4)	78 (28.4)	
Mild	3,272 (29.0)	3,086 (28.9)	108 (33.1)	78 (28.4)	0.400
Moderate	3,473 (30.8)	3,283 (30.7)	103 (31.6)	87 (31.6)	
Severe	1,606 (14.2)	1,532 (14.3)	42 (12.9)	32 (11.6)	
Mitral valve regurgitation					
None	1,070 (7.6)	1,021 (7.6)	32 (7.7)	17 (5.4)	
Mild	4,960 (35.2)	4,689 (35.1)	164 (39.7)	107 (34.3)	0.067
Moderate	4,689 (33.3)	4,431 (33.2)	138 (33.4)	120 (38.5)	
Severe	3,368 (23.9)	3,221 (24.1)	79 (19.1)	68 (21.8)	
Tricuspid valve regurgitation					
None	1,257 (9.0)	1,210 (9.1)	31 (7.5)	16 (5.1)	
Mild	6,865 (49.2)	6,491 (49.1)	207 (49.8)	167 (53.4)	0.172
Moderate	4,197 (30.1)	3,969 (30.0)	134 (32.2)	94 (30.0)	
Severe	1,640 (11.7)	1,560 (11.8)	44 (10.6)	36 (11.5)	
AoV regurgitation					
None	8,426 (64.4)	8,330 (67.2)	63 (15.9)	33 (10.9)	
Mild	4,084 (31.2)	3,747 (30.2)	182 (45.8)	155 (51.3)	<0.001
Moderate	492 (3.8)	270 (2.2)	119 (30.0)	103 (34.1)	
Severe	91 (0.7)	47 (0.4)	33 (8.3)	11 (3.6)	
LVEDD (mm)	68.0 [61.0-75.0]	68.0 [61.0-75.0]	69.0 [63.0-77.0]	68.0 [62.0-74.0]	0.009

Table 1. *(continued)*

	Overall population (n=15,267)	No AoV procedure (n=14,482)	AoV replacement (n=457)	AoV repair (n=328)	p-value
Main LVAD strategy					
BTT	4,272 (28.0)	4,087 (28.2)	116 (25.4)	69 (21.0)	0.001
BTC	4,221 (27.7)	4,016 (27.7)	126 (27.6)	79 (24.1)	
Destination therapy	6,563 (43.0)	6,177 (42.7)	206 (45.1)	180 (54.9)	
Rescue therapy	125 (0.8)	122 (0.8)	3 (0.7)	0 (0.0)	
Bridge to recovery	55 (0.4)	51 (0.4)	4 (0.9)	0 (0.0)	
Other	28 (0.2)	26 (0.2)	2 (0.4)	0 (0.0)	
Concomitant procedures					
Congenital surgery	1,030 (6.7)	965 (6.7)	39 (8.5)	26 (7.9)	0.201
Mitral valve surgery	538 (3.5)	484 (3.3)	26 (5.7)	28 (8.5)	<0.001
Tricuspid valve surgery	533 (3.5)	486 (3.4)	26 (5.7)	21 (6.4)	<0.001
Pulmonary valve surgery	8 (0.1)	7 (0.0)	1 (0.2)	0 (0.0)	0.268
RVAD surgery	99 (0.7)	90 (0.7)	8 (2.1)	1 (0.3)	0.005
Other concomitant surgery	2,732 (17.9)	2,584 (17.8)	85 (18.6)	63 (19.2)	0.754

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

Early, late and conditional survival

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

Patients without an AoV procedure stayed for a shorter period on the intensive care (7 [5-13] days), compared to patients with an AoV replacement (10 [6-17] days) and patients with an AoV repair (8 [5-14] days, p<0.001). Similarly, patients without an AoV procedure stayed for a shorter period in the hospital (19 [14-28] days) compared to patients with an AoV replacement (21 [16-36] days) and patients with an AoV repair (20 [14-30] days, p<0.001). During the initial hospitalization, in 843 (5.8%) patients without an AoV procedure, 44 (9.6%) patients with an AoV replacement and 8 (2.4%) patients with an AoV repair died (p<0.001).

As shown in Supplementary Figure 3, mechanical AoV replacements (82.7%, 50.6%, respectively) have the worse early and late survival followed by biological AoV replacement (85.6%, 56.4%, respectively), AoV repair (87.4%, 60.9%, respectively), while no AoV procedure (90.4%, 62.4%, respectively) has the best early and late survival (p<0.001, p=0.001, respectively). The baseline characteristics of the patients with biological and mechanical AoV replacement, AoV repair and no AoV procedure are shown in Supplementary Table 4).

Patients with an AoV procedure and an INTERMACS class 2 or 3 had a significant worse survival, compared to patients without an AoV procedure, while no survival difference was observed in patients with an INTERMACS class 1 or 4 and higher (Supplementary Figure 4A-C). The causes of death are shown in Supplementary Table 5.

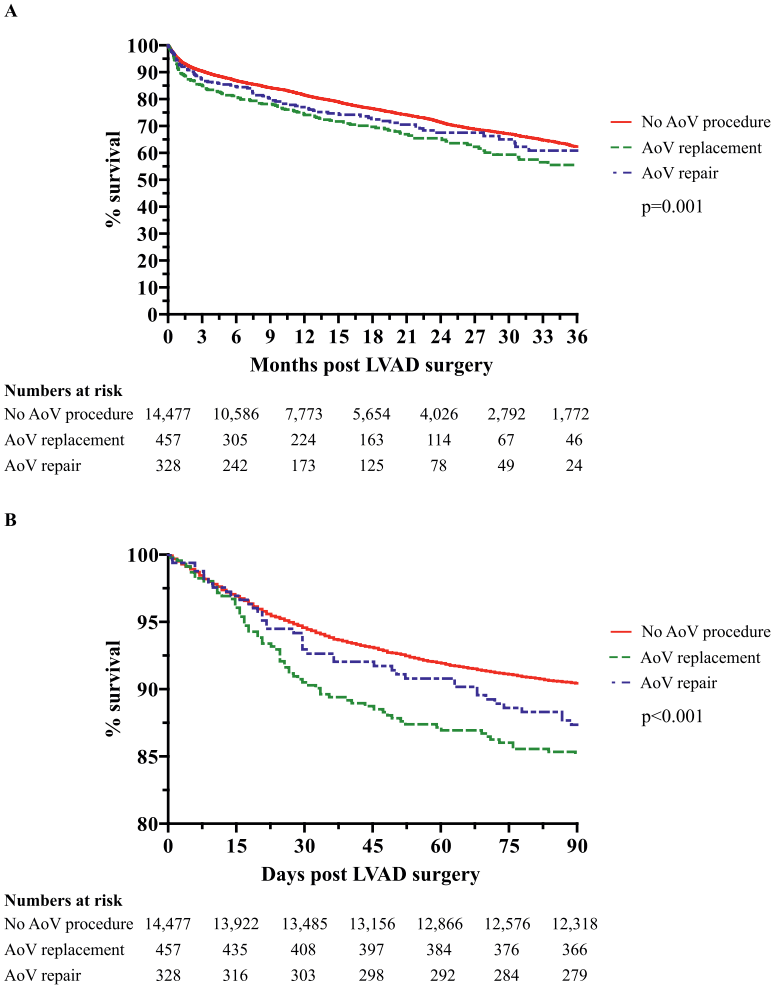

Figure 1. A Early and **B** late survival stratified to AoV procedure post-LVAD surgery

When competing outcomes are analyzed between the patient cohorts, patients with an AoV replacement (29.0%) and AoV repair (29.4%) were less often transplanted at 36 months post-LVAD surgery compared to patients without AoV procedure (36.3%) (Supplementary Figure 5A-C).

In patients who did not proceed towards heart transplantation, patients without an AoV procedure had the best survival (Supplementary Figure 6). While no significant difference was observed in early or medium term survival between patients who received the LVAD as a bridge to transplantation or as destination therapy, as shown in Supplementary Figure 7.

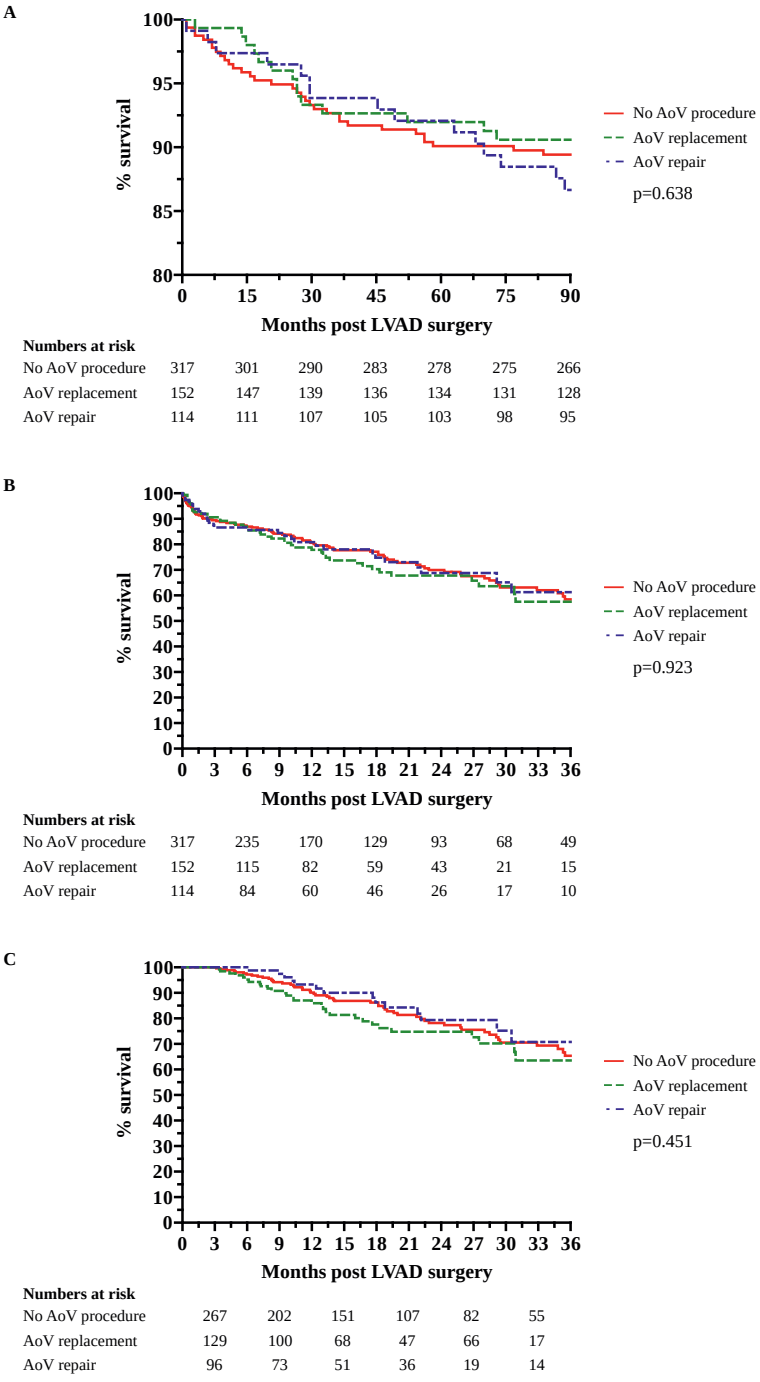

Figure 2. A Early, **B** late, and **C** conditional survival in patients with moderate to severe AoV regurgitation at baseline, stratified to no AoV procedure, AoV replacement and AoV repair post-LVAD surgery.

Survival in patients with moderate to severe AR

The baseline and clinical characteristics of 583 patients with a documented moderate to severe AoV regurgitation at baseline has been shown in Supplementary Table 6. As shown in Figure 2A-C, no significant differences in the early, late or conditional survival rates were observed between patients without an AoV procedure (89.4%, 58.5%, 65.4%, respectively), AoV replacement (90.6%, 57.5%, 63.5%, respectively) or AoV repair (86.7%, 61.3%, 70.8%, respectively). The early, late and conditional survival of patients without an AoV procedure, stratified to AR at baseline is shown in Supplementary Figure 8A-C, while the late survival of patients without an AoV procedure, AoV replacement and AoV repair, stratified to AR at baseline are shown in Supplementary Figure 9A-C.

Causes of death

The causes of early and late death post-LVAD surgery are shown in Tables 2 and Supplementary Table 7. Multisystem organ failure was the most frequent cause of early death (27.7%), followed by circulatory failure (16.9%) and neurological events (15.9%). The most frequent cause of late death was neurological events (19.2%) followed by multisystem organ failure (17.5%) and circulatory failure (17.2). The causes of death in patients surviving the first 90 days post-LVAD surgery are shown in Supplementary Table 8.

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

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

p-value for distribution between groups: 0.454

AoV, Aortic Valve; LVAD, Left Ventricular Assist Device; RV, Right Ventricular

** including hepatic dysfunction, renal dysfunction, pancreatitis*

Table 3. Multivariable predictors of early all-cause mortality post-LVAD surgery, stratified to AoV procedure

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

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

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

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

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

Multivariable model

Independent risk factors for early mortality post-LVAD surgery after multivariable adjustment are shown in Table 3. The replacement of the AoV was significantly associated with an increased risk for early all-cause mortality, both unadjusted (HR 1.604 [1.255-2.050], p<0.001) as adjusted for other significant predictors (HR 1.477 [1.154-1.890], p=0.002, while AoV repair was no significant predictor, compared to no AoV procedure. Similarly, AoV replacement was an predictor for late all-cause mortality, unadjusted (HR 1.360 [1.152-1.605], p<0.001) and adjusted 1.226 [1.037-1.449], p=0.017) (Table 4).

Discussion

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

Untreated significant AoV regurgitation could be very hemodynamically compromising due to the short circulation loop, while less severe AoV regurgitation might be less cumbersome. Surprisingly, in up to 15% of our patients who underwent an AoV procedure, no AoV regurgitation was reported prior to LVAD surgery. In these patients, the decision for an AoV procedure could have been made based on the peri-operative echocardiogram, showing a significant AoV regurgitation. Additionally, these patients might have undergone a concomitant AoV procedure in order to replace or oversew the AoV due to a pre-existing mechanical AoV, as is recommended [5]. However, both peri-operative echocardiographic data as well as replacement of a mechanical AoV were not collected in the IMACS database, so these hypotheses could not be tested. However, as our results indicate that AoV replacement is an independent predictor for mortality, stringent criteria for a concomitant AoV procedure at the time of LVAD surgery might be warranted, especially in patients with only a mild AoV regurgitation. Additionally, less invasive procedures for the treatment of significant AoV regurgitation in LVAD patients have been suggested. Only small studies have investigated the usage of a transcatheter aortic valve replacement (TAVR) procedure to treat significant AoV regurgitation in patients already on LVAD support, showing promising results [11-13]. Using a TAVR procedure concomitant with LVAD surgery could reduce the circulatory

bypass time, reducing the risk of myocardial ischemia, as shown in a recent case-report [14]. However, experience and evidence with this off-label use of the TAVR procedure are very limited, and this technique might have additional limitations such as the challenging aspect of these kind of procedures in LVAD patients. Additional trials are highly needed in order to determine the optimal strategy for the treatment of significant AoV regurgitation at the time of LVAD surgery. Especially since our results demonstrated that in patients with a significant AoV regurgitation, the survival rates between patients with and without an AoV procedure was similar.

Early and late survival

Previous studies investigating the association between survival and AoV procedures reported conflicting results, with some studies indicating a worse survival [15-18], while others reported similar or better survival rates in patients with a concomitant AoV procedure [19-23]. However, most of these studies were single-center studies and were limited by the lower number of patients with a concomitant AoV procedure (with only one of them including more than 100 patients with an AoV procedure), and some reported only outcomes of multiple concomitant cardiac procedures combined. The largest study used the INTERMACS dataset, and included 6,721 adult LVAD patients, with 125 patients undergoing concomitant AoV closure, 95 AoV repair, and 85 AoV replacement between June 2006 and December 2012 [15]. In the INTERMACS study, patients undergoing a concomitant AoV procedure had significantly lower 1-year survival rates (patients with an AoV repair 79%, AoV replacement 72% and AoV closure 64%) compared to patients without an AoV procedure (81%, p=0.0003). In comparison to the INTERMACS study, our study reflects a more contemporary, worldwide LVAD population, a much higher number of LVAD patients were included, with a higher number of AoV procedures. The late survival rates in our study were higher compared to the INTERMACS study, most likely reflecting the improvement in LVAD management and survival over time. Similar to the INTERMACS study, our results demonstrated a lower survival rate in patients with an AoV procedure, although, in our study, patients with an AoV replacement had the lowest survival, compared to patients with an AoV closure in the INTERMACS study.

Surprisingly, in patients with moderate or severe AR no significant survival differences were observed between patients with and without concomitant AoV procedures. Additionally, in patients without a concomitant AoV procedure, no significant survival difference was observed between patients with and without AR. Only a trend towards a better survival was observed in patients with AVR and AR compared to patients

without AR. These results suggests that the increased risk of a AoV procedure, might out weight its benefits.

Only biological prosthesis are recommended for concomitant AoV replacement, and it is recommended to perform a concomitant AoV procedure at the time of LVAD surgery in patients with a mechanical AoV [5]. Despite these recommendations, a small number of patients still received a concomitant mechanical AoV during LVAD surgery. Our results, clearly demonstrates that patients with a mechanical AoV have the worst survival, thus supporting the recommendations to only use biological prosthesis in LVAD patients.

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

Causes of death

In our combined cohort of LVAD patients, the most common causes of early death were multisystem organ failure, circulatory failure, and neurological events post-LVAD surgery, similar to previous report [24]. The lower survival in patients with an AoV replacement appears to be accompanied by an increase in multisystem organ failure, while patients with an AoV repair died more often due to a circulatory failure compared to patients without an AoV procedure. Surprisingly, fatal neurological events occurred frequently, and more often in patients without an AoV procedure, compared to patients with a concomitant AoV replacement or repair. Potentially, antithrombotic and antiplatelet therapy was introduced earlier in patients with an AoV procedure compared to patients without an AoV procedure, thus preventing fatal neurological events. However, detailed information on the timing of the introduction of antithrombotic and

antiplatelet therapy was lacking. Unfortunately, no granular data was available in the IMACS database for more specification of the causes of early and late death.

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

Competing outcomes

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

Limitations

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

Conclusion

This is the largest study comparing the short- and long-term survival of concomitant AoV procedures in continuous-flow LVAD patients with pre-existing AoV regurgitation. Concomitant AoV surgery, especially replacement, is associated with lower survival rates compared to patients without an AoV procedure. Only in patients with moderate to severe AR, no survival difference was observed in patients who underwent concomitant AoV surgery, compared to those without AoV surgery. These results suggest that resolving less severe AR might not outweigh the risk of AoV surgery. Therefore, additional research is urgently needed to determine the optimal strategy in order to treat or not to treat AoV regurgitation at the time of LVAD surgery.

