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FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN

master in de biomedische wetenschappen: klinische moleculaire wetenschappen

Masterproef

Improving heart failure morbidity through individually tailored disease management

Promotor :
Prof. Dr. Wilfried MULLENS
dr. Quirine SWENNEN

Jürgen Duchenne

Masterproef voorgedragen tot het bekomen van de graad van master in de biomedische wetenschappen , afstudeerrichting klinische moleculaire wetenschappen

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List of abbreviations

ACE-I: Angiotensin converting enzyme inhibitor

ADHF: Acute decompensated heart failure

ARB: Angiotensin receptor blocker

CI: Confidence interval

CO: Cardiac output

CRT: Cardiac resynchronization therapy

HF: Heart failure

HR: Hazard ratio

ICD: Implantable cardioverter defibrillator

IQR: Interquartile range

LA: Left atrium

LD: Loop diuretics

LV: Left ventricle

LVEF: Left ventricular ejection fraction

MRA: Mineralocorticoid receptor antagonists

NYHA: New York Heart Association

RAS: Renin-angiotensin system

RV: Right ventricle

SD: Standard deviation

SNS: Sympathetic nervous system

ZOL: Ziekenhuis Oost-Limburg

Abstract

Background and objectives: Heart failure (HF) is not a disease on its own, but rather a complex clinical condition characterized by cardiac and non-cardiac morbidity, with high morbidity and mortality and incremental costs for health care. The objective of this thesis was to investigate if optimal patient care through an individually tailored approach would lead to better outcomes. Treatment of ambulatory HF patients with reduced ejection fraction (HFrEF) with renin-angiotensin system (RAS) blocker and β-blocker therapy at guideline-recommended target dose has shown to effectively reduce all-cause mortality and HF admissions. However, the benefits in HF patients with preserved ejection fraction (HFpEF), as well as uptitration after a hospitalization remain uncertain. Therefore, a first study was set up to assess the impact of RAS and β-blocker uptitration in HFrEF versus HFpEF patients after hospital admission. Next to an optimal neurohumoral blocker therapy, elaborate HF care also comprises an extensive disease management program. A second study was set up to investigate the feasibility and impact of a hospital-wide, individually tailored and transmural disease management program in reducing acute decompensated HF (ADHF) and all-cause readmission rates and improving clinical outcome, in patients admitted for advanced HF.

Methods: The first study reviewed consecutive HF patients (209 HFrEF and 108 HFpEF), included after an index hospitalization, and followed RAS and β-blocker dosage over a period of 6 months. Patients with RAS and β-blocker dosage increase were compared to patients without uptitration, and long term outcomes were analyzed. The second study investigated 55 consecutive patients, rehospitalized within one year for ADHF. Admitted patients received a tag in their electronic health record, triggering HF caregiver contacts and subsequent guideline-recommended protocol-driven care on each cardiac and non-cardiac hospitalization and outpatient evaluation, as well as low-threshold to contact the dedicated caregiver after discharge.

Results: The first study indicated that uptitration of RAS or β-blockers was more feasible in younger patients with lower co-morbidity burden. However, after correction for age and several clinical parameters, uptitration of RAS blockers was able to significantly reduce the all-cause mortality or HF readmission in HFrEF patients, which was not seen for β-blocker uptitration. No benefit of uptitration was observed in HFpEF patients. The second study revealed that implementation of the transmural disease management program for patients with advanced HF, significantly reduces the number of ADHF hospitalizations per patient per year. A similar significant reduction was apparent in the overall yearly all-cause hospitalization rate, as well as the total amount of follow-up time spent in hospital. Participation in cardiac device telemonitoring also clearly increased during follow-up.

Conclusions: Uptitration of RAS blockers after a HF hospitalization is more feasible in younger patients with low co-morbidity burden, and is an independent predictor of outcome in HFrEF but not HFpEF patients. Additionally, follow-up of advanced HF patients through a transmural disease management is associated with favorable clinical outcome and reduced readmissions.