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Supplementary data:

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

		95% CI for HR		
Variables	**HR**	**Lower**	**Upper**	**p-value**
Demographics				
Age (years)	1.030	1.025	1.035	<0.001
Sex (men vs. women)	0.914	0.808	1.034	0.153
BSA (m^2)	0.936	0.790	1.110	0.448
BMI (kg/m^2)	1.007	0.999	1.015	0.076
Ischemic etiology	1.317	1.188	1.459	<0.001
Atrial fibrillation	1.294	1.147	1.458	<0.001
Blood type				
O	*ref*	*ref*	*ref*	*ref*
A	1.067	0.952	1.195	0.265
B	1.133	0.969	1.325	0.118
AB	1.091	0.839	1.419	0.515
INTERMACS class (1-3 vs. 4-7)	1.404	1.201	1.641	<0.001
IABP	1.337	1.201	1.489	<0.001
ECMO	2.580	2.216	3.002	<0.001
≥3 inotropic use	1.526	1.263	1.843	<0.001
Laboratory				
Creatinine (mg/dL)	1.801	1.597	2.032	<0.001
BUN (mg/dL)	1.013	1.011	1.015	<0.001
AST (U/L)	1.001	1.001	1.001	<0.001
Total bilirubin (mg/dL)	1.294	1.226	1.365	<0.001
WBC ($_{x10}{}^{9}$/L)	1.000	0.999	1.000	0.698
Platelets ($_{x10}{}^{9}$/L)	0.997	0.996	0.998	<0.001
INR	1.296	1.192	1.411	<0.001
Albumin (g/dL)	0.552	0.509	0.600	<0.001
Hemoglobin (g/dL)	0.852	0.831	0.874	<0.001
Hemodynamic				
Mean RA pressure (mmHg)	1.020	1.013	1.026	<0.001
Pulmonary artery wedge pressure (mmHg)	0.996	0.991	1.002	0.185
Systolic pulmonary artery pressure (mmHg)	0.997	0.994	1.001	0.131
Diastolic pulmonary artery pressure (mmHg)	0.993	0.987	0.999	0.015
Cardiac output (L/min)	1.028	0.985	1.073	0.201
Severe RV dysfunction	1.204	1.047	1.383	0.009
Severe LV dysfunction (<20%)	0.884	0.794	0.983	0.023
Moderate or severe tricuspid regurgitation	1.258	1.136	1.394	<0.001
Moderate or severe mitral regurgitation	0.799	0.722	0.885	<0.001
Device strategy				
BTT	*ref*	*ref*	*ref*	*ref*
BTC	1.097	0.941	1.279	0.236

Supplementary Table 1. *(continued)*

Variables	HR	95% CI for HR Lower	Upper	p-value
DT	1.598	1.401	1.823	<0.001
Rescue therapy	2.473	1.275	4.797	0.007
Bridge to recovery	4.937	3.526	6.913	<0.001
Other	1.492	0.479	4.651	0.490

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

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

Variables	HR	95% CI for HR Lower	Upper	p-value
Demographics				
Age (years)	1.027	1.024	1.030	<0.001
Sex (men vs. women)	0.969	0.897	1.047	0.425
BSA (m^2)	1.005	0.907	1.113	0.929
BMI (kg/m^2)	1.006	1.001	1.010	0.020
Ischemic etiology	1.347	1.265	1.434	<0.001
Atrial fibrillation	1.164	1.079	1.255	<0.001
Blood type				
O	*ref*	*ref*	*ref*	*ref*
A	1.140	1.064	1.222	<0.001
B	1.081	0.980	1.193	0.120
AB	1.121	0.951	1.321	0.174
INTERMACS class (1-3 vs. 4-7)	1.217	1.116	1.327	<0.001
IABP	1.214	1.135	1.299	<0.001
ECMO	1.707	1.517	1.921	<0.001
≥3 inotropic use	1.258	1.103	1.434	0.001
Laboratory				
Creatinine (mg/dL)	1.614	1.498	1.739	<0.001
BUN (mg/dL)	1.009	1.008	1.010	<0.001
AST (U/L)	1.001	1.000	1.001	<0.001
Total bilirubin (mg/dL)	1.106	1.067	1.147	<0.001
WBC ($_{x10}^{9}$/L)	1.000	0.999	1.000	0.393
Platelets ($_{x10}^{9}$/L)	0.999	0.998	0.999	<0.001
INR	1.161	1.093	1.233	<0.001
Albumin (g/dL)	0.716	0.680	0.754	<0.001
Hemoglobin (g/dL)	0.897	0.883	0.910	<0.001

Supplementary Table 2. *(continued)*

Variables	HR	95% CI for HR Lower	Upper	p-value
Hemodynamic				
Mean RA pressure (mmHg)	1.015	1.011	1.019	<0.001
Pulmonary artery wedge pressure (mmHg)	0.997	0.994	1.001	0.122
Systolic pulmonary artery pressure (mmHg)	1.000	0.998	1.002	0.909
Diastolic pulmonary artery pressure (mmHg)	0.995	0.991	0.998	0.004
Cardiac output (L/min)	1.032	1.006	1.060	0.017
Severe RV dysfunction	1.108	1.015	1.209	0.022
Severe LV dysfunction (<20%)	0.903	0.846	0.965	0.002
Moderate or severe tricuspid regurgitation	1.117	1.049	1.189	0.001
Moderate or severe mitral regurgitation	0.829	0.779	0.883	<0.001
Device strategy				
BTT	*ref*	*ref*	*ref*	*ref*
BTC	1.072	0.975	1.179	0.149
DT	1.541	1.420	1.672	<0.001
Rescue therapy	1.519	0.895	2.576	0.121
Bridge to recovery	2.335	1.763	3.091	<0.001
Other	0.743	0.278	1.984	0.553

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

Supplementary Table 3. Number of missing values

Demographics	
Age	0 (0.0)
Men	23 (0.2)
BSA	244 (1.6)
BMI	421 (2.8)
Ischemic etiology	415 (2.7)
Comorbidities	
CVA	415 (2.7)
DM	334 (2.2)
Current smoker	604 (4.0)
Dialysis	23 (0.2)
Current ICD therapy	1,969 (12.9)
History of CABG	1,898 (12.4)
Atrial fibrillation	642 (4.2)
NYHA-classification	1,252 (8.2)
INTERMACS classification	96 (0.6)

Supplementary Table 3. *(continued)*

IABP prior to LVAD surgery	387 (2.5)
ECMO prior to LVAD surgery	389 (2.5)
Ventilator prior to LVAD surgery	38 (0.2)
History of AoV replacement/repair	1,898 (12.4)
Laboratory	
Creatinine	1,317 (8.6)
BUN	403 (2.6)
AST	1,334 (8.7)
ALT	1,708 (11.2)
LDH	6,381 (41.8)
Total bilirubin	1,571 (10.3)
WBC	176 (1.2)
Platelets	179 (1.2)
INR	760 (5.0)
Albumin	1,725 (11.3)
Hemoglobin	305 (2.0)
Hemodynamics	
RA pressure	5,460 (35.8)
PCWP	4,774 (31.3)
Systolic PAP	2,524 (16.5)
Diastolic PAP	2,665 (17.5)
Cardiac output	3,790 (24.8)
Echocardiographic	
LVEF	11,176 (73.2)
RVEF	3,975 (26.0)
Mitral valve regurgitation	1,180 (7.7)
Tricuspid valve regurgitation	1,308 (8.6)
AoV regurgitation	2,174 (14.2)
LVEDD	3,145 (20.6)
Main LVAD strategy	3 (0.0)
Concomitant procedure	
Congenital surgery	0 (0.0)
Mitral valve surgery	0 (0.0)
Tricuspid valve surgery	0 (0.0)
Pulmonary valve surgery	0 (0.0)
RVAD surgery	1,750 (11.5)
Other concomitant surgery	0 (0.0)

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

Supplementary Table 4. Baseline and clinical characteristics stratified to AoV procedure in LVAD patients

	Overall population (n=15,267)	No AoV procedure (n=14,482)	AoV replacement (n=457)		AoV repair (n=328)	p-value
			Biological (n=386)	Mechanical (n=71)		
Demographics						
Age (years)	58.0 [49.0-66.0]	58.0 [48.0-66.0]	62.0 [53.8-69.0]	63.0 [53.0-69.0]	64.0 [57.0-69.0]	<0.001
Men	12,093 (79.3)	11,433 (79.1)	333 (86.3)	63 (91.3)	264 (80.5)	<0.001
BSA (m^2)	2.04 [1.85-2.25]	2.04 [1.86-2.25]	1.99 [1.82-2.18]	2.00 [1.87-2.20]	1.96 [1.81-2.16]	<0.001
BMI (kg/m^2)	27.4 [23.8-32.0]	27.5 [23.9-32.1]	26.2 [22.7-30.3]	26.1 [23.2-30.6]	25.1 [22.8-29.4]	<0.001
Ischemic etiology	5,721 (38.5)	5,451 (38.6)	121 (35.0)	26 (38.8)	123 (39.5)	0.571
Comorbidities						
CVA	655 (4.4)	621 (4.4)	20 (5.5)	1 (1.4)	13 (4.1)	0.450
DM	1,477 (9.9)	1,417 (10.0)	30 (8.0)	7 (9.9)	23 (7.0)	0.193
Current smoker	866 (5.9)	818 (5.9)	27 (7.6)	2 (2.9)	19 (5.8)	0.394
Dialysis	444 (2.9)	423 (2.9)	13 (3.4)	3 (4.2)	5 (1.5)	0.398
Current ICD therapy	10,392 (78.1)	9,860 (78.1)	229 (77.1)	50 (75.8)	253 (81.9)	0.594
History of CABG	2,544 (19.0)	2,415 (19.1)	56 (17.7)	12 (18.2)	61 (19.4)	0.936
Atrial fibrillation	3,125 (21.4)	2,953 (21.3)	77 (22.2)	23 (32.4)	72 (22.8)	0.124
NYHA-classification						
NYHA I/II	174 (1.2)	164 (1.2)	6 (1.7)	1 (1.4)	3 (1.0)	
NYHA III	2,690 (19.2)	2,558 (19.3)	67 (18.9)	12 (17.1)	53 (17.0)	0.918
NYHA IV	11,151 (79.6)	10,557 (79.5)	282 (79.4)	57 (81.4)	255 (82.0)	
INTERMACS classification						
INTERMACS 1	2,373 (15.6)	2,269 (15.8)	50 (13.1)	10 (14.5)	44 (13.4)	
INTERMACS 2	5,173 (34.1)	4,887 (34.0)	142 (37.1)	23 (33.3)	121 (36.9)	
INTERMACS 3	5,179 (34.1)	4,914 (34.1)	131 (34.2)	25 (36.2)	109 (33.2)	
INTERMACS 4	1,968 (13.0)	1,873 (13.0)	46 (12.0)	9 (13.0)	40 (12.2)	0.699
INTERMACS 5	315 (2.1)	296 (2.1)	7 (1.8)	2 (2.9)	10 (3.0)	
INTERMACS 6	95 (0.6)	86 (0.6)	6 (1.6)	0 (0.0)	3 (0.9)	
INTERMACS 7	68 (0.4)	66 (0.5)	1 (0.3)	0 (0.0)	1 (0.3)	

Supplementary Table 4. *(continued)*

	Overall population (n=15,267)	No AoV procedure (n=14,482)	AoV replacement (n=457)		AoV repair (n=328)	p-value
			Biological (n=386)	Mechanical (n=71)		
IABP prior to LVAD surgery	4,302 (28.9)	4,109 (29.1)	84 (23.0)	21 (29.6)	88 (26.8)	0.063
ECMO prior to LVAD surgery	891 (6.0)	853 (6.0)	14 (3.8)	4 (5.6)	20 (6.1)	0.359
Ventilator prior to LVAD surgery	1,934 (12.7)	1,845 (12.8)	42 (10.9)	6 (8.5)	41 (12.5)	0.503
History of AoV replacement/repair	396 (3.0)	282 (2.2)	71 (22.5)	14 (21.2)	29 (9.2)	<0.001
Laboratory						
Creatinine, mg/dL	1.20 [0.98-1.50]	1.20 [0.97-1.50]	1.25 [1.05-1.55]	1.30 [1.05-1.60]	1.20 [1.00-1.50]	0.008
BUN, mg/dL	25.0 [18.0-37.3]	25.0 [18.0-37.0]	29.0 [20.0-40.0]	31.0 [22.0-40.0]	26.0 [18.0-36.0]	<0.001
AST, U/L	29.0 [21.0-44.0]	29.0 [21.0-44.0]	30.0 [22.0-44.0]	33.0 [220-51.5]	30.0 [21.5-42.0]	0.342
ALT, U/L	29.0 [19.0-49.0]	29.0 [19.0-49.0]	29.0 [18.0-46.0]	27.0 [19.0-54.0]	29.0 [20.0-52.0]	0.910
LDH, (U/L)	279.0 [220.0-391.0]	279.0 [220.0-391.0]	292.0 [223.0-383.0]	283.0 [218.0-419.0]	276.5 [216.3-395.0]	0.902
Total bilirubin, mg/dL	1.0 [0.6-1.6]	1.0 [0.6-1.6]	1.1 [0.7-1.7]	1.2 [0.7-1.7]	1.1 [0.7-1.7]	0.022
WBC, $x10^9$/L	7.9 [6.3-10.2]	7.9 [6.3-10.2]	7.7 [6.1-9.8]	8.2 [6.4-10.0]	7.5 [6.0-10.4]	0.165
Platelets, $x10^9$/L	188.0 [142.0-242.0]	188.0 [142.0-242.0]	188.0 [133.8-232.0]	166.0 [131.0-236.0]	176.5 [131.3-226.0]	0.002
INR	1.2 [1.1-1.4]	1.2 [1.1-1.4]	1.3 [1.1-1.5]	1.2 [1.1-1.4]	1.2 [1.1-1.4]	0.001
Albumin, g/dL	3.5 [3.0-3.8]	3.5 [3.0-3.8]	3.4 [3.0-3.8]	3.5 [3.2-3.9]	3.4 [3.0-3.8]	0.353
Hemoglobin, g/dL	11.3 [9.8-12.8]	11.3 [9.8-12.8]	11.2 [9.9-12.6]	11.2 [9.8-12.6]	11.2 [9.7-12.5]	0.733
Hemodynamics						
RA pressure, mmHg	11.0 [7.0-16.0]	11.0 [7.0-16.0]	11.0 [7.0-17.0]	12.0 [8.8-15.3]	10.5 [7.0-15.0]	0.256
PCWP, mmHg	25.0 [19.0-31.0]	25.0 [19.0-31.0]	25.0 [19.0-31.5]	25.5 [21.8-31.3]	25.0 [19.0-32.0]	0.495
Systolic PAP, mmHg	50.0 [40.0-60.0]	50.0 [40.0-60.0]	51.0 [41.3-63.0]	53.5 [38.0-63.0]	50.0 [40.0-60.0]	0.031
Diastolic PAP, mmHg	25.0 [19.0-30.0]	25.0 [19.0-30.0]	25.0 [20.0-31.0]	27.0 [20.0-34.0]	24.0 [18.0-29.0]	0.055
Cardiac output, L/min	3.93 [3.14-4.80]	3.96 [3.15-4.80]	4.00 [3.28-4.79]	3.50 [2.80-4.66]	3.79 [3.00-4.55]	0.038

Supplementary Table 4. *(continued)*

	Overall population (n=15,267)	No AoV procedure (n=14,482)	AoV replacement (n=457)		AoV repair (n=328)	p-value
			Biological (n=386)	Mechanical (n=71)		
Echocardiographic						
LVEF						
≥40%	347 (8.5)	327 (8.5)	16 (15.2)	2 (10.0)	2 (1.8)	
30-39%	484 (11.8)	460 (11.9)	7 (6.7)	5 (25.0)	2 (10.7)	0.021
20-29%	3,260 (79.7)	3,067 (79.6)	82 (78.1)	13 (65.0)	98 (87.5)	
RVEF						
Normal	2,941 (26.0)	2,790 (26.1)	62 (22.8)	11 (20.4)	78 (28.4)	
Mild	3,272 (29.0)	3,086 (28.9)	91 (33.5)	17 (31.5)	78 (28.4)	0.634
Moderate	3,473 (30.8)	3,283 (30.7)	86 (31.6)	17 (31.5)	87 (31.6)	
Severe	1,606 (14.2)	1,532 (14.3)	33 (12.1)	9 (16.7)	32 (11.6)	
Mitral valve regurgitation						
None	1,070 (7.6)	1,021 (7.6)	29 (8.3)	3 (4.6)	17 (5.4)	
Mild	4,960 (35.2)	4,689 (35.1)	143 (41.1)	21 (32.3)	107 (34.3)	0.045
Moderate	4,689 (33.3)	4,431 (33.2)	116 (33.3)	22 (33.8)	120 (38.5)	
Severe	3,368 (23.9)	3,221 (24.1)	60 (17.2)	19 (29.2)	68 (21.8)	
Tricuspid valve regurgitation						
None	1,257 (9.0)	1,210 (9.1)	25 (7.2)	6 (8.7)	16 (5.1)	
Mild	6,865 (49.2)	6,491 (49.1)	172 (49.6)	35 (50.7)	167 (53.4)	0.277
Moderate	4,197 (30.1)	3,969 (30.0)	110 (31.7)	24 (34.8)	94 (30.0)	
Severe	1,640 (11.7)	1,560 (11.8)	40 (11.5)	4 (5.8)	36 (11.5)	
AoV regurgitation						
None	8,426 (64.4)	8,330 (67.2)	52 (15.3)	11 (19.0)	33 (10.9)	
Mild	4,084 (31.2)	3,747 (30.2)	153 (45.1)	29 (50.0)	155 (51.3)	<0.001
Moderate	492 (3.8)	270 (2.2)	102 (30.1)	17 (29.3)	103 (34.1)	
Severe	91 (0.7)	47 (0.4)	32 (9.4)	1 (1.7)	11 (3.6)	
LVEDD (mm)	68.0 [61.0-75.0]	68.0 [61.0-75.0]	70.0 [63.0-77.0]	69.0 [65.0-79.0]	68.0 [62.0-74.0]	0.021

Supplementary Table 4. *(continued)*

	Overall population (n=15,267)	No AoV procedure (n=14,482)	AoV replacement (n=457)		AoV repair (n=328)	p-value
			Biological (n=386)	Mechanical (n=71)		
Main LVAD strategy						
BTT	4,272 (28.0)	4,087 (28.2)	106 (27.5)	10 (14.1)	69 (21.0)	0.001
BTC	4,221 (27.7)	4,016 (27.7)	104 (26.9)	22 (31.0)	79 (24.1)	
Destination therapy	6,563 (43.0)	6,177 (42.7)	169 (43.8)	37 (52.1)	180 (54.9)	
Rescue therapy	125 (0.8)	122 (0.8)	2 (0.5)	1 (1.4)	0 (0.0)	
Bridge to recovery	55 (0.4)	51 (0.4)	3 (0.8)	1 (1.4)	0 (0.0)	
Other	28 (0.2)	26 (0.2)	2 (0.5)	0 (0.0)	0 (0.0)	
Concomitant procedure						
Congenital surgery	1,030 (6.7)	965 (6.7)	36 (9.3)	3 (4.2)	26 (7.9)	0.128
Mitral valve surgery	538 (3.5)	484 (3.3)	23 (6.0)	3 (4.2)	28 (8.5)	<0.001
Tricuspid valve surgery	533 (3.5)	486 (3.4)	25 (6.5)	1 (1.4)	21 (6.4)	<0.001
Pulmonary valve surgery	8 (0.1)	7 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0.334
RVAD surgery	99 (0.7)	90 (0.7)	6 (1.9)	2 (3.0)	1 (0.3)	0.009
Other concomitant surgery	2,732 (17.9)	2,584 (17.8)	66 (17.1)	13 (26.8)	63 (19.2)	0.224

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

Supplementary Table 5. Causes of late death in different INTERMACS class patients, stratified to AoV procedure in LVAD patients post-LVAD surgery