Samenvatting

Achtergrond en doelstellingen: Hartfalen (HF) kan niet aangezien worden als een alleenstaande ziekte, maar is eigenlijk meer een complex klinisch syndroom, gekenmerkt door comorbiditeiten van zowel cardiale als niet-cardiale oorsprong. Optimale behandeling van patiënten is bijgevolg best opgezet volgens een individueel afgesteld principe. Studies met ambulante HF patiënten met verminderde ejectie fractie (HFrEF), behandeld met *guideline* voorgeschreven dosis aan renine-angiotensine systeem (RAS) en β neurohumorale blokkers, hebben al een effectieve vermindering in mortaliteit en HF hospitalisaties aangetoond. Er is echter nog onzekerheid over het effect op HF patiënten met behouden ejectie fractie (HFpEF) en over dosis verhoging na hospitalisaties. Bijgevolg werd een studie opgezet om de impact van RAS en β-blokker dosis verhoging na hospitalisaties na te gaan bij beide patiënten groepen. Naast een optimale behandeling met neurohumorale blokkers, omvat geavanceerde HF zorg best ook een uitgebreid zorgprogramma. Deze opvatting leidde tot het opzetten van een tweede studie om de haalbaarheid en impact van een individueel aangepast, transmuraal en over het ganse ziekenhuis toegepaste HF zorgprogramma na te gaan. De studie onderzocht de impact van het programma op het verlagen van rehospitalisaties omwille van acuut gedecompenseerd HF (ADHF).

Methoden: De eerste studie volgde 209 HFrEF en 108 HFpEF patiënten na een initiële hospitalisatie, door het documenteren van de RAS en β-blokker dosis verhoging over een periode van 6 maanden. Vervolgens werden patiënten met RAS en β-blokker dosis verhoging vergeleken met patiënten zonder dosis verhoging. De tweede studie volgde 55 opeenvolgende patiënten die binnen één jaar gerehospitaliseerd waren voor uitgebreide HF behandeling. Na activatie van een *tag* in het elektronisch dossier werd de patiënt bij elke volgende hospitalisatie (van zowel cardiale, als niet-cardiale oorsprong) én raadpleging, behandeld volgens *guideline* en protocol voorgeschreven zorg, met telkens ook uitgebreide en laagdrempelige contactmomenten.

Resultaten: De eerste studie toonde aan dat patiënten, bij wie RAS of β-blokkers konden worden verhoogd significant jonger waren en minder comorbiditeiten vertoonden. Desalniettemin bleek dat na correctie voor leeftijd en bepaalde klinische parameters, enkel dosis verhoging van RAS blokkers aanleiding gaf tot een significante reductie in mortaliteit en HF rehospitalisaties bij patiënten met HFrEF. Dosis verhoging bij HFpEF had geen bijkomend positief effect. De tweede studie toonde aan dat na het invoeren van een transmuraal HF zorgprogramma voor patiënten met ernstig HF, het aantal ADHF hospitalisaties per patiënt per jaar, significant kan verlagen. Daarnaast was ook de jaarlijkse incidentie aan hospitalisaties en de totale tijd dat patiënten waren opgenomen in het ziekenhuis tijdens *follow-up* significant verlaagd. Bijkomend was er een duidelijke stijging in de deelname aan HF zorg via *device* telemonitoring.

Conclusies: Dosis verhoging van RAS blokkers na HF hospitalisaties blijkt beter mogelijk te zijn bij jongere patiënten met weinig comorbiditeiten. Bovendien toont de studie aan dat verhoging van RAS maar niet β-blokkers een onafhankelijke predictor is voor een verbetering van de klinische toestand van HFrEF patiënten, maar niet voor HFpEF patiënten. Daarnaast blijkt dat opvolging van patiënten met ernstig HF via een individueel aangepast en transmuraal zorgprogramma leidt tot een significante reductie in HF rehospitalisaties en een duidelijke verbetering van de klinische toestand.