	Overall population (n=3,890)	No AoV procedure (n=3,657)	AoV replacement (n=143)	AoV repair (n=90)
INTERMACS class 1				
Device related	11 (1.5)	11 (1.6)	0 (0.0)	0 (0.0)
RV-failure	31 (4.3)	30 (4.4)	1 (4.8)	0 (0.0)
Withdrawal of support	74 (10.3)	72 (10.5)	2 (2.7)	0 (0.0)
Circulatory failure	123 (17.2)	115 (16.8)	3(14.3)	5 (41.7)
Multisystem Organ Failure	160 (22.3)	156 (22.8)	2 (9.5)	2 (16.7)
Neurological events	122 (17.0)	119 (17.4)	3 (14.3)	0 (0.0)
Major infection	66 (9.2)	62 (9.1)	2 (9.5)	2 (16.7)
Respiratory failure	26 (3.6)	26 (3.8)	0 (0.0)	0 (0.0)
Digestive/liver failure	5 (0.7)	5 (0.7)	0 (0.0)	0 (0.0)
Cancer	7 (1.0)	7 (1.0)	0 (0.0)	0 (0.0)
Hematologic failure	3 (0.4)	3 (0.4)	0 (0.0)	0 (0.0)
Other	88 (12.3)	77 (11.3)	8 (38.1)	3 (25.0)
INTERMACS class 2-3				
Device related	59 (2.3)	51 (2.1)	6 (6.1)	2 (3.0)
RV-failure	105 (4.1)	97 (4.1)	5 (5.1)	3 (4.5)
Withdrawal of support	297 (11.6)	283 (11.8)	7 (7.1)	7 (10.6)
Circulatory failure	440 (17.2)	417 (17.4)	6 (6.1)	17 (25.8)
Multisystem Organ Failure	426 (16.7)	388 (16.2)	24 (24.5)	14 (21.2)
Neurological events	507 (19.9)	481 (20.1)	18 (18.4)	8 (12.1)
Major infection	211 (8.3)	200 (8.4)	7 (7.1)	4 (6.1)
Respiratory failure	131 (5.1)	122 (5.1)	5 (5.1)	4 (6.1)
Digestive/liver failure	40 (1.6)	39 (1.6)	1 (1.0)	0 (0.0)
Cancer	28 (1.1)	27 (1.1)	1 (1.0)	0 (0.0)
Hematologic failure	16 (0.6)	12 (0.5)	4 (4.1)	0 (0.0)
Other	294 (11.5)	273 (11.4)	14 (14.3)	7 (10.6)
INTERMACS class 4 and higher				
Device related	12 (2.0)	11 (2.0)	1 (4.5)	0 (0.0)
RV-failure	31 (5.2)	31 (5.6)	0 (0.0)	0 (0.0)
Withdrawal of support	69 (11.7)	64 (11.5)	2 (9.1)	3 (25.0)
Circulatory failure	102 (17.2)	92 (16.5)	9 (40.9)	1 (8.3)
Multisystem Organ Failure	89 (15.0)	86 (15.4)	1 (4.5)	2 (16.7)
Neurological events	117 (19.8)	111 (19.9)	4 (18.2)	2 (16.7)
Major infection	44 (7.4)	41 (7.3)	1 (4.5)	2 (16.7)
Respiratory failure	48 (8.1)	46 (8.2)	1 (4.5)	1 (8.3)
Digestive/liver failure	5 (0.8)	5 (0.9)	0 (0.0)	0 (0.0)
Cancer	7 (1.2)	7 (1.3)	0 (0.0)	0 (0.0)
Hematologic failure	5 (0.8)	5 (0.9)	0 (0.0)	0 (0.0)
Other	63 (10.6)	59 (10.6)	3 (13.6)	1 (8.3)

LVAD, Left Ventricular Assist Device; AoV, Aortic Valve; RV, Right Ventricular

Supplementary Table 6. Baseline and clinical characteristics stratified to AoV procedure in LVAD patients with moderate to severe AoV regurgitation at baseline

	Overall population (n=583)	No AoV procedure (n=317)	AoV replacement (n=152)	AoV repair (n=114)	p-value
Demographics					
Age (years)	62.0 [53.0-69.0]	63.0 [53.5-69.0]	60.0 [52.0-66.0]	63.0 [56.8-69.0]	0.094
Men	477 (82.0)	260 (82.3)	131 (86.2)	864 (75.4)	0.077
BSA (m^2)	1.97 [1.80-2.16]	1.98 [1.78-2.18]	2.00 [1.83-2.19]	1.90 [1.80-2.09]	0.081
BMI (kg/m^2)	25.4 [22.5-29.5]	25.3 [22.2-29.4]	26.6 [23.3-30.0]	24.6 [22.0-27.7]	0.059
Ischemic etiology	213 (39.7)	124 (42.3)	44 (32.4)	45 (41.7)	0.130
Comorbidities					
CVA	17 (3.0)	9 (2.9)	5 (3.4)	3 (2.7)	0.930
DM	49 (8.5)	32 (10.1)	12 (8.2)	5 (4.4)	0.168
Current smoker	30 (5.3)	8 (2.6)	12 (8.2)	10 (8.8)	0.008
Dialysis	15 (2.6)	9 (2.8)	3 (2.0)	3 (2.6)	0.857
Current ICD therapy	391 (75.0)	208 (74.0)	95 (73.1)	88 (80.0)	0.608
History of CABG	108 (20.4)	67 (23.8)	23 (16.8)	18 (16.4)	0.125
Atrial fibrillation	3,125 (21.4)	2,953 (21.3)	100 (23.9)	72 (22.8)	0.350
NYHA-classification					
NYHA I/II	7 (1.3)	4 (1.3))	2 (1.4)	1 (1.0)	
NYHA III	98 (18.1)	59 (19.8)	23 (16.8)	16 (15.2)	0.804
NYHA IV	435 (80.6)	235 (78.9)	112 (81.8)	88 (83.8)	
INTERMACS classification					
INTERMACS 1	84 (14.6)	50 (16.0)	20 (13.3)	14 (12.3)	
INTERMACS 2	202 (35.1)	107 (34.3)	57 (38.0)	38 (33.3)	
INTERMACS 3	188 (32.6)	95 (30.4)	51 (34.0)	42 (36.8)	
INTERMACS 4	78 (13.5)	45 (14.4)	18 (12.0)	15 (13.2)	0.780
INTERMACS 5	17 (3.0)	9 (2.9)	3 (2.0)	5 (4.4)	
INTERMACS 6	4 (0.7)	3 (1.0)	1 (0.7)	0 (0.0)	
INTERMACS 7	3 (0.5)	3 (1.0)	0 (0.0)	0 (0.0)	

Supplementary Table 6. *(continued)*

	Overall population (n=583)	No AoV procedure (n=317)	AoV replacement (n=152)	AoV repair (n=114)	p-value
IABP prior to LVAD surgery	130 (22.7)	75 (23.7)	36 (25.4)	19 (16.7)	0.210
ECMO prior to LVAD surgery	28 (4.9)	17 (5.4)	4 (2.8)	7 (6.1)	0.395
Ventilator prior to LVAD surgery	66 (11.3)	36 (11.4)	15 (9.9)	15 (13.2)	0.704
History of AoV replacement/repair	27 (5.1)	13 (4.6)	13 (9.5)	1 (0.9)	0.008
Laboratory					
Creatinine, mg/dL	1.22 [1.00-1.53]	1.27 [1.00-1.59]	1.27 [1.05-1.56]	1.18 [1.00-1.50]	0.113
BUN, mg/dL	27.0 [20.0-42.0]	28.0 [20.0-43.0]	26.7 [19.0-37.5]	27.0 [19.0-35.3]	0.449
AST, U/L	31.0 [22.0-46.0]	30.0 [22.0-44.0]	33.0 [23.0-50.8]	33.0 [24.0-42.0]	0.293
ALT, U/L	30.0 [20.0-51.0]	28.5 [19.0-46.0]	32.5 [19.3-51.0]	33.0 [22.0-63.0]	0.113
LDH, (U/L)	287.0 [220.5-426.5]	309.0 [229.0-464.3]	280.5 [213.0-395.0]	260.0 [216.0-395.0]	0.207
Total bilirubin, mg/dL	1.1 [0.7-1.7]	1.1 [0.7-1.6]	1.1 [0.7-2.0]	1.2 [0.7-1.9]	0.548
WBC, $x10^9$/L	7.8 [6.1-10.3]	7.8 [6.1-10.4]	8.1 [6.5-9.8]	7.5 [5.7-10.6]	0.463
Platelets, $x10^9$/L	188.0 [141.0-241.0]	186.0 [136.5-252.0]	198.0 [153.0-231.5]	175.5 [141.0-229.3]	0.412
INR	1.2 [1.1-1.4]	1.2 [1.1-1.4]	1.2 [1.1-1.4]	1.2 [1.1-1.3]	0.234
Albumin, g/dL	3.4 [3.0-3.8]	3.3 [3.0-3.7]	3.4 [3.0-3.8]	3.5 [3.0-3.8]	0.270
Hemoglobin, g/dL	11.0 [9.7-12.6]	10.7 [9.4-12.3]	11.1 [10.0-12.8]	11.6 [10.0-12.9]	0.021
Hemodynamics					
RA pressure, mmHg	11.0 [7.0-17.0]	12.0 [7.0-18.0]	10.0 [7.0-15.0]	12.0 [6.0-15.0]	0.272
PCWP, mmHg	25.0 [18.5-32.0]	24.0 [18.0-31.0]	26.0 [20.0-32.0]	25.0 [18.0-31.0]	0.359
Systolic PAP, mmHg	50.0 [40.0-62.0]	50.0 [40.0-62.0]	50.0 [40.0-61.0]	50.0 [40.0-62.0]	1.000
Diastolic PAP, mmHg	25.0 [20.0-30.0]	25.0 [20.0-31.0]	24.0 [20.0-30.0]	24.0 [19.0-30.0]	0.844
Cardiac output, L/min	3.90 [3.00-4.70]	3.90 [3.00-4.60]	4.10 [3.13-4.80]	3.60 [2.80-4.80]	0.298

Supplementary Table 6. *(continued)*

	Overall population (n=583)	No AoV procedure (n=317)	AoV replacement (n=152)	AoV repair (n=114)	p-value
Echocardiographic					
LVEF					
≥40%	13 (7.0)	4 (4.4)	8 (15.0)	1 (2.5)	
30-39%	27 (14.6)	19 (20.7)	4 (7.5)	4 (10.0)	0.034
20-29%	145 (78.4)	69 (75.0)	41 (77.4)	35 (87.5)	
RVEF					
Normal	117 (26.3)	66 (27.4)	23 (27.4)	28 (28.9)	
Mild	131 (29.4)	66 (27.4)	43 (40.2)	22 (22.7)	0.182
Moderate	135 (30.3)	76 (31.5)	28 (26.2)	31 (32.0)	
Severe	62 (13.9)	33 (13.7)	13 (12.1)	16 (16.5)	
Mitral valve regurgitation					
None	24 (4.2)	11 (3.6)	8 (5.5)	5 (4.5)	
Mild	193 (34.0)	107 (34.6)	54 (37.0)	32 (28.6)	0.581
Moderate	211 (37.2)	114 (36.9)	55 (37.7)	42 (37.5)	
Severe	139 (24.5)	77 (24.9)	29 (19.9)	33 (29.5)	
Tricuspid valve regurgitation					
None	34 (6.1)	21 (7.1)	9 (6.1)	4 (3.5)	
Mild	238 (42.7)	114 (38.4)	66 (44.9)	58 (50.9)	0.178
Moderate	201 (36.0)	108 (36.4)	55 (37.4)	38 (33.3)	
Severe	85 (15.2)	54 (18.2)	17 (11.6)	14 (12.3)	
AoV regurgitation					
Moderate	493 (84.4)	270 (85.2)	119 (78.3)	103 (90.4)	0.023
Severe	91 (15.6)	47 (14.8)	33 (21.7)	11 (9.6)	
LVEDD (mm)	68.0 [62.0-75.0]	67.0 [60.1-74.0]	70.5 [63.0-78.0]	68.0 [63.0-75.0]	0.037

Supplementary Table 6. *(continued)*

	Overall population (n=583)	No AoV procedure (n=317)	AoV replacement (n=152)	AoV repair (n=114)	p-value
Main LVAD strategy					
BTT	135 (23.2)	73 (23.0)	40 (26.3)	22 (19.3)	0.373
BTC	160 (27.4)	86 (27.1)	43 (28.3)	31 (27.2)	
Destination therapy	278 (47.7)	150 (47.3)	67 (44.1)	61 (53.5)	
Rescue therapy	5 (0.9)	5 (1.6)	0 (0.0)	0 (0.0)	
Bridge to recovery	4 (0.7)	3 (0.9)	1 (0.7)	0 (0.0)	
Other	1 (0.2)	0 (0.0)	1 (0.7)	0 (0.0)	
Concomitant procedure					
Congenital surgery	40 (6.9)	13 (4.1)	12 (7.9)	15 (13.2)	0.004
Mitral valve surgery	28 (4.8)	10 (3.2)	10 (6.6)	8 (7.0)	0.125
Tricuspid valve surgery	21 (3.6)	9 (2.8)	7 (4.6)	5 (4.4)	0.556
Pulmonary valve surgery	1 (0.2)	0 (0.0)	1 (0.7)	0 (0.0)	0.242
RVAD surgery	5 (0.9)	1 (0.3)	4 (3.0)	0 (0.0)	0.017
Other concomitant surgery	163 (28.0)	108 (34.1)	38 (25.0)	17 (14.9)	<0.001

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

Supplementary Table 7. Causes of late death stratified to AoV procedure in LVAD patients post-LVAD surgery

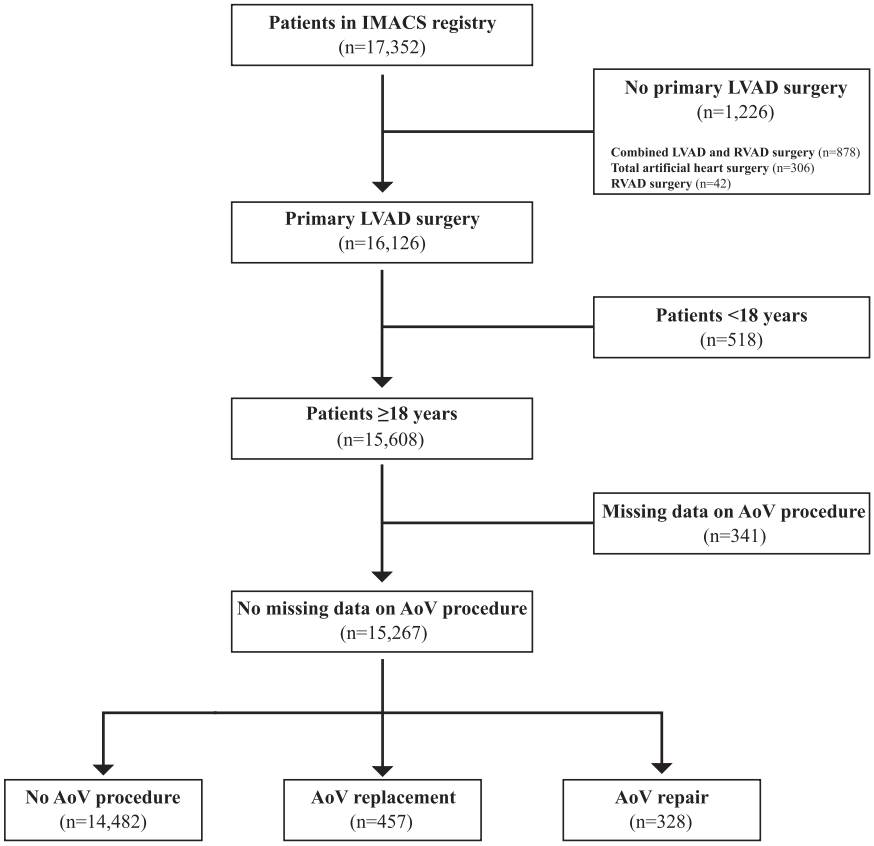
	Overall population (n=3,890)	No AoV procedure (n=3,657)	AoV replacement (n=143)	AoV repair (n=90)
Neurological events	748 (19.2)	713 (19.5)	25 (17.5)	10 (11.1)
Multisystem Organ Failure	681 (17.5)	635 (17.4)	28 (19.6)	18 (20.0)
Circulatory failure	688 (17.2)	627 (17.1)	18 (12.6)	23 (25.6)
Withdrawal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

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

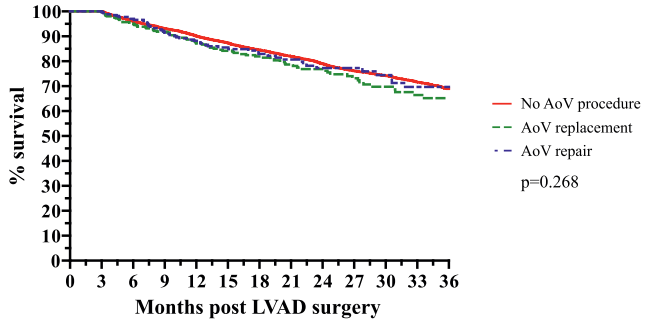
Supplementary Table 8. Causes of death in patients alive 90 days post-LVAD surgery

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

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



Supplementary Figure 1. Inclusion flowchart

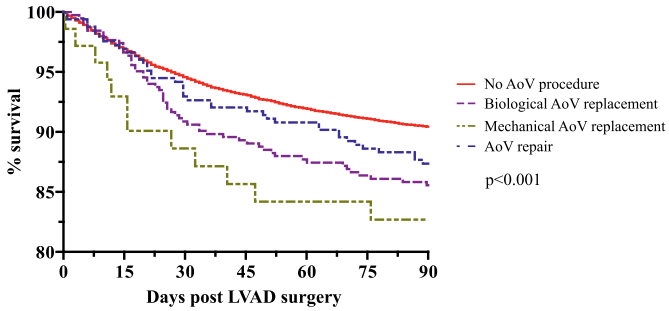


Numbers at risk

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

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

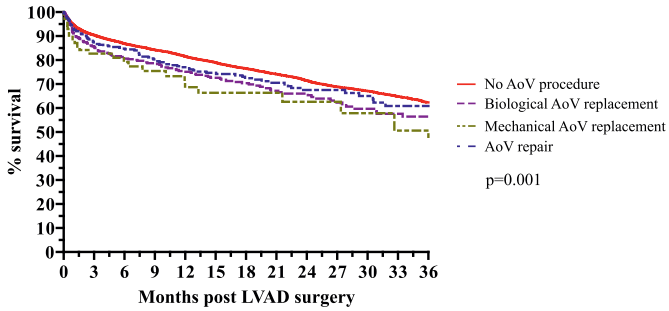
A



Numbers at risk

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

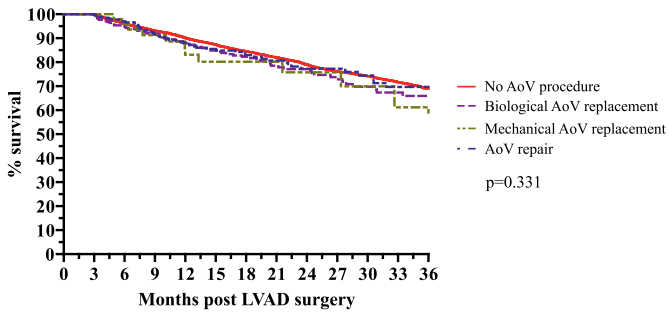
B



Numbers at risk

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

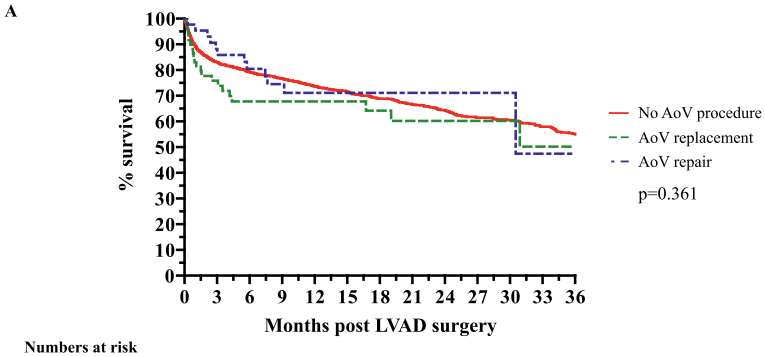
C



Numbers at risk

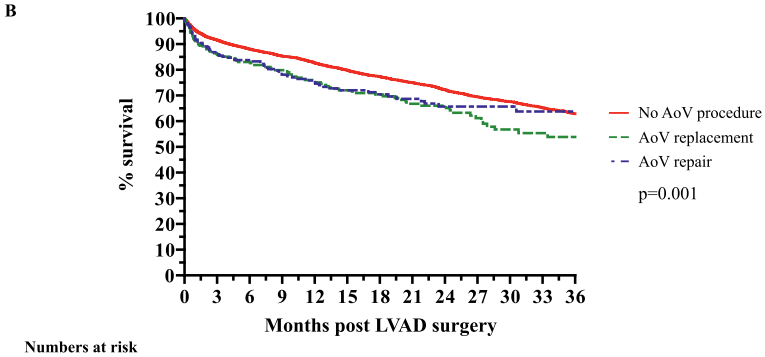
No AoV procedure	12,318	9,077	6,631	4,806	3,357	2,252
Biological AoV replacement	312	231	169	117	76	49
Mechanical AoV replacement	54	36	25	18	15	7
AoV repair	279	203	143	103	57	36

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



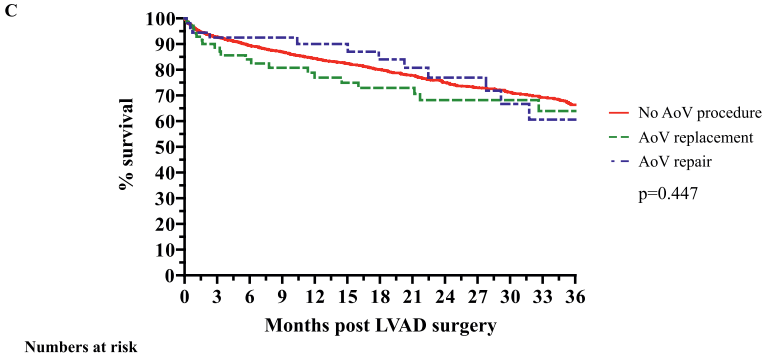
Numbers at risk

No AoV procedure	2,265	1,434	985	678	459	305	196
AoV replacement	61	29	22	16	11	6	4
AoV repair	44	28	16	9	5	2	1



Numbers at risk

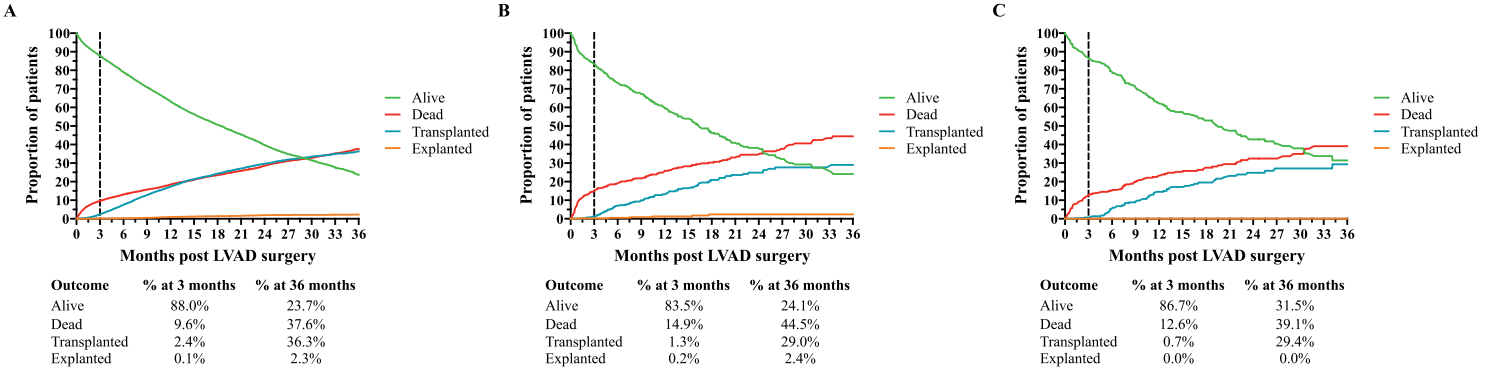
No AoV procedure	9,800	7,274	5,328	3,846	2,714	1,864	1,155
AoV replacement	321	221	160	111	75	43	29
AoV repair	230	175	124	88	53	35	17



Numbers at risk

No AoV procedure	2,321	1,812	1,410	1,092	825	603	406
AoV replacement	71	52	39	34	26	17	13
AoV repair	54	39	33	28	20	12	7

Supplementary Figure 4. Late survival in patients with **A** INTERMACS class 1, **B** INTERMACS class 2 or 3, and **C** INTERMACS class 4 or higher at baseline, stratified to no AoV procedure, AoV replacement and AoV repair.

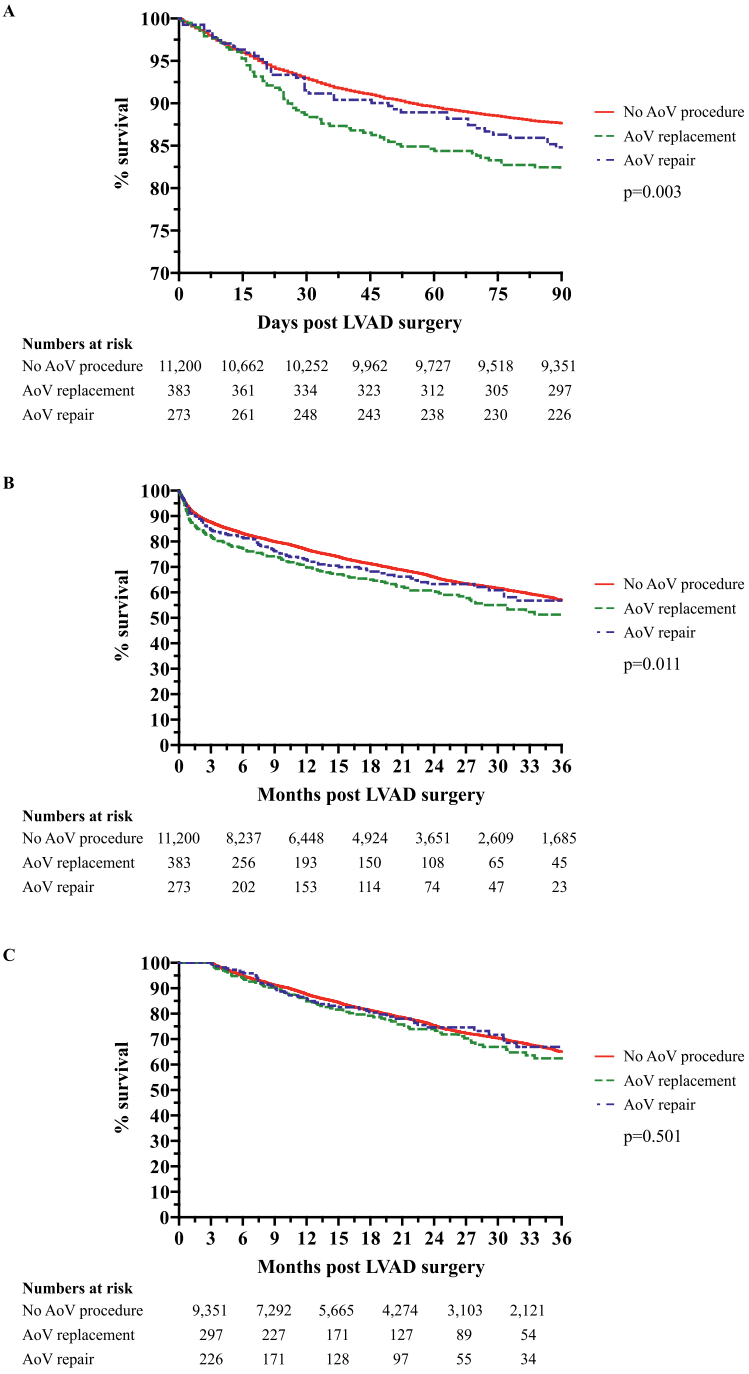


Outcome	% at 3 months	% at 36 months
Alive	88.0%	23.7%
Dead	9.6%	37.6%
Transplanted	2.4%	36.3%
Explanted	0.1%	2.3%

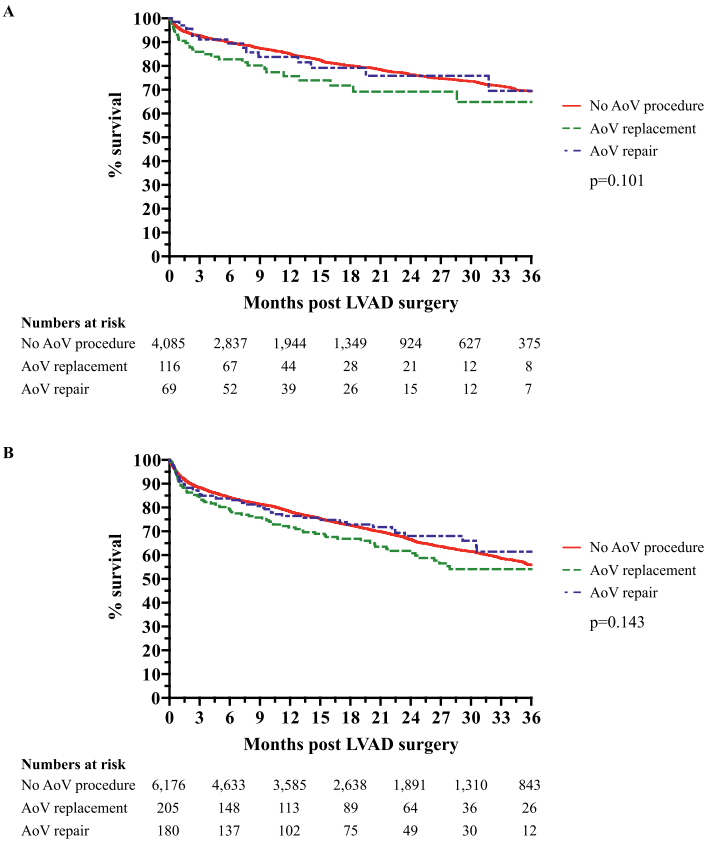
Outcome	% at 3 months	% at 36 months
Alive	83.5%	24.1%
Dead	14.9%	44.5%
Transplanted	1.3%	29.0%
Explanted	0.2%	2.4%

Outcome	% at 3 months	% at 36 months
Alive	86.7%	31.5%
Dead	12.6%	39.1%
Transplanted	0.7%	29.4%
Explanted	0.0%	0.0%

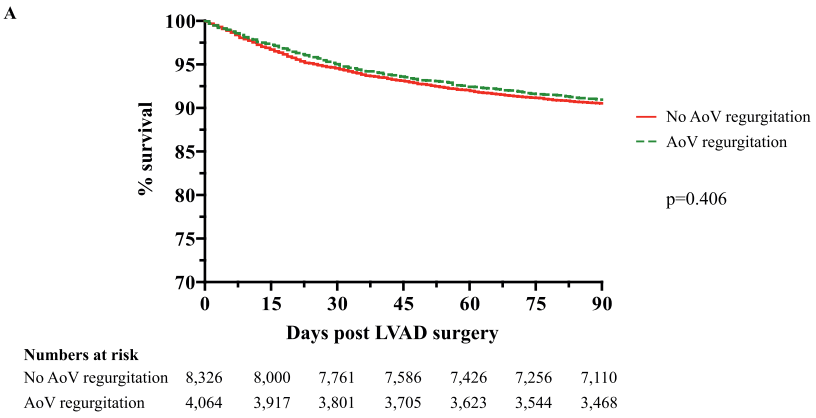
Supplementary Figure 5. Competing outcomes for patients with **A** no AoV procedure, **B** AoV replacement, and **C** AoV repair



Supplementary Figure 6. A Early, **B** late, and **C** conditional survival in patients who did not proceed towards heart transplantation, stratified to no AoV procedure, AoV replacement and AoV repair.

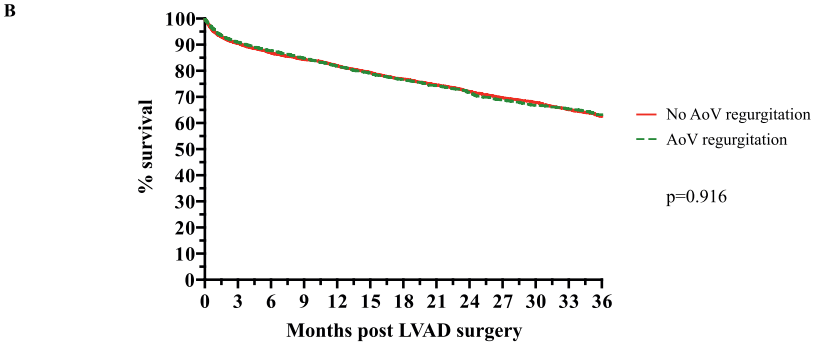


Supplementary Figure 7. Late survival in patients **A** with an LVAD as bridge to transplantation and, **B** an LVAD as destination therapy, stratified to no AoV procedure, AoV replacement and AoV repair.



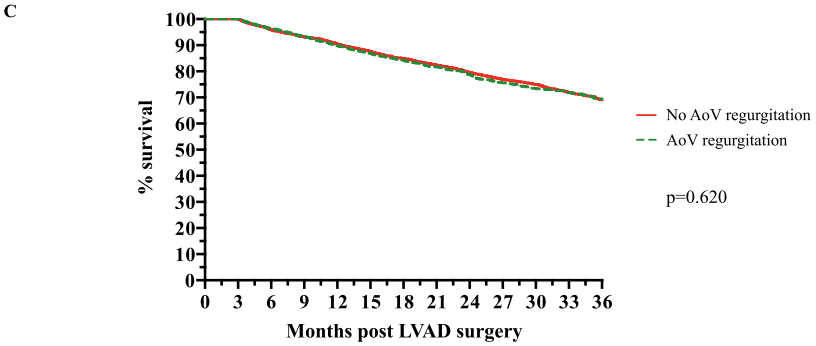
Numbers at risk

No AoV regurgitation	8,326	8,000	7,761	7,586	7,426	7,256	7,110
AoV regurgitation	4,064	3,917	3,801	3,705	3,623	3,544	3,468



Numbers at risk

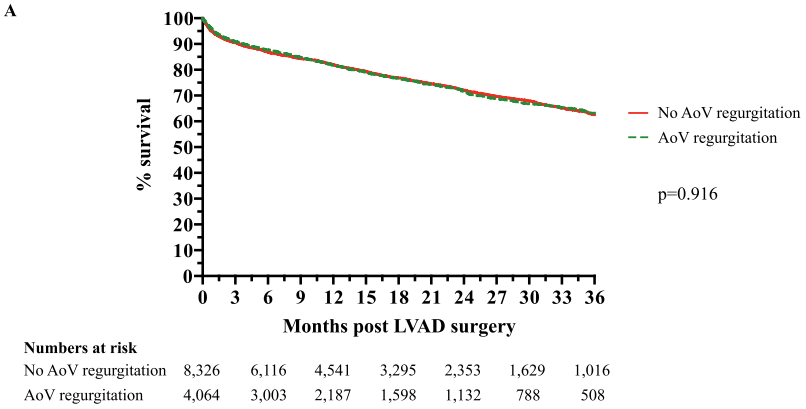
No AoV regurgitation	8,326	6,115	4,541	3,295	2,353	1,629	1,016
AoV regurgitation	4,064	3,003	2,187	1,598	1,132	788	508



Numbers at risk

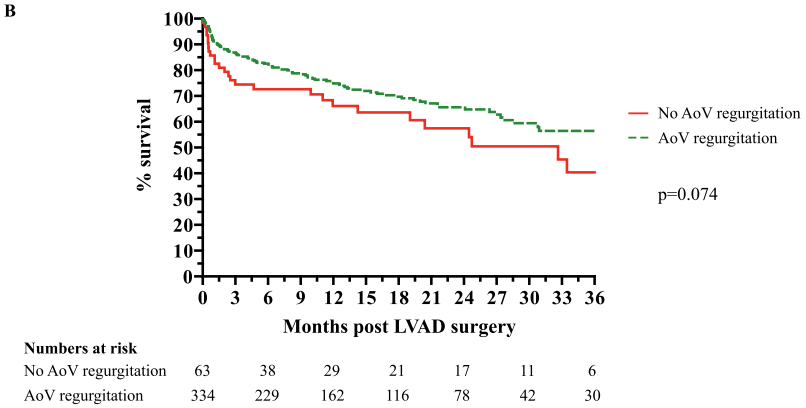
No AoV regurgitation	7,110	5,290	3,880	2,813	1,971	1,300
AoV regurgitation	3,468	2,550	1,869	1,348	943	633

Supplementary Figure 8. A Early, **B** late, and **C** conditional survival in patients without a concomitant AoV procedure, stratified to no AR and AR at baseline.



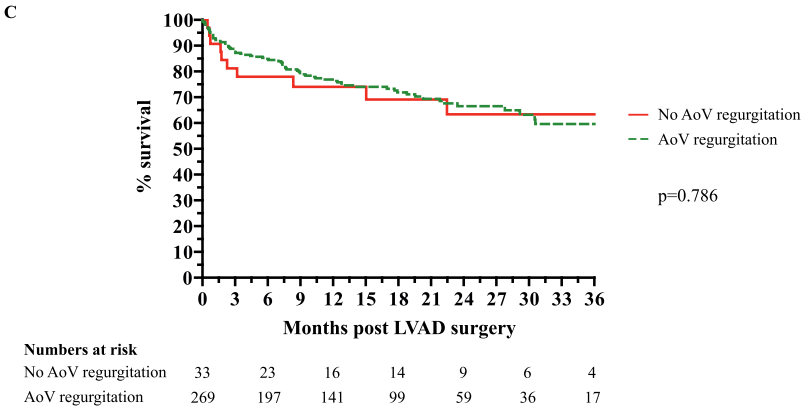
Numbers at risk

No AoV regurgitation	8,326	6,116	4,541	3,295	2,353	1,629	1,016
AoV regurgitation	4,064	3,003	2,187	1,598	1,132	788	508



Numbers at risk

No AoV regurgitation	63	38	29	21	17	11	6
AoV regurgitation	334	229	162	116	78	42	30



Numbers at risk

No AoV regurgitation	33	23	16	14	9	6	4
AoV regurgitation	269	197	141	99	59	36	17

Supplementary Figure 9. Late survival in patients **A** without AoV procedure, **B** with AoV replacement, and **C** with AoV repair, stratified to no AR and AR at baseline.

23

Rate of thromboembolic and bleeding events in patients with concomitant aortic valve surgery and left ventricular assist device implantation: an analysis of the IMACS database

Veenis JF*, Yalcin YC*, Brugts JJ, Antonides CFJ, Veen KM, Muslem R, Bekkers JA, Gustafsson F, Tedford RJ, Bogers AJJC, Caliskan K
* Equal contributions

Under embargo

Submitted

24

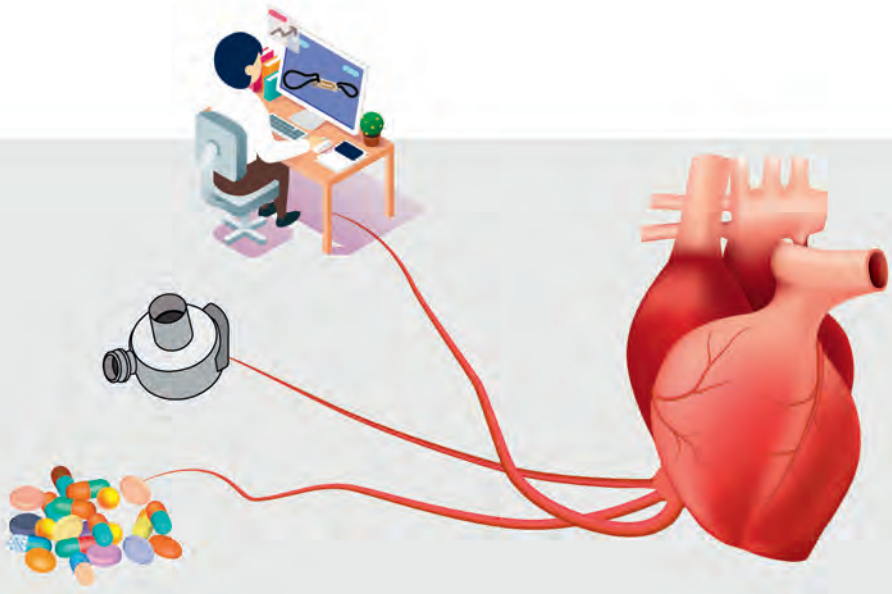
Prevalence of iron deficiency and iron administration in LVAD and heart transplantation patients

Veenis JF, Radhoe SP, Roest S, Caliskan K, Constantinescu AA, Manintveld OC, Brugts JJ

Under embargo

Submitted

E



Epilogue

Chapter 25 - Summary and general discussion

Dutch summary (Nederlandse samenvatting)

List of publications

PhD portofolio

About the author

Acknowledgements (Dankwoord)

25

Summary and general discussion

Summary

Nowadays, heart failure (HF) management has become complex and includes a combination of various pharmacological drugs, lifestyle interventions, (remotely) monitoring strategies, and invasive treatment options, including valvular interventions, heart transplantation and left ventricular assist device (LVAD) surgery. Although HF care has significantly improved over the last decades, many challenges still need to be addressed to improve and optimize the care for the rapidly growing HF population. Therefore, this thesis is focused on the quality of chronic HF care in a real-world large contemporary study in the Netherlands as well as quality of care in advanced HF care for LVAD patients with the aim to improve overall HF and LVAD management. Additionally, we have investigated a new strategy of remote hemodynamic monitoring of chronic HF and LVAD patients.