1. Introduction

1.1. Heart failure definition and classification

Heart failure (HF) is a complex clinical syndrome characterized by typical signs and symptoms and is considered to be the common end-result of underlying functional or structural heart diseases. However, the heart does not 'fail' in the sense of ceasing to beat (as occurs during cardiac arrest). Rather, it weakens, usually over the course of months or years, leading to an impaired ability to act as a pump. While a variety of causes (ischemic heart disease, heart valve pathology, dilated cardiomyopathy, etc.) exist, all of them finally result in an impaired pump function or filling of the heart.

The specific effects of HF on the body depend on whether it occurs on the left or the right side of the heart (**Figure 1** for normal heart anatomy). Over time however, in either form of HF, the systemic blood supply decreases until it becomes inadequate to supply tissues and organs, which can eventually lead to the breakdown of vital systems and possibly death.

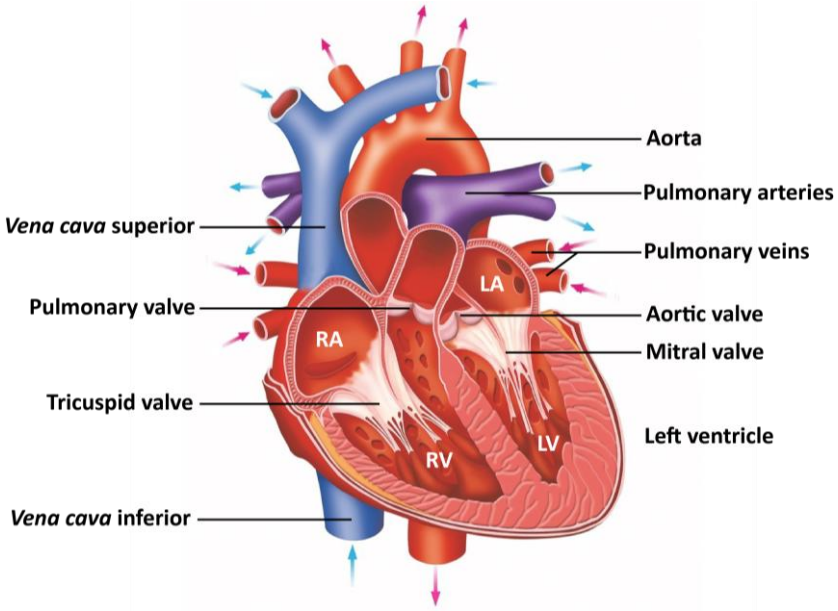

Figure 1: *Normal heart anatomy. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. Adapted from (1).*

HF severity, from a clinical point of view, is commonly classified using the New York Heart Association (NYHA) classification system which categorizes patients in one of four classes, based upon the physical disability caused by their HF (2, 3). Patients with NYHA Class I HF have cardiac disease without any limitations or symptoms during ordinary activity. Those in NYHA Class II have a slight limitation of physical activity. They are comfortable at rest, but ordinary physical activity will result in fatigue, palpitation, dyspnea, or angina. NYHA Class III patients are still comfortable at rest but have a

marked limitation in physical activity with symptoms occurring with less than ordinary activity. NYHA Class IV patients may have symptoms at rest and are unable to carry out any physical activity without HF symptoms. According to the National Heart, Lung, and Blood Institute, 35% of patients have Class I HF, followed by 35% with Class II, 25% with Class III, and 5% with Class IV HF (4). Mortality also rises as patients progress through the various NYHA classifications (5).

1.2. Heart failure pathophysiology

Heart failure with reduced ejection fraction

Left ventricle (LV) HF (or left sided HF) can be the result of either abnormal systolic or diastolic action. Systolic HF (or HF with reduced ejection fraction, HFrEF) is characterized by a weakened systolic pump function, with impaired cardiac output (CO), which may in turn lead to body-wide hypoperfusion (**Figure 2**). In addition, to compensate for systolic LV dysfunction, the LV tends to dilate which causes increased ventricular wall stress and adversely impacts on myocardial oxygen consumption. Another consequence of impaired pump function is an increase