Part A – Assess the current quality of heart failure care in The Netherlands and identify patient groups in which heart failure care could be optimized

In the first part of this thesis, we aimed to provide insight into the quality of HF care provided by the outpatient HF clinics in The Netherlands. By assessing the adherence to the pharmacological recommendations made in the European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic HF, a better understanding of the quality of care could be made. In addition, we investigated the quality of HF care in specific subgroups of chronic HF patients to differentiate where HF care needs to improve. The *chronisch hartfalen ESC-richtlijn cardiologische praktijk kwaliteitsproject hartfalen* (CHECK-HF) registry contains detailed information on patient characteristics, prescription rates and prescribed dosages of beta-blockers, renin-angiotensin system (RAS) inhibitors, and mineralocorticoid receptor antagonists (MRAs), in 10910 Dutch chronic HF patients included from the outpatient clinics from 34 Dutch centers, between 2013 and 2016. Overall, 8360 patients diagnosed with HF with reduced ejection fraction (HFrEF) where included, while 2550 patients were diagnosed with HF with preserved ejection fraction (HFpEF). Several factors makes the CHECK-HF registry to an unique HF research project. Firstly, approximately half of all centers with an outpatient HF clinic in The Netherlands included patients in this registry. Additionally, data obtained in the registry was collected by the local HF teams and were based on recent patient visits and patient records. Therefore, the data in the CHECK-HF registry truly reflects the current status of HF care at Dutch outpatient clinics. A graphical overview of the prescription rates of HF medication in the different subgroups is provided in Figure 1.

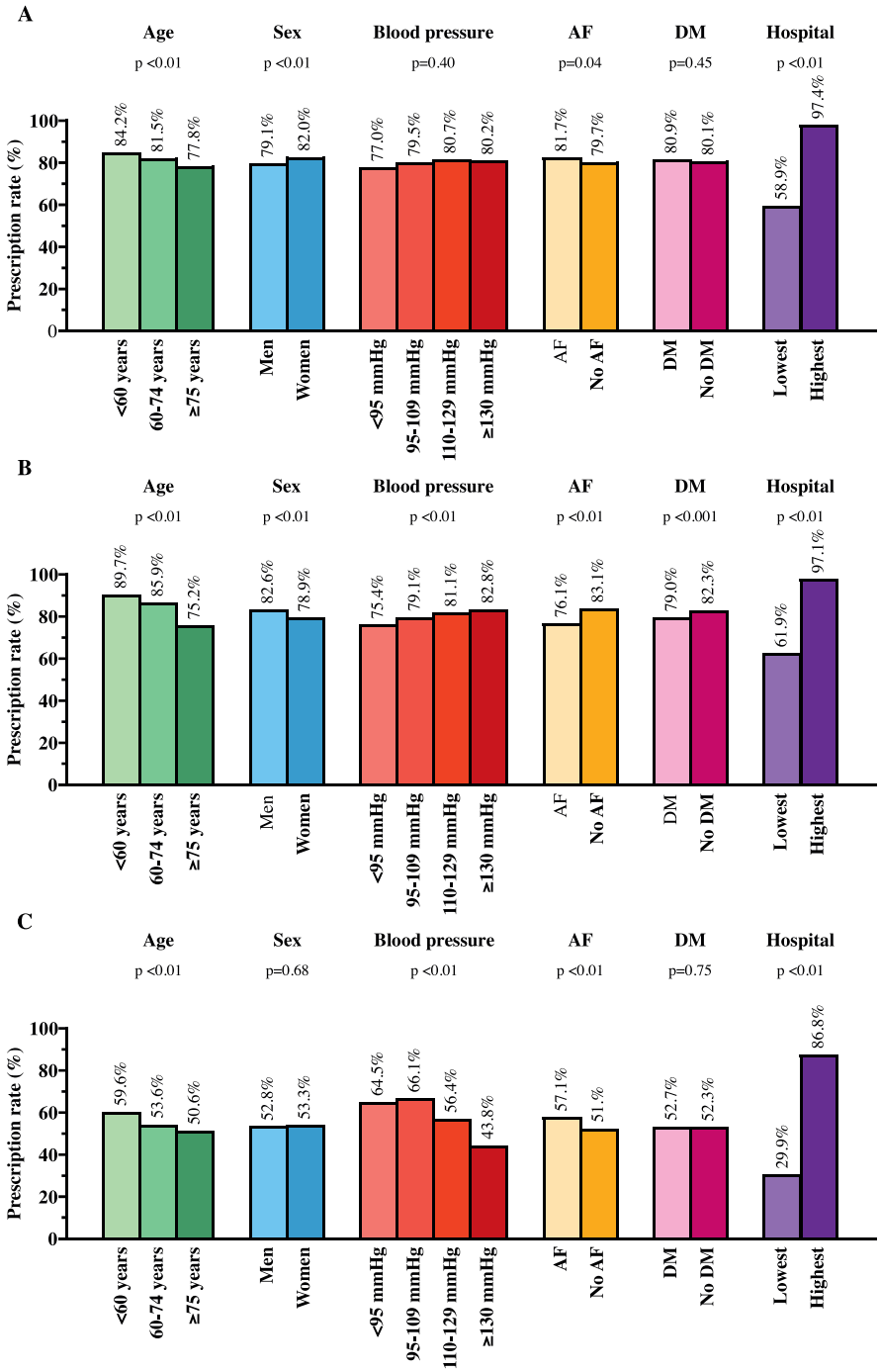


Figure 1. Summary of differences in prescription rates in **A** beta-blockers, **B** RAS-inhibitors and **C** MRA's between subgroups at Dutch outpatient heart failure clinics

In **Chapter 2**, the age-related treatment differences in HFrEF patients are described. A clear relation between an increase in age and a decrease in guideline adherence was observed. The observed differences in guideline-adherence could not fully be explained by differences in baseline characteristics, such as the New York heart association (NYHA) classification or the presence of comorbidities. Although elderly HF patients were less likely to receive the guideline-recommended therapy, even the majority of the very elderly HFrEF patients, aged ≥80 years (octogenarian), still received two or more of the guideline-recommended HF drugs, but not at the recommended dose, as was investigated in **Charter 3**.

Only small differences in the treatment of chronic HF between men and women were observed, which partially could be explained by observed differences in baseline characteristics and comorbidities, as shown in **Chapter 4**. Additionally, the potential impact of implementing a hypothetical sex-specific target dose for beta-blockers and RAS-inhibitors for women, at 50% of the guideline-recommended target has been investigated. When these sex-specific target dose would be implemented, more women would be considered to be treated optimally. Additionally, according to these hypothetical sex-specific target doses, a significant proportion of the female HFrEF patients might be overdosed which might not result in additional treatment benefit.

In **Chapters 5, 6, and 7**, effects of hypertension, atrial fibrillation, and diabetes mellitus (all frequent comorbidities in HF patients) on the guideline-adherence have been described. A large proportion of the HFrEF patients included in the CHECK-HF registry had a systolic blood pressure of 130 mmHg or higher. Guideline-recommended HF drugs, as well as triple HF therapy, were more often prescribed to patients with lower systolic blood pressure, however, at the expense of lower prescribed dosages. In contrast, the guideline adherence was lower in patients with a systolic blood pressure of ≥130 mmHg. Atrial fibrillation was a common comorbidity at the Dutch outpatient HF clinics and significantly affected the prescribed HF treatment. Patients with atrial fibrillation were frequently treated with the guideline-recommended drugs. Small, but significant differences in the prescribed HF therapy was observed between diabetic and non-diabetic HF patients, even after adjustments for differences in baseline characteristics and other comorbidities. Additionally, a considerable proportion of this Dutch HF population would be eligible for the newly introduced sodium-glucose cotransporter-2 (SGLT-2) inhibitor, based on the eligibility criteria currently used in the clinical trials.

The HF care at Dutch outpatient clinics has been compared to the HF care provided at outpatient clinics in the United States of America (USA), analyzed in the Change the Management of Patients with Heart Failure (CHAMP-HF) registry, in both **Chapter 5 and 7**. As shown, both the prescription rate as well as the number of patients that received the target dose was higher in The Netherlands than in the USA HF population.

Chapter 8 highlights the differences in HF population and treatment between different HF outpatient clinics in The Netherlands. The observed differences in patient demographics could not fully explain the observed differences in prescription rates and prescribed dosages, which is a signal that improvements still can be made in guideline adherence.

A large proportion of patients in the CHECK-HF registry were diagnosed with HFpEF, and their clinical profile and medical management have been investigated in **Chapter 9**. Although no evidence-based treatment exists for HFpEF patients, many received drugs that are indicated for HFrEF patients. These drugs were most likely prescribed for the treatment of comorbidities, which were common in HFpEF patients. Additionally, HFrEF medication might have been prescribed to HFpEF patients for lack of an alternative.

In conclusion, the results from the CHECK-HF registry provide a unique insight into the HF management at Dutch outpatient clinics. Many HF patients received guideline-recommended HF therapy, although the prescribed dosages were lower than recommended. Additionally, we have identified several specific patient categories, including elderly and patients with comorbidities such as hypertension, in whom the HF care could be optimized further.

It must be acknowledged that, due to the cross-sectional design of the CHECK-HF registry, no causal interference could be tested. Additionally, as clinical outcomes were not registered, we were unable to investigate to what extent survival in this population was affected by not adhering to the guideline-recommended treatment. The strengths of the CHECK-HF registry lies in its large scale, reflecting the real-world practice at Dutch outpatient clinics. These results provide new insight into the contemporary treatment of HF patients in a real-world setting. The findings demonstrated are very informative for the clinicians treating HF patients, since they provide new insight into the guideline-adherence and identifies specific patient groups in whom guideline adherence is lower compared to other patient groups.

Part B – Assess the impact of remote hemodynamic monitoring in chronic heart failure patients

In the second part of this thesis, remote monitoring strategies, specifically remote hemodynamic monitoring, in chronic HF patients, was investigated.

Chapter 10 provides an up-to-date overview of the currently available literature on remote monitoring strategies in chronic HF patients. Several non-invasive remote monitoring strategies, ranging from simple single variable up to very complex and intensive multivariable strategies, have been proposed and investigated by multiple large multicenter prospective studies, randomized controlled trials, and real-world registries over the recent decades. Overall, a modest beneficial effect on all-cause mortality and HF-related hospitalizations was observed in non-invasive monitoring strategies. The positive effect was primarily observed in more complex strategies, monitoring multiple variables non-invasively. Remote monitoring using implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) devices failed to reduce mortality or hospitalization rates in chronic HF patients. Remote hemodynamic monitoring can detect a rise in cardiac filling pressures weeks before an episode of exacerbation of HF. The CardioMEMS device, allowing for pulmonary artery pressure monitoring, appears to be the most promising remote hemodynamic monitoring device currently available and has been proven to be safe and effective in preventing HF-related hospitalizations in both HFrEF and HFpEF patients.

The Dutch hemodynamic monitoring in heart failure (MONITOR HF) Trial aims to evaluate the improvement in quality of life, reduction of HF hospitalizations and the cost-effectiveness of CardioMEMS remote monitoring on top of standard care in The Netherlands. **Chapter 11** describes the design of this randomized control trial.

The optimal time of day to monitor the pulmonary artery pressure using the CardioMEMS device has been described in **Chapter 12**. The variability of measurements was the lowest early in the morning, making this the most ideal moment to monitor the pulmonary artery pressures.

Remote hemodynamic monitoring can provide unique and additional insight in patient management and the effects of regular therapies. As illustrated by the case described in **Chapter 13**, the hemodynamic effects of valvular interventions, such as the MitraClip, can be safely and effectively monitored by the CardioMEMS system.

In conclusion, many remote monitoring strategies in chronic HF patients have been investigated. Remote hemodynamic monitoring using the CardioMEMS device appears to be the most promising remote hemodynamic monitoring strategy in chronic HF patients. Additionally, the remote hemodynamic feedback has the potential to be used in other patient groups or indications as well.

Part C –Determine the safety and feasibility of remote hemodynamic monitoring in left ventricular assist device patients

In the third part of this thesis, we have investigated the safety and feasibility of remote hemodynamic monitoring in end-stage HF patients who transitioned towards LVAD.

A complete overview of all available literature on monitoring strategies in LVAD patients has been provided in **Chapter 14**. Several potential remote monitoring strategies have been proposed and assessed. Although these developments are encouraging, further development is necessary before they can be used for remote LVAD management. Combining remote hemodynamic monitoring using the CardioMEMS system with LVAD support could be the next step forward in remote LVAD management.

Chapter 15 describes the trends over time of the pulmonary artery pressures of a patient with 'fixed' pulmonary hypertension on LVAD support. As shown, LVAD support can be used to reverse so-called 'fixed' pulmonary artery hypertension. The CardioMEMS system allows for a save and adequate remote monitoring of this process, revealing previously unknown information of pulmonary artery pressure and treatment effects.

The safety and feasibility of pulmonary artery pressure guided treatment, using the CardioMEMS system, in patients who proceeds towards an LVAD has been tested in the hemodynamic guidance with CardioMEMS in patients with a left ventricular assist device (HEMO-VAD) pilot study, which design has been described in **Chapter 16**.

In **Chapter 17**, the short-term effects of remote hemodynamic monitoring in LVAD patients have been investigated. No CardioMEMS device-related safety issues occurred during the first three months post-LVAD surgery. Patients without the ability to normalize the mean pulmonary artery pressure (mPAP) shortly prior to LVAD surgery identifies a group of patients who were at a very high risk of all-cause mortality or LVAD-related complications, such as acute kidney injury or right ventricular failure. Additionally, the quality of life of patients without the ability to normalize their mPAPs

increases significantly less compared to patients who could be hemodynamically optimized shortly prior to LVAD surgery.

Chapter 18 highlights the long-term safety of remote hemodynamic monitoring using the CardioMEMS device in LVAD patients, with no occurrence of device-related complications or failures during the entire one-year follow-up. Additionally, all-cause mortality, LVAD-related adverse events, and all-cause hospitalizations occurred less often in patients who had normalization of their mPAP shortly prior to LVAD surgery. The quality of life increased in all patients post-LVAD surgery. However, the increase was larger and sustained better in patients who were able to normalize their mPAPs.

We conclude that remote monitoring of LVAD patients could aid clinicians in optimizing LVAD management. Remote hemodynamic monitoring using the CardioMEMS device can safely be used in LVAD patients. The additional hemodynamic feedback provided by this system can be used as preoperative optimization of hemodynamics, as a risk predictor for worse clinical outcome, and for outpatient remote monitoring and management.

Part D – Optimizing left ventricular assist device management

In the last part of this thesis we have studied these LVAD-related challenges: the effectiveness of a cardiac implantable electronic device with a defibrillator function (CIED-D, consisted of ICD and CRT with defibrillator function) therapy during LVAD support, the impact of age and sex on LVAD outcomes, concomitant aortic valve replacement during LVAD surgery, and iron deficiency.

In **Chapter 19**, we investigated whether carrying an active CIED-D in LVAD patients was associated with improved outcomes within the observational postgraduate course in heart failure ventricular assist device (PCHF-VAD) registry. The PCHF-VAD registry is an observational study, including continuous-flow LVAD patients from 12 European HF tertiary referral centers. An active CIED-D in patients with LVAD support was associated with reduced all-cause mortality. No significant differences were observed in the HF-related hospitalization rates, the number of device-related infections requiring systemic antibiotics, or major bleeding events.

Chapter 20 and 21 provides detailed analyses of the age- and sex-related impact on LVAD outcomes and management, assessed within continuous flow LVAD patients included in the PCHF-VAD registry. An increase in age was independently associated with an increased risk of all-cause mortality. Additionally, elderly LVAD patients were

at a higher risk for hemocompatibility related complications and had more often new onset of atrial fibrillation or flutter. In contrast, elderly LVAD patients had a significantly lower risk of device-related infection requiring systemic antibiotics.

LVAD therapy was significantly less often utilized in women. Although women who underwent LVAD surgery were in a more clinical ill and unstable condition, no survival differences between men and women were observed. In contrast, women were more often weaned from LVAD support.

We have investigated the effects of concomitant aortic valve procedure during LVAD surgery in detail using the international society of heart and lung transplantation mechanically assisted circulatory support (IMACS) registry. In **Chapter 22**, the short- and long-term survival of patients with concomitant aortic valve procedures and LVAD surgery has been studied. In LVAD patients, concomitant aortic valve surgery was an independent predictor of both early and late mortality. Interestingly, the survival rates of patients who were diagnosed with mild aortic valve regurgitation were negatively impacted by concomitant aortic valve replacement. In contrast, in patients with moderate-to-severe aortic valve regurgitation, no survival differences were observed between patients with or without a concomitant aortic valve procedure.

In order to provide additional insight into the risks of concomitant aortic procedures in LVAD patients, the association with hemocompatibility related complications have been assessed in **Chapter 23**. No association between concomitant aortic valve replacement and an increased rate of thromboembolic events was observed. In contrast, concomitant aortic valve surgery was an independent risk factor for major bleeding events post-LVAD surgery.

The prevalence of iron deficiency in LVAD and heart transplantation patients has been described in **Chapter 24**. Although the guidelines recommend the regular screening of chronic HF patients for iron deficiency, not all advanced HF patients were screened for iron deficiency in the year prior to LVAD surgery or heart transplantation. The prevalence of iron deficiency was very high prior to LVAD surgery or heart transplantation and increased even further post-surgery. The majority of patients with an iron deficiency received iron administration.

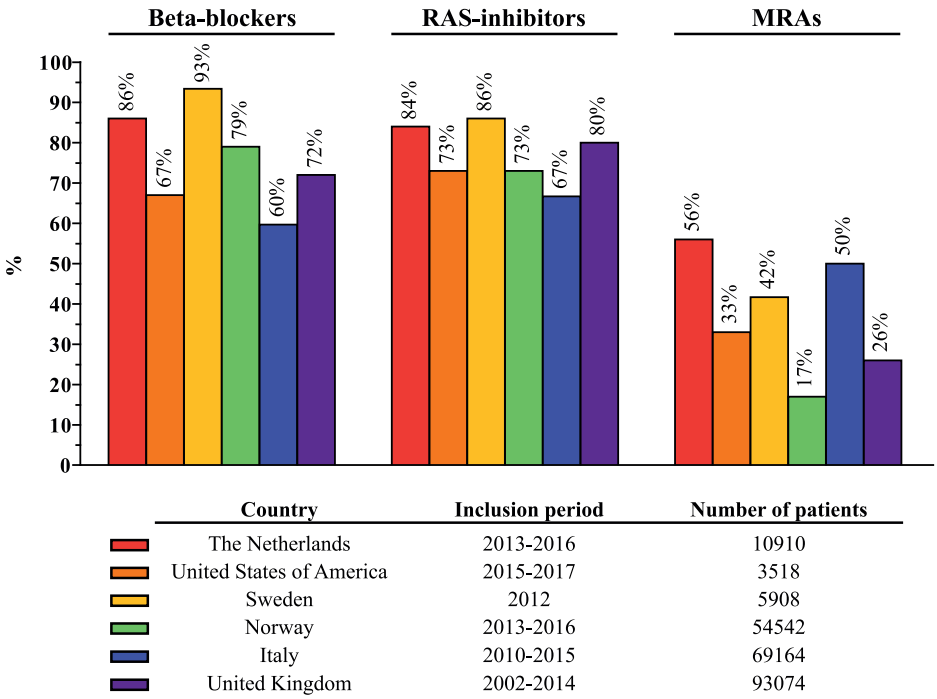
General discussion and future perspectives

Quality of heart failure care in The Netherlands; the importance of registries

Assessing the quality of care is an old concept, firstly introduced in the beginning of the 20th century. Since the 1980's more universal methods and definitions have been introduced. [1] The degree to which the provided health care increases the likelihood of desired health outcomes in a manner consistent with current professional knowledge is a frequently used definition for the quality of care. [2] Prescribing and optimizing the guideline-recommended therapy in chronic heart failure (HF) patients significantly improves mortality, morbidity, and quality of life. [3] Therefore, the level of adherence to these guidelines, including the prescription rates and prescribed dosages, could be used as a parameter for the quality of HF care.

As shown in this thesis, many Dutch HF patients with a reduced ejection fraction (HFrEF) seen at the outpatient clinics received the guideline-recommended HF drugs, indicating that Dutch outpatient clinics provide a high quality of HF care. We believe that the quality of care should not only be measured by the adherence to the guidelines but should also be compared to other countries. The prescription rates of HF drugs in HFrEF patients in other Western countries are shown in Figure 2. [4-8] As shown, the prescription rates at Dutch outpatient HF clinics were very high, compared to counties such as Italy, Norway, United Kingdom and the United States of America (USA), and similar to Sweden. These results indicate that the quality of HF care was very high, especially compared to other Western countries.

Multiple factors could influence the prescription rates between countries. First of all, we should not underestimate the crucial role of dedicated HF nurses. Organizing the HF care in a specialized setting, with a coordinating role for the HF nurses, leads to better guideline adherence, as well as a better up-titration of the prescribed dosages. [9-11] Additionally, the accessibility to specialized HF care might have differed. In general, health care insurance is universally carried in all European countries in contrast to the USA. This might have led to lower availability of HF care and access to prescribed HF medication in the USA. Finally, it has been suggested that American treating physicians might overemphasize the possibility and the risks of side effects of HF drugs. [12] This could have resulted in lower prescription rates in the USA.



Country	Inclusion period	Number of patients
The Netherlands	2013-2016	10910
United States of America	2015-2017	3518
Sweden	2012	5908
Norway	2013-2016	54542
Italy	2010-2015	69164
United Kingdom	2002-2014	93074

Figure 2. Prescription rates of HF drugs in several Western countries

Areas to optimize and individualize chronic heart failure care in The Netherlands

Although the quality of HF care in The Netherlands is outstanding, several areas of HF management could be optimized further. First of all, similar to other countries, the prescribed dosages of HF drugs are lower than the guideline-recommended target dosages. [3, 13] Since all HF drugs have a dose-dependent effect on the survival, prescribing the target dose or maximum tolerated dose is of great importance. [14, 15] Multiple strategies to further up-titrate HF dosages have been proposed, including medication up-titration protocols, regular monitoring, feedback of benchmarked clinical indicators, and involvement of HF nurses in the up-titration of HF drugs. [13] However, the ideal up-titration strategy is still up for debate, and additional research to determine the best approach is urgently needed.

Secondly, the HF therapy in elderly HF patients, and specifically in octogenarians, should be further improved. This thesis demonstrates that both the prescription rates and prescribed dosages decreased with an increase in age in The Netherlands.

Several age-related factors have been associated with suboptimal HF therapy, such as frailty, cognitive impairment, polypharmacy as well as frequent comorbidities. [16] However, using a slow up-titrating approach, with a close monitoring and awareness of comorbidities and frailty could result in an optimized and individualized therapy, even in octogenarian HF patients. [17, 18]

A clear association exists between hypertension and an increased risk of mortality and HF-related hospitalizations in chronic HF patients. [19, 20] Surprisingly, more than 40% of all HFrEF patients from the Dutch CHECK-HF registry had a systolic blood pressure of 130mmHg or higher, potentially at an increased risk for adverse events. Even more strikingly, these patients did not receive the maximum HF therapy, with room for improvement in both the prescription rates and prescribed dosages. Treating physicians might be reluctant to optimize HF therapy out of fear to introduce symptomatic hypotension. One could argue that hypotension should not be considered a side-effect but as a wanted effect of the therapy. Although no target blood pressure has been defined, and blood pressure treatment varies greatly between professionals and outpatient clinics, we believe that slowly up-titration combined with close monitoring should be used to optimize the HF therapy in every patient up to the guideline-recommended or maximum tolerated dosage.

New developments could improve HF care in the Netherlands even further, and lead to a more tailored approach. Currently, a one-size-fits-all strategy is used as per the 2016 European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic HF. [3] However, the recently published results from the BIOlogy Study to Tailored Treatment in Chronic Heart Failure (BIOSTAT-CHF) study contributed to the discussion of whether gender-specific guidelines are indicated. [21] In this subanalysis, the authors demonstrated that women had the maximum reduction in mortality and HF-related hospitalizations at approximately 50% of the guideline-recommended target dose for beta-blockers and RAS-inhibitors, while the maximum risk reduction in men was achieved at the guideline-recommended target dose. As shown in this thesis, a larger proportion of women would be considered to be adequately treated, with a large proportion of women who might have been overdosed when these hypothetical gender-specific target doses would be used. As these results are based on a single posthoc analysis, we should not directly implement them into the current clinical practice, and the current guideline-recommended target dose should be maintained for both men and women for the time being. Additional research is urgently needed, investigating

whether gender-specific guidelines are indicated, potentially leading to a better tailored approach for men and women.

Research in the new drug, sodium-glucose cotransporter-2 (SGLT-2) inhibitor, has gained a lot of attention recently. Initially, this drug was tested as a new antidiabetic but also showed beneficial effects on cardiovascular endpoints. [22-24] Recently, the DAPA-HF trial demonstrated positive outcomes in chronic HF patients, regardless whether they had diabetes or not. [25] Currently, several other trials are investigating the effects of SGLT-2 inhibitors in HF patients as well, and if positive, SGLT-2 inhibitors will be added as a new treatment option in HF management. [26, 27] Determine the potential clinical impact of new drugs can be very important to assess the potential impact these drugs could have on the clinical practice. As shown in this thesis, based on the inclusion criteria currently used in the clinical trials, more than 30% of the Dutch HF population would be eligible for SGLT-2 inhibitor treatment.

Optimal monitoring strategies in chronic heart failure

Close monitoring in chronic HF patients is considered to be a cornerstone in HF management. Over the last decades, technological improvements have been made to remote monitoring, which led to an increase in the use of remote monitoring strategies in cardiac care, as well as in HF management. [28] In HF care, remote monitoring strategies can be divided into three main categories, (1) non-invasive remote monitoring, (2) remote monitoring using cardiac implantable electronic devices (CIEDs, consisted of ICD and CRT devices), and (3) remote hemodynamic monitoring. [29] The ideal remote monitoring strategy is still up to debate, especially since each remote monitoring strategy has its own up and downsides.

Non-invasive remote monitoring usually uses one or a combination of the following methods, regular telephone calls, remote monitoring of blood pressure, heart rate or weight, and monitoring of signs and symptoms. The effectiveness of these monitoring strategies has been extensively investigated, with very inconsistent results. However, overall a small benefit of non-invasive remote monitoring in reducing mortality and HF-related hospitalization has been shown, especially in the more advanced non-invasive remote monitoring strategies. [30] Due to its non-invasive character, as well as the relatively low costs, non-invasive remote monitoring is relatively easy to implement in a wide variety of chronic HF patients.

Many chronic HF patients have a CIED, and many of the newer generations of these devices allow for remote monitoring. This could make remote monitoring of chronic HF patients using these implanted devices an ideal option. Unfortunately, many studies have shown that this strategy is not effective in improving patients outcomes. [31]

Hemodynamic remote monitoring has become available with the introduction of implantable pressure measuring devices, such as the CardioMEMS system. Multiple trials and real-world data registries have shown that the CardioMEMS is safe and effective in preventing HF-related hospitalizations in New York heart association (NYHA) functional class III HF patients. [32-34] The CardioMEMS device is implanted during a right-sided heart catheterization, making it a more invasive strategy. Additionally, the costs associated with the implantation are considerably higher compared to non-invasive remote monitoring strategies.

Based on the current evidence, we believe that all chronic HF patients should be remotely monitored. However, the ideal monitoring strategy is still up for debate. Based on the current evidence and the information on costs, we would suggest that less symptomatic chronic HF patients, defined as patients with an NYHA class of I or II, should be monitored using an extensive non-invasive remote monitoring strategy. More symptomatic HF patients, defined as NYHA class III, would benefit more from remote hemodynamic monitoring. Additional research is urgently needed to guide this discussion further. Information on the cost-effectiveness of remote monitoring is especially needed, as well as the effectivity of remote hemodynamic monitoring in less symptomatic chronic HF patients and its association with quality of life. Currently, trials are being conducted in order to provide more insight into these research questions. [35, 36]

Expanding the field on remote hemodynamic monitoring

Although remote hemodynamic monitoring is currently only used to monitor chronic HF patients to prevent congestion and HF-related hospitalizations, we believe that this technique could be used in different areas as well.

In the recent CardioMEMS studies, more than half of all treatment adjustments were caused by changes in diuretics. [33, 34] These results suggest that the majority of medication changes were made to optimize the volume status, guided by the hemodynamic feedback. Based on the first results from the CHAMPION trial, treatment guidelines have been proposed. [37] These guidelines recommend to use diuretics to reach and maintain an optimal volume status. However, we believe that diuretics and volume correction

are only the first step in the remote hemodynamic monitoring of chronic HF patients. When a patient is in a euvolemic status, the hemodynamic feedback should be used to optimize the HF treatment further. Adjustments in the dose of renin-angiotensin-system (RAS) inhibitors, mineralocorticoid receptor antagonists (MRAs), as well as nitrates or other vasodilators, could be used to optimize the hemodynamic status. [38] The additional hemodynamic feedback can reassure and guide the treating physicians during the up-titrating HF medication, and a normalization of the pulmonary artery pressures could be used as a marker for successful treatment optimization.

Left-sided valvular diseases can cause an increase in the left atrial pressure, and consequently the pulmonary artery pressures could rise. [39] Pulmonary artery hypertension is an indication for valvular intervention, as is recommended by the 2017 ESC Guidelines for the management of valvular heart disease. [40] Therefore, regular echocardiographic assessment is recommended, and invasive measurements of the pulmonary artery pressures should be performed when pulmonary hypertension is suspected. [40] We hypothesize that remote hemodynamic monitoring could be used to monitor patients with a left-sided valvular disease remotely, and could be used in the decision making whether valvular intervention is indicated. Additionally, the hemodynamic effects of these interventions could be remotely monitored. Unfortunately, this strategy could be limited due to the additional costs associated with remote hemodynamic monitoring.

However, chronic HF patients are frequently diagnosed with a left-sided valvular disease. [41] In these patients, remote hemodynamic monitoring that is already used for the monitoring of congestion, could also be used for the remote monitoring of the progression of the valvular disease, and aid in the clinical decision making whether an intervention is indicated in the HF patient population.

Irreversible pulmonary hypertension is a contraindication for heart transplantation, as the right ventricle of the donor heart is not capable of overcoming the fixed high pulmonary vascular resistance after a period of stunning by ischemia. Therefore, it is recommended by the International Society of Heart and Lung Transplantation to regularly (preferably at 3- to 6-months intervals) perform diagnostic right-heart catheterizations, especially in patients with reversible pulmonary hypertension. [42] Alternatively, we believe that remote hemodynamic monitoring could be a suitable alternative for the regular diagnostic right-heart catheterizations. It will reduce the burden on the hospital resources and limit the discomfort for the patient. Additionally,

remote hemodynamic monitoring allows for a daily assessment of the pulmonary artery pressures, which could be very dynamic. However, the reversibility of pulmonary hypertension cannot be tested using the currently available remote hemodynamic monitoring systems. Therefore, when pulmonary hypertension is diagnosed based on remote hemodynamic monitoring, reversibility should be tested using classic right-heart catheterization. One could argue that remote hemodynamic monitoring would be too costly. However, this remotely monitoring strategy could reduce the number of right-heart catheterizations required, reducing the burden on hospital resources.

Patients with end-stage HF, in which the patients have become refractory to medical therapy, could be treated with left ventricular assist device (LVAD) support. However, shortly after LVAD surgery, severe complications such as right ventricular (RV) failure and acute kidney injury (AKI) can occur. [43, 44] Although multiple risk-scores have been proposed [43, 45], it remains challenging to select the right patients and determine the proper timing of LVAD surgery, and guidance in the optimizing of patients is lacking. All these factors are crucial to improve outcomes after LVAD surgery.

Remote hemodynamic monitoring could be used to determine the ideal timing of LVAD surgery. In patients with remote hemodynamic monitoring, no effects of treatment changes were observed in the period before LVAD surgery. Additionally, when the hemodynamic information was available for the treating physician, the time until the patient went for LVAD surgery was shorter. [46] These results suggest that remote hemodynamic feedback could aid in the proper timing of LVAD surgery.

As shown in this thesis, remote hemodynamic monitoring shortly prior to LVAD surgery could safely identify patients with an increased risk for LVAD-related complications. Furthermore, the hemodynamic feedback can also be used to optimize the patient status further, and the response to treatment changes can be used to determine the ideal LVAD implantation window.

The implementation of remote hemodynamic monitoring in end-stage HF patients who are eligible for heart transplantation or LVAD surgery could be considered too costly. However, a significant proportion of these patients deteriorated from stable NYHA class III HF. The evidence for remote monitoring in chronic NYHA class III HF is growing rapidly. We believe that more and more patients eligible for heart transplantation or LVAD therapy will already have a remote monitoring device. This will make it easier and

relatively cheaper to implement remote monitoring strategies in these end-stage HF patients as well.

As discussed, we believe that remote hemodynamic monitoring can be used in many additional areas of HF and cardiac care, then for what it is currently used. However, these hypotheses are based on a small number of patients, posthoc analyses, and pilot studies. Therefore, additional research is needed to investigate the true potential of remote hemodynamic monitoring.

Optimizing and individualizing left ventricular assist device therapy

The current widely used LVAD devices provide only static and calculated pump parameters without the option of remote monitoring. This limits LVAD management, and remote monitoring is currently not available. Remotely obtained hemodynamic feedback could be used to guide and optimize medical therapy in LVAD patients. [46] Additionally, the pump settings could be optimized to achieve the best hemodynamic parameters, the number of outpatient visits might be reduced, and the quality of life of LVAD patients might increase further. Furthermore, adverse events, such as gastrointestinal bleedings, might be detected in an earlier stage by a sudden change in the hemodynamic feedback. [47] Earlier detection allows for a timely intervention, potentially preventing hospitalizations and a worse outcome. Additional research is currently undertaken to assess the efficacy of remote hemodynamic monitoring in LVAD patients on a larger scale (NCT03247829).

Besides remote monitoring, we identified several other areas in LVAD management that could be optimized. Ventricular arrhythmias can be a life threating condition in non-LVAD patients. In contrast, LVAD patients are generally not significantly affected by ventricular arrhythmias since the LVAD provides sufficient forward blood flow. [48] However, ventricular arrhythmias might introduce or worsening preexisting RV failure with a harmful effect on the overall survival of LVAD patients. [49] Therefore, CIED with a defibrillation function (CIED-D) could have a beneficial effect in LVAD patients. However, inconsistent results have been published, with several, mostly single-center, retrospective studies from the USA demonstrated no beneficial effects of CIED-Ds. In contrast, data from European centers suggested a better survival in patients with CIED-D therapy. [50] Differences in implantation rates of CIED-Ds as well as baseline characteristics between the American and European populations might have contributed in a more homogenous CIED-D patient group in the European studies. [51] These patients were more likely to have an elevated risk for ventricular arrhythmias

and sudden cardiac death, and were more likely to benefit more from CIED-D therapy. Based on the current evidence and the results from this thesis, we would recommend not to replace a CIED-D in patients without ventricular arrhythmias, or with many inappropriate shocks. Replacement or even implantation of a CIED-D should be considered in patients with significant ventricular arrhythmias, especially when joined by RV failure.

Although no strict age contraindication for heart transplantation exists in the current guidelines, it is recommended to very carefully select patients > 70 years of age. [3, 42] However, no recommendations are available to guide LVAD teams in the patient selection based on age. Based on the results in this thesis, we believe that no strict age eligibility criteria should be implemented in LVAD care. Although the all-cause mortality rate was significantly higher in elderly LVAD patients, the overall survival was still good, even in patients of ≥ 65 years. However, we would recommend to carefully select patients ≥ 65 years, especially since these patients are also at a higher risk for major bleeding events, as well as hemocompatibility related adverse events. Therefore more vigilant monitoring of elderly LVAD recipients might be indicated. Additionally, other comorbidities are more frequent in elderly patients, which might limits the beneficial effect of LVAD implantation.

Despite women comprise approximately half of the end-stage HF population, they are underrepresented in clinical LVAD trials. [52, 53] Similarly, women are less frequent supported with an LVAD in the clinical practice. [54] Women who undergo LVAD surgery are more frequent instable and critical ill, indicating that women might be referred for LVAD surgery in a later stage. Additional research is needed to investigate why the utilization of LVAD therapy is lower in women.

It remains unclear whether sex-related survival differences exists. Studies investigating the elderly pulsatile-flow LVADs showed a worse survival in women, while in modern continuous-flow LVAD no difference between men and women was observed. [54, 55] Pulsatile-flow LVADs were larger devices, while women have a smaller intrathoracic volume, which could have contributed to the higher mortality in women with the larger pulsatile-flow LVADs. Further research is warranted to assess whether the survival of women on LVAD support could be improved by a more timely referral and better implantation timing.

Concomitant aortic valve procedures during left ventricular assist device therapy

A short loop circulation, with insufficient unloading of the LV and forward blood flow to supply all organs, can occur due to aortic valve (AoV) regurgitation during LVAD support. [56] The presence of AoV regurgitation in LVAD patients has been associated with an increased risk of mortality. [57] Therefore, concomitant AoV surgery is frequently used to correct the AoV regurgitation. However, this strategy is also associated with an increased risk of mortality, especially in patients with only mild AoV regurgitation preoperatively. Additionally, patients undergoing concomitant AoV surgery are at an increased risk for major bleeding events postoperatively. Potentially, this increased risk is caused by a prolongation of the cardiopulmonary bypass time, which is associated with an increased risk of mortality. [58]

These results demonstrate that the decision to perform concomitant AoV surgery should not be taken lightly. Based on this thesis, we would recommend only perform concomitant AoV surgery in patients with at moderate-to-severe AoV regurgitation before LVAD surgery, as is recommended by the current guidelines. [59] In these patients, the gained beneficial effect of resolving the AoV regurgitation appears to outweigh the additional risks of the additional procedure. In patients with less severe AoV regurgitation, the benefits do not outweigh the risk, and concomitant AoV surgery should not be performed.

Iron deficiency in advanced heart failure patients

Similarly to chronic HF patients, iron deficiency is highly prevalent in LVAD patients. [60] Iron is essential for the function of cardiomyocytes, and iron deficiency is associated with a decreased function of the left and right ventricle. [61, 62] Only the left ventricular is supported by the LVAD, and the LVAD depends on a good right ventricle function. Right ventricular failure is a common and severe complication in LVAD patients. [43] Therefore, adequately screening for and treatment of iron deficiency in LVAD patients could prevent severe right ventricular failure and improve the overall outcome of LVAD patients.

Future perspectives

Over the last decades, heart failure care has developed rapidly and we expect this trend to continue in the upcoming years. We expect that new drugs will be developed for the treatment of heart failure patients, especially in patients with a preserved ejection fraction. Multiple heart failure registries are currently conducted. We expect that the insight provided from these studies will aid in the improvement of the quality of heart failure care. In the next decade, these insights should be used to determine the ideal target dose for each patient group. Additionally, an effective up-titration strategy needs to be developed in order to prescribe the desired target dose in each patient.

With the rapidly growing heart failure population, remote monitoring will become increasingly important. We expect that a standardized remote monitoring package will become available. Less symptomatic heart failure patients will be remotely monitored using non-invasive techniques, while invasive remote monitoring options will be used to keep a close eye on more symptomatic and ill patients. The information of all these patients will be processed at a central location, using the latest technologies and machine learning techniques. An intuitive and clear overview of this data will be provided for the treating physicians, clearly indicating which patients needs additional care.

Finally, we expect further development of left ventricular assist devices. We expect that the devices will become even smaller, allowing for less invasive implantation techniques. This new generation of devices could also be used to partially support the left ventricle, making them more useful as a bridge to recovery. Technologies for wireless charging will be incorporated, allowing for a completely independent device without the need for a driveline. Last but not least, these newer generation devices are expected to provide real-time hemodynamic data, as well as information on the valvular opening and functions, which will be able to be monitored remotely. Based on this information, the pump setting can be altered automatically while the patient is at home.

Conclusion

This thesis contributes to the knowledge regarding the many challenges that still need to be addressed to further optimize heart failure and left ventricular assist device care. We demonstrated that the care for chronic heart failure patients at Dutch outpatient clinics is of high quality, especially compared to other Western countries. In addition, we identified specific areas, including the prescribed dosages, the prescription for the elderly, and the treatment of hypertension that could be further optimized. Furthermore, the potential clinical impact of new developments such as gender-specific target dosages and the introduction of sodium-glucose cotransporter-2 inhibitors have been assessed and could have a significant effect on heart failure management.

Depending on the severity of heart failure, different monitoring strategies might be indicated. Non-invasive remote monitoring might be indicated in less symptomatic heart failure patients, while more symptomatic patients might benefit more from remote hemodynamic monitoring. Furthermore, we have identified potential new areas were remote hemodynamic monitoring could be used, including the monitoring of valvular heart diseases, monitoring of pulmonary artery pressures in heart failure patients on the heart transplantation waiting list as well as monitoring of patients going for left ventricular assist device surgery.

We have investigated the hybrid construction of remote hemodynamic monitoring and left ventricular assist support for the first time prospectively, and have demonstrated that this strategy is safe and feasible. The hemodynamic feedback can be used to identify patients at very high risk for left ventricular assist device-related complication. Additionally, remote hemodynamic monitoring can be used to determine the ideal left ventricular assist device implantation window and allows for remote outpatient monitoring and optimization.

We have identified several challenges in left ventricular assist device management, which could be addressed to optimize and individualize the left ventricular assist device care, including iron deficiency, age- and sex-related outcomes, and the use of cardiac implantable devices. Our results highlight the importance of careful consideration of whether concomitant aortic valve surgery is indicated during left ventricular assist device surgery. With this thesis, we hope to address many challenges in heart failure care, which could be the next step towards a more optimal and a tailored approach for each heart failure patient.

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Dutch summary (Nederlandse samenvatting)

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Samenvatting

Hartfalen zorg is tegenwoordig erg complex, en bestaat uit een combinatie van medicamenteuze behandeling, leefregels, monitoringstrategieën (op afstand) en invasieve behandelopties, waaronder klepinterventies, harttransplantatie en steunhart (ook wel 'left ventricular assist device', LVAD) implantatie. Ondanks dat de hartfalen behandeling de afgelopen decennia aanzienlijk is verbeterd, zijn er nog vele uitdagingen die moeten worden aangepakt om de zorg voor de snelgroeiende hartfalen populatie te verbeteren en te optimaliseren. Daarom richt dit proefschrift zich op de kwaliteit van de Nederlandse chronische hartfalen zorg in een grote hedendaagse 'real-world' studie en de kwaliteit van de zorg voor LVAD patiënten met het doel om de zorg voor deze patiënten te verbeteren. Daarnaast hebben we een nieuwe methode voor de monitoring van chronische hartfalen en LVAD patiënten op afstand onderzocht.

Deel A – Vaststellen van de kwaliteit van hartfalen zorg in Nederland, en identificatie van patiëntengroepen waarin de hartfalen behandeling zou kunnen worden verbeterd

Met het eerste deel van dit proefschrift hebben we inzicht willen verkrijgen in de huidige kwaliteit van hartfalen zorg verleend op de Nederlandse hartfalen poliklinieken. Dit inzicht kan worden verkregen door de naleving van de behandelrichtlijn van de European Society of Cardiology (ESC) voor hartfalen te onderzoeken. Tevens hebben we de kwaliteit van de hartfalen zorg in specifieke patiëntengroepen met chronisch hartalen onderzocht om zo in kaart te brengen waar de hartfalen zorg verbeterd kan worden. De *chronisch hartfalen ESC-richtlijn cardiologische praktijk kwaliteitsproject hartfalen* (CHECK-HF) registratie bevat gedetailleerd informatie over patiëntkarakteristieken, voorschrijfpercentages en voorgeschreven doseringen van bètablokkers, renine-angiotensine-systeem (RAS) inhibitoren en mineralocorticoïde receptorantagonisten (MRA's) van 10910 Nederlandse chronische hartfalen patiënten die tussen 2013 en 2016 behandeld werden op de poliklinieken van 34 Nederlandse centra. In totaal waren 8360 patiënten gediagnosticeerd met hartfalen met een gereduceerde ejectiefractie (HFrEF) en 2550 patiënten gediagnosticeerd met hartfalen met een behouden ejectiefractie (HFpEF) geïncludeerd. Verschillende aspecten maakt de CHECK-HF registratie tot een uniek onderzoeksproject. Als eerste heeft ongeveer de helft van alle Nederlandse centra met een hartfalen polikliniek patiënten geïncludeerd in deze registratie. Daarnaast is de data in de registratie verzameld door leden uit de lokale hartfalen behandelteams

en was die gebaseerd op de meest recente polibezoek en patiëntendossier. Hierdoor weerspiegelt de data uit de CHECK-HF registratie de huidige stand van zaken op de Nederlandse hartfalenpoliklinieken.

In **Hoofdstuk 2** zijn de leeftijdsspecifieke verschillen in de behandeling van chronische hartfalen patiënten beschreven. Met een stijging van de leeftijd daalde de naleving van de richtlijnen. Het verschil in de naleving van de richtlijnen kon niet volledig worden verklaard door de verschillen in baseline karakteristieken zoals de New York heart association (NYHA) classificatie of de aanwezigheid van comorbiditeiten. Ondanks dat de kans kleiner was dat oudere hartfalen patiënten de door de richtlijn aanbevolen behandeling ontvingen, ontving de meerderheid van de tachtigjarige HFrEF patiënten, twee of meer van de richtlijn aanbevolen hartfalen medicatie. Echter werden deze medicamenten niet op de aanbevolen dosering voorgeschreven, zoals is onderzocht in **Hoofdstuk 3**.

Slechts kleine verschillen in de behandeling tussen mannen en vrouwen werden geobserveerd, waarvan een deel verklaard kon worden de verschillen in de baseline karakteristieken en comorbiditeiten, zoals **Hoofdstuk 4** laat zien. Daarnaast hebben we de potentiele impact van het toepassen van een hypothetische geslacht-specifieke streefdosering, met een streefdosering van 50% van de door de richtlijn aanbevolen dosering voor bètablokkers en RAS-inhibitors voor vrouwen, onderzocht. Indien deze geslacht-specifieke streefdosering toegepast zou worden, zouden meer vrouwen de streefdosering ontvangen. Daarnaast zou een significant deel van de vrouwelijke HFrEF patiënten dan een te hoge dosering ontvangen, mogelijk zonder extra toegevoegde behandeleffect.

In **Hoofdstuk 5, 6 en 7** zijn de effecten van vaak voorkomende comorbiditeiten zoals hypertensie, atriumfibrilleren en diabetes mellitus op de naleving van de behandelrichtlijnen beschreven. Een groot deel van de HFrEF patiënten uit de CHECK-HF registratie hadden een systolische bloeddruk van 130 mmHg of hoger. De door de richtlijn aanbevolen hartfalen medicatie en de combinatie van alle drie de hartfalen medicamenten werd vaker voorgeschreven in patiënten met een lagere systolische bloeddruk. Daarentegen, patiënten met een systolische bloeddruk ≥130 mmHg werden minder vaak volgens de richtlijn behandeld. Atriumfibrilleren was een vaak voorkomende comorbiditeit in de Nederlandse poliklinische hartfalen patiënten en beïnvloedde de voorgeschreven hartfalen behandeling significant. Patiënten met atriumfibrilleren ontvingen vaak de aanbevolen behandeling. Kleine maar significante

verschillen in de hartfalenbehandeling tussen patiënten met en zonder diabetes werden gevonden, ook na correctie voor verschillen in de baseline karakteristieken en overige comorbiditeiten. Wanneer de toelatingseisen uit de huidige klinische trials toegepast zouden worden zou een substantieel deel van de Nederlandse hartfalen populatie in aanmerking komen voor behandeling met de nieuwe sodium-glucose cotransporter-2 (SGLT-2) inhibitors.

De hartfalen zorg verleend op de Nederlandse poliklinieken is vergeleken met de hartfalen zorg verleend op de poliklinieken in de Verenigde Staten van Amerika, welke onderzocht is in de *Change the Management of Patients with Heart Failure* (CHAMP-HF) registratie, in **Hoofdstuk 5 en 7**. Nederlandse hartfalen patiënten kregen vaker de in de richtlijn aanbevolen hartfalen medicamenten en de streefdosering voorgeschreven in vergelijking met de Amerikaanse hartfalen populatie.

Hoofdstuk 8 benadrukt de verschillen in hartfalen populaties en behandeling tussen de verschillende hartfalen poliklinieken in Nederland. Verschillen in de demografische patiëntengegevens konden de gevonden verschillen in aantal voorgeschreven medicamenten en doseringen niet volledig verklaren. Dit geeft aan dat het naleven van de behandelrichtlijn nog verder verbeterd zou kunnen worden.

Een groot gedeelte van de patiënten geïncludeerd in de CHECK-HF registratie waren gediagnostiseerd met HFpEF. Het klinische profiel en de medicamenteuze behandeling van deze patiënten is onderzocht in **Hoofdstuk 9**. Hoewel er geen 'evidence-based' behandelingen beschikbaar zijn voor HFpEF patiënten, ontvingen veel HFpEF patiënten medicatie dat geïndiceerd is voor de behandeling van HFrEF patiënten. Deze medicamenten waren waarschijnlijk voorgeschreven voor de behandeling van veel voorkomende comorbiditeiten. Daarnaast zouden deze HFrEF medicijnen voorgeschreven kunnen zijn aan de HFpEF patiënten bij een gebrek aan een alternatieve behandeling.

Concluderend, de resultaten van de CHECK-HF registratie geven een uniek inzicht in de hartfalen behandeling op Nederlandse hartfalen poliklinieken. Veel hartfalen patiënten worden behandeld met de in de richtlijn aanbevolen hartfalen behandeling, echter is de voorgeschreven dosering lager dan is aanbevolen. We hebben verschillende patiëntencategorieën geïdentificeerd, waaronder ouderen en patiënten met comorbiditeiten zoals hypertensie, waarin de hartfalen behandeling verder geoptimaliseerd zou kunnen worden.

Door het cross-sectionele studie design kon causaliteit niet onderzocht worden. Verder waren er geen klinische uitkomsten geregistreerd. Hierdoor konden we het effect van het minder frequent voorschrijven van in de richtlijn aanbevolen hartfalen medicatie op de overleving van de hartfalen populatie niet onderzoeken. De CHECK-HF registratie heeft een zeer groot aantal patiënten geïncludeerd, die samen een goede afspiegeling geven van de echte praktijk op de Nederlandse hartfalen poliklinieken. Dit is een van de sterke punten van deze hartfalen registratie. De resultaten van de CHECK-HF registratie geven nieuw inzicht in de hedendaagse behandeling van hartfalen patiënten in een 'real-world' setting. Deze bevindingen zijn erg informatief voor hartfalen cardiologen aangezien ze nieuw inzicht geven in de naleving van de richtlijnen en er specifieke patiëntencategorieën zijn geïdentificeerd waarin de richtlijn naleving lager is dan in de overige patiëntencategorieën.

Deel B – Vaststellen van de impact van hemodynamische monitoring van chronische hartfalen patiënten op afstand

In het tweede deel van dit proefschrift zijn strategieën om chronische hartfalen patiënten op afstand te kunnen monitoren, en voornamelijk hemodynamische monitoring op afstand, onderzocht.

Hoofdstuk 10 geeft een up-to-date overzicht van de beschikbare literatuur over op afstand monitoring strategieën in chronische hartfalen patiënten. Verschillende niet invasieve monitoring strategieën, variërend van simpele univariabele tot erg complexe en intensieve multivariabele strategieën, zijn de afgelopen decennia voorgesteld en onderzocht door meerdere grote multicenter prospectieve studies, gerandomiseerde gecontroleerde onderzoeken, en 'real-world' registraties. Niet invasieve monitoring strategieën hadden een bescheiden positief effect op de overleving en hartfalen gerelateerde ziekenhuisopnames. Dit positieve effect werd voornamelijk waargenomen in de meer complexe strategieën, bestaande uit niet invasieve monitoring van meerdere variabelen. Het op afstand monitoren van chronische hartfalen patiënten middels implanteerbare cardioverter defibrillator (ICD) of cardiale resynchronisatietherapie (CRT) apparaten had geen effect op de overleving of het aantal ziekenhuisopnames. Op afstand hemodynamische monitoring kan een stijging van de vullingsdrukken in het hart weken voordat een episode van hartfalen exacerbatie ontstaat detecteren. Het CardioMEMS systeem kan de pulmonaal arterie druk monitoren en is momenteel de meest belovende strategie voor hemodynamische monitoring op afstand. Het is aangetoond dat deze strategie veilig en effectief is om hartfalen gerelateerde ziekenhuisopnames in zowel HFrEF als HFpEF patiënten te voorkomen.

De Nederlandse *hemodynamic monitoring in heart failure* (MONITOR HF) Trial onderzoekt of CardioMEMS monitoring bovenop de standaard zorg kan zorgen voor een verbetering in de kwaliteit van leven, vermindering van het aantal hartfalen gerelateerde ziekenhuisopnames en onderzoekt de kosteneffectiviteit in Nederland. De opzet van dit gerandomiseerd gecontroleerd onderzoek is omschreven in **Hoofdstuk 11**.

Het ideale moment op de dag om de pulmonaal arterie druk met de CardioMEMS te meten is omschreven in **Hoofdstuk 12**. De variabiliteit tussen de metingen was het kleinst vroeg in de ochtend, waardoor dit het meest ideale moment is om de pulmonaal arterie drukken te monitoren.

Hemodynamische monitoring op afstand kan unieke informatie en extra inzicht geven in de patiënten management en het effect van vaak gebruikte behandeling. Zoals geïllustreerd is in de casus omschreven in **Hoofdstuk 13**, kunnen de hemodynamische effecten van klepinterventies zoals de MitraClip veilig en effectief worden gemonitord met behulp van de CardioMEMS.

Concluderend, veel verschillende strategieën voor de op afstand monitoring van chronische hartfalen patiënten zijn onderzocht. De CardioMEMS systeem is de meest belovende techniek om patiënten hemodynamisch op afstand te kunnen monitoren. Verder heeft hemodynamische monitoring op afstand de potentie om voor andere indicaties en in andere patiëntencategorieën gebruikt te kunnen worden.

Deel C – Vaststellen van de veiligheid en haalbaarheid van hemodynamische monitoring op afstand in steunhart patiënten

We hebben de veiligheid en haalbaarheid van hemodynamische monitoring op afstand in patiënten met eindstadium hartfalen die overgingen op ondersteuning van een LVAD onderzocht in het derde deel van dit proefschrift.

Een overzicht van alle beschikbare literatuur van de verschillende monitoring strategieën in LVAD patiënten wordt gegeven in **Hoofdstuk 14**. Er zijn verschillende mogelijke strategieën voor monitoring op afstand voorgesteld en onderzocht. Deze ontwikkelingen zijn veelbelovend, echter is doorontwikkeling noodzakelijk voordat deze strategieën in de zorg voor LVAD patiënten kunnen worden toegepast. Het combineren van op afstand hemodynamische monitoring via de CardioMEMS met LVAD therapie kan de volgende stap voorwaarts zijn voor LVAD zorg op afstand.

Hoofdstuk 15 omschrijft de pulmonaal arterie drukken over de tijd in een LVAD patiënt met 'gefixeerde' pulmonale hypertensie. LVAD ondersteuning kan gebruikt worden om zogenoemde 'gefixeerde' pulmonale hypertensie te behandelen. Het CardioMEMS systeem kan gebruikt worden om dit proces veilig en adequaat op afstand te monitoren. Hiermee wordt tot nu toe onbekende informatie over longdrukken en het effect van behandelingen inzichtelijk.

De veiligheid en haalbaarheid van pulmonaal arterie druk gestuurde behandeling middels het CardioMEMS systeem in patiënten die in aanmerking komen voor LVAD implantatie is onderzocht in de *hemodynamic guidance with CardioMEMS in patients with a left ventricular assist device* (HEMO-VAD) pilot studie. De opzet van deze pilot studie is omschreven in **Hoofdstuk 16**.

In **Hoofdstuk 17** zijn de korte termijn effecten van op afstand hemodynamische monitoring van LVAD patiënten onderzocht. Gedurende de eerste drie maanden na LVAD implantatie deden er zich geen CardioMEMS gerelateerde veiligheidsproblemen voor. Patiënten waarbij voor LVAD implantatie de gemiddelde pulmonaal arterie druk (mPAP) niet genormaliseerd kan worden vormen een patiëntengroep die een sterk verhoogd risico hebben om te overlijden en LVAD gerelateerde complicaties waaronder acute nierschade en rechter ventrikel falen te ontwikkelen. Bovendien neemt de kwaliteit van leven significant minder toe in patiënten waarbij de mPAP niet genormaliseerd kan worden in vergelijking met patiënten waarbij dat wel lukt.

Hoofdstuk 18 benadrukt de veiligheid van hemodynamische monitoring op afstand middels de CardioMEMS in LVAD patiënten. Gedurende het volledige eerste jaar van follow-up zijn er geen device gerelateerde complicaties of storingen waargenomen. In de patiënten waarin de mPAP kort voor LVAD implantatie genormaliseerd kon worden was de sterfte en het aantal LVAD gerelateerde complicaties en ziekenhuisopnames lager. Na de LVAD implantatie verbeterde de kwaliteit van leven in alle patiënten. Echter, deze verbetering was sterker en hield langer aan in patiënten met een normalisatie van de mPAP voorafgaande aan de LVAD implantatie.

We concluderen dat op afstand monitoring van LVAD patiënten clinici kan helpen om de LVAD zorg te optimaliseren. De CardioMEMS kan veilig worden gebruikt om op afstand LVAD patiënten hemodynamisch te monitoren. De additionele hemodynamische feedback die wordt geleverd door het CardioMEMS systeem kan gebruikt worden in de preoperatieve optimalisatie van de hemodynamische status van de patiënt, als

risicovoorspeller voor slechtere klinische uitkomst en om de patiënten op afstand te kunnen monitoren en behandelen.

Deel D – Optimaliseren van steunhart zorg

In het laatste deel van dit proefschrift hebben we de volgende LVAD gerelateerde uitdagingen onderzocht: de effectiviteit van cardiaal geïmplanteerde elektronische apparaat met een shock functie (CIED-D, bestaande uit een ICD en CRT met een defibrillatie functie) tijdens LVAD ondersteuning, de impact van leeftijd en geslacht op LVAD uitkomsten, gelijktijdige aortaklep vervanging gedurende de LVAD implantatie en ijzerdeficiëntie.

In **Hoofdstuk 19** hebben we in de observationele *postgraduate course in heart failure ventricular assist device* (PCHF-VAD) registratie onderzocht of een actieve CIED-D geassocieerd was met verbeterde uitkomsten in LVAD patiënten. De PCHF-VAD registratie is een observationele studie waarin LVAD patiënten werden geïncludeerd vanuit 12 Europese tertiaire hartfalen verwijzingscentra. Een actieve CIED-D in LVAD patiënten was geassocieerd met een verlaagde mortaliteit, verlaagd aantal device gerelateerde infecties waarvoor systemische antibiotica noodzakelijk waren en significante minder bloedingen.

Hoofdstuk 20 en 21 geven gedetailleerd analyses van de invloed van leeftijd en geslacht op LVAD uitkomsten en management in de PCHF-VAD registratie. Een toename in leeftijd was onafhankelijk geassocieerd met een verhoogde risico op mortaliteit. Verder hadden oudere LVAD patiënten een verhoogd risico op 'hemocompatibiliteit' gerelateerde complicaties en hadden vaker een nieuwe episode van atriumfibrilleren of flutter. Oudere LVAD patiënten hadden daarentegen een significant lager risico op device gerelateerde infectie waarvoor systemische antibiotica noodzakelijk waren.

LVAD therapie wordt significant minder vaak gebruikt in vrouwen. Desondanks dat vrouwen die een LVAD implantatie ondergaan vaker zieker en instabieler waren, werden er geen verschillen in overleving tussen manen en vrouwen gevonden. Daarentegen kon de LVAD ondersteuning in vrouwen vaker worden afgebouwd.

We hebben de effecten van het gelijktijdig vervangen van de aortaklep tijdens LVAD implantatie in detail onderzocht in de *international society of heart and lung transplantation mechanically assisted circulatory support* (IMACS) registratie. In **Hoofdstuk 22** zijn de korte en lange termijn overleving onderzocht van patiënten met een gelijktijdige vervanging

van de aortaklep en LVAD implantatie. Gelijktijdige vervanging van de aortaklep was een onafhankelijke voorspeller voor vroege en late sterfte in LVAD patiënten. In patiënten met slechts een milde aortaklepinsufficiëntie had gelijktijdige aortaklepvervanging een negatief effect op de overleving van LVAD patiënten. In patiënten met een matig tot ernstige aortaklepinsufficiëntie daarentegen waren er geen verschillen in de overleving tussen patiënten met en zonder een gelijktijdige aortaklepvervanging.

Om meer inzicht in het risico van gelijktijdige aortaklepvervanging te krijgen, is de associatie van 'hemocompatibiliteit' gerelateerde complicaties onderzocht in **Hoofdstuk 23**. Er werd geen associatie tussen gelijktijdige aortaklepvervanging en een verhoogd risico op trombo-embolische events gevonden. Gelijktijdige aortaklepvervanging was daarentegen een onafhankelijke riscofactor voor significante bloedingen na LVAD implantatie.

De prevalentie van ijzerdeficiëntie in LVAD en harttransplantatie patiënten is omschreven in **Hoofdstuk 24**. Ondanks dat de richtlijn regelmatige screening voor ijzerdeficiëntie in chronische hartfalen patiënten aanbeveelt, waren niet alle eindstadium hartfalen patiënten gescreend op ijzerdeficiëntie in het jaar voordat zij een LVAD implantatie of harttransplantatie ondergingen. De prevalentie van ijzerdeficiëntie was zeer hoog voorafgaande aan de LVAD implantatie of harttransplantatie en was zelfs hoger na de operatie. Het grootste gedeelte van de patiënten met een ijzerdeficiëntie werd behandeld met ijzersuppletie.

Toekomst perspectieven

De hartfalen zorg heeft zich de afgelopen decennia snel ontwikkeld en we verwachten dat deze trend zich de komende jaren zal doorzetten. We verwachten dat nieuwe medicamenten ontwikkeld zullen worden voor de behandeling van hartfalen, voornamelijk voor patiënten met een behouden ejectiefractie. Meerdere hartfalen registraties worden momenten uitgevoerd. We verwachten dat de informatie uit deze studies zullen bijdragen aan de verbetering van de hartfalen zorg. In het komende decennium zullen deze nieuwe inzichten gebruikt moeten worden om de ideale target dosis voor elke patiëntencategorie te bepalen. Daarnaast moet er een effectieve titratie strategie worden ontwikkeld zodat de gewenste streefdosering wordt voorgeschreven aan elke patiënt.

Met de snel toenemende hartfalen populatie zal monitoring op afstand steeds belangrijker worden. We verwachten dat een gestandaardiseerd pakket voor monitoring op afstand beschikbaar zal komen. Minder symptomatische hartfalen patiënten zullen op afstand worden gemonitord met niet invasieve technieken, terwijl invasieve monitoring opties gebruikt zullen worden om meer symptomatische patiënten nauwlettend in de gaten te houden. Alle informatie van deze patiënten zal op een centrale locatie verwerkt worden, gebruikmakend van de meest recente technologie en 'machine learning' technieken. De data zal op een intuïtieve en overzichtelijke manier worden gepresenteerd aan de behandeld arts, waarbij patiënten die extra zorg nodig hebben duidelijk zichtbaar zijn.

Tot slot verwachten we dat de steunharten continu verder ontwikkeld zullen worden. We verwachten dat de steunharten steeds kleiner zullen worden, waardoor minder invasieve implantatie technieken gebruikt kunnen worden. Deze nieuwe generatie steunharten zouden dan ook gebruikt kunnen worden voor de partiële ondersteuning van de linker ventrikel, waardoor ze meer geschikt worden als overbruggingsbehandeling tot de linker ventrikel functie is hersteld. Draadloze oplaadtechnieken zullen worden geïntegreerd waardoor een volledig geïmplanteerd steunhart ontwikkeld kan worden, zonder een driveline. Als laatste verwachten we dat deze nieuwe generatie steunharten 'real-time' informatie geven over de hemodynamica, het openen van de hartkleppen en de klepfunctie dat op afstand gemonitord kan worden. Gebaseerd op deze informatie kunnen de pompinstellingen automatisch aangepast worden terwijl de patiënt thuis is.

Conclusie

Dit proefschrift draagt bij aan de kennis met betrekking tot de vele uitdagingen die nog moeten worden aangepakt om de hartfalen en steunhart zorg verder te verbeteren. We hebben aangetoond dat de Nederlandse hartfalen poliklinieken een hoge kwaliteit van zorg aan chronische hartfalen patiënten verlenen, voornamelijk in vergelijking met andere westerse landen. Daarnaast hebben we specifieke gebieden in de hartfalen zorg geïdentificeerd, waaronder de voorgeschreven dosering, het voorschrijven bij ouderen en de behandeling van hypertensie, die verder geoptimaliseerd kunnen worden. Verder hebben we de klinische impact van nieuwe ontwikkelingen zoals geslacht specifieke streefdoseringen en de introductie van een sodium-glucose cotransporter-2 inhibitor onderzocht. Deze nieuwe ontwikkelingen kunnen een significante effect hebben op de hartfalen zorg.

Afhankelijk van de ernst van het hartfalen kunnen verschillende monitoring strategieën geïndiceerd zijn. Niet invasieve monitoring kan gebruikt worden om minder symptomatische hartfalen patiënten op afstand in de gaten te houden, terwijl meer symptomatische patiënten meer profijt zullen hebben van hemodynamische monitoring op afstand. Verder hebben we potentieel nieuwe gebieden geïdentificeerd waar hemodynamische monitoring op afstand gebruikt zou kunnen worden, waaronder monitoring in patiënten met een aangedane hartklep, monitoring van pulmonaal arterie drukken in hartfalenpatiënten op de harttransplantatie wachtlijst en de monitoring van patiënten die voor steunhart implantatie gaan.

We hebben de hybride combinatie van de hemodynamische monitoring op afstand en steunhart ondersteuning voor de eerste keer prospectief onderzocht. We hebben laten zien dat deze combinatie veilig en haalbaar is. De hemodynamische informatie kan gebruikt worden om patiënten met een zeer hoog risico voor steunhart gerelateerde complicaties te identificeren. Verder kan de op afstand gemonitorde hemodynamische informatie gebruikt worden om de ideale steunhart implantatie moment vast te stellen. Verder kan deze techniek gebruikt worden om steunhart patiënten vanuit de polikliniek te monitoren en optimaliseren.

We hebben verschillende uitdagingen in de zorg voor patiënten met een steunhart geïdentificeerd welke aangepakt kunnen worden om de zorg voor patiënten met een steunhart te verbeteren en optimaliseren, waaronder ijzerdeficiëntie, leeftijd en geslacht specifieke uitkomsten en het gebruik van cardiale geïmplanteerde apparaten. Onze resultaten benadrukken het belang van een goede afweging of gelijktijdige aortaklepvervanging tijdens een steunhart implantatie geïndiceerd is. In dit proefschrift hebben we vele uitdagingen uit de hartfalen zorg geprobeerd aan te pakken, wat de volgende stap zou kunnen zijn naar een meer geoptimaliseerde en geïndividualiseerde aanpak voor elke hartfalen patiënt.

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Submitted manuscripts

22. **Veenis JF***, Uijl A*, Brunner-La Rocca HP, van Empel V, Linssen GCM, Asselbergs FW, van der Lee C, Eurlings LWM, Kragten H, Al-Windy NYY, van der Spank A, Koudstaal S, Brugts JJ, Hoes AW. Clinical profile and management of patients with heart failure with preserved ejection fraction in the CHECK-HF registry. Submitted.
    * Equal contributions
23. **Veenis JF**, Radhoe SP, Linssen GCM, Van der Lee, Eurlings LWM, Kragten H, Al-Windy NYY, Van der Spank A, Koudstaal S, Brunner-La Rocca HP, Brugts JJ. Diabetes and contemporary treatment for chronic heart failure in a large real-world heart failure population. Submitted
24. Crnko S, Brugts JJ, **Veenis JF**, de Jonge N, Sluijter JPG, Oerlemans MIF, van Laake LW. Morning pulmonary artery pressure measurements by CardioMEMS are most stable and advocated to use for remote monitoring of pressure tends. Submitted
25. Radhoe SP, **Veenis JF**, Van Mieghem NM, Brugts JJ. The effect of transcatheter aortic valve implantation on pulmonary artery pressures in a patient suffering from chronic heart failure: a case report. Submitted
26. **Veenis JF**, Radhoe SP, van Mieghem NM, Manintveld OC, Bekkers JA, Caliskan K, Brugts JJ. Safety and feasibility of a hybrid construction of hemodynamic guidance

by pulmonary artery pressure monitoring and LVAD management: Main findings of the proof of concept HEMO-VAD study. Submitted.

27. **Veenis JF**, Radhoe SP, Roest S, Caliskan K, Constantinescu AA, Manintveld AC, Brugts JJ. Prevalence of iron deficiency and iron administration in LVAD and heart transplantation patients. Submitted.
28. Ammirati E, Brambatt M, Braun OO, Shah P, Cipriani M, Bui Q, **Veenis JF**, Lee E, Xu R, Hong K, Van de Heyning C, Perna E, Timmermans P, Cikes M, Brugts JJ, Verones G, Minto J, Smith S, Gjesdal G, Gernhofer Y, Partida C, Potena L, Masetti M, Boschi S, Loforte A, Jakus N, Milicic D, Nilsson JE, De Bock D, Sterken C, Van den Bossche K, Rega F, Tran H, Singh R, Montomoli J, Mondino M, Greenberg B, Russo CF, Pretorius V, Klein L, Frigerio M, Adler E. Outcome of patients on heart transplant list treated with a continuous-flow left ventricular assist device: insights from the Trans-Atlantic registry on VAd and TrAnsplant (TRAViATA). Submitted
29. Radhoe SP, **Veenis JF***, Jakus N*, Timmermans P, Pouleur AC, Rubís P, Van Craenebroeck EM, Gaizauskas E, Barge-Caballero E, Paolillo S, Grundmann S, D'Amario D, Braun O, Gkouziouta A, Planinc I, Skoric B, Flammer AJ, Gasparovic H, Biocina B, Milicic D, Ruschitzka F, Cikes M, Brugts JJ. How does age affect the clinical course after left ventricular assist device implantation: results from the PCHF-VAD. Submitted
    * Equal contributions
30. **Veenis JF***, Jakus N*, Radhoe SP, Timmermans P, Pouleur AC, Rubís P, Van Craenebroeck EM, Gaizauskas E, Barge-Caballero E, Paolillo S, Grundmann S, D'Amario D, Braun O, Gkouziouta A, Planinc I, Skoric B, Flammer AJ, Gasparovic H, Biocina B, Milicic D, Ruschitzka F, Cikes M, Brugts JJ. Left ventricular assist device utilization and survival outcomes according to sex. Submitted
    * Equal contributions
31. **Veenis JF***, Yalcin YC*, Brugts JJ, Antonides CFJ, Veen KM, Muslem R, Bekkers JA, Gustafsson F, Tedford RJ, Bogers AJJC, Caliskan K. Rate of thromboembolic and bleeding events in patients with concomitant aortic valve surgery and left ventricular assist device implantation: an analysis of the IMACS database. Submitted
    * Equal contributions
32. Roest S, Manintveld OC, Kolff MAE, Akca F, **Veenis JF**, Constantinescu AA, Brugts JJ, Birim O, Van Osch-Gevers LM, Szili-Torok T, Caliskan K. Increasing donor age and the risk of permanent pacemaker implantation post-heart transplantation. Submitted

Book chapter

1. **Veenis JF**, Brugts JJ. Hartfalen medicatie in Nederland en verschillen naar leeftijd, geslacht en bloeddruk. CardioActueel 2020

Summary of PhD training and teaching activities

Name PhD student:	J.F. Veenis
Erasmus MC Department:	Cardiology
Research School:	COEUR, Erasmus MC
PhD period:	2017-2020
Title thesis:	Optimized and individualized medicine in heart failure therapy "*the next step forward*"
Promotor:	Prof. dr. F. Zijlstra
Copromotor:	Dr. J.J. Brugts

1. PhD training	Year	Workload (ECTS)
General academic skills		
Research Integrity	2019	0.3
Research skills		
Biostatistical Methods I: Basic Principles	2018	5.7
OpenClinica course	2018	0.5
Presentations		
Oral presentation NVVC Voorjaarscongres 2018	2018	0.5
Poster presentation ESC HF 2018 (2x)	2018	0.6
Oral presentation NVVC Najaarscongres 2018	2018	0.5
Poster presentation ISHLT 2019	2019	0.3
Oral presentation NVVC Voorjaarscongres 2019	2019	0.5
Poster presentation ESC HF 2019	2019	0.3
Oral presentation ESC HF 2019	2019	0.5
Oral presentation NVVC Najaarscongres 2019	2019	0.5
ePoster presentation ACC/AHA 2020 (3x)	2020	0.9
ePoster presentation ISHLT 2020 (2x)	2020	0.6
(Digital) Oral presentation ISHLT 2020	2020	0.5
ePoster presentation ESC HF 2020 (5x)	2020	1.5
ePoster presentation ESC eCongres 2020	2020	0.3
(Digital) Oral presentation ESC eCongres 2020	2020	0.5

1. PhD training	Year	Workload (ECTS)
International conferences and symposia		
NVVC Najaarscongres 2017	2017	0.6
NVVC Voorjaarscongres 2018	2018	0.3
ESC Heart Failure 2018	2018	1.2
NVVC Najaarscongres 2018	2018	0.6
BeNeVAD meeting 2018	2018	0.5
Connecting Heart Failure Care in Rijnmond	2018	0.5
ISHLT Meeting 2019	2019	1.2
NVVC Voorjaarscongres 2019	2019	0.6
ESC Heart Failure 2019	2019	1.2
NVVC Najaarscongres 2019	2019	0.6
ACC/AHA eMeeting 2020	2020	0.9
ISHLT eMeeting 2020	2020	1.2
ESC HF eCongres 2020	2020	1.2
ESC eCongres 2020	2020	1.2
Seminars and workshops		
Sex and Gender in Cardiovascular Research (COEUR)	2018	0.5
Pathophysiology of ischemic heart disease (COEUR)	2018	1.0
Heart Failure (COEUR)	2018	0.5
Imaging for Ischemic Heart and Brain Disease (COEUR)	2018	0.5
Vascular Clinical Epidemiology (COEUR)	2019	0.5
Pulmonary Hypertension across life (COEUR)	2019	0.5
New pharmacological targets in age-related cardiovascular disease (COEUR)	2019	0.5
The Future of Arrhythmia Management: From Substrate to Signal	2019	0.3
Didactic skills		
Ted like Masterclass presentation	2018	0.5
Other		
Hartfalen Spreekuur 2018	2018	0.3
ExCOEURsie Regionale Tuchtraad	2018	0.2
COEUR PhD day 2019	2019	0.3
Hartfalen Spreekuur 2019	2019	0.3
Landelijke Assistenten Congres Cardiologie	2019	0.3

2. Teaching activities	Year	Workload (ECTS)
Lecturing		
Cathlab nurse CardioMEMS training	2018	0.3
Cathlab nurse CardioMEMS training	2019	0.3
ICCU CardioMEMS training	2019	0.3
Cathlab nurse CardioMEMS training	2019	0.3
Pulmonale druksensor – Vroege detectie van hartfalen – Landelijke Assistenten Congres Cardiologie	2019	0.6
Webinar 3e Nationale CHECK-HF meeting – Diabetes & Bloeddruk	2020	0.3
Cardiovascular Research meeting	2020	0.5
Supervision of students		
Supervising systematic review 2nd year med students	2017-2018	0.3
Supervising systematic review 2nd year med students	2018-2019	0.3
Supervising systematic review 2nd year med students	2019-2020	0.3
Supervising master thesis, 4th year medicine student 'CardioMEMS – MONITOR-HF trial'	2020	1.0
Other		
Journal Club (Ambulatory Hemodynamic Monitoring Reduces Heart Failure Hospitalizations in "Real-World" Clinical practice)	2018	0.1
Journal Club (Two-Year Outcomes with a Magnetically Levitated Cardiac Pump in Heart Failure)	2018	0.1
Journal Club (Digoxin-mortality: randomized vs. observational comparison in the DIG trial)	2019	0.1
Total		**37.3**

About the author

Jesse Veenis was born on September 5th, 1992 in Capelle aan den IJssel, The Netherlands.

He graduated from the Comenius College (Atheneum), Capelle aan den IJssel in 2010. Afterward, he started studying Medicine at the Erasmus University Rotterdam, The Netherlands, after being selected via the decentral selection procedure. During his second year, he joined the congenital cardiology research group of prof. dr. Jolien Roos, at the Erasmus Medical Center Rotterdam, The Netherlands. Afterward, he joined the clinical epidemiology research group of dr. Ron van Domburg. During this period he participated in several research projects from multiple research groups, including interventional cardiology, cardiologic imaging, cardiac rehabilitation, and cardiac clinical epidemiology as well as the pulmonary department. He continued his research activities during his clinical rotations, up to his graduation in February 2017.

After obtaining his medical degree, he started working at the Department of Internal Medicine in the Maasstad Ziekenhuis, Rotterdam, The Netherlands to obtain clinical experience and broaden his overall vision. In September 2017, he started working as a Ph.D. candidate in the research group of dr. Jasper Brugts at the department of Cardiology, Erasmus Medical Center Rotterdam. During this period, he worked on several national and international research projects concerning heart failure, left ventricular assist devices, and telemonitoring and presented his findings at multiple national and international congresses.

After finishing his Ph.D., he will continu to pursue his career as a general practitioner.

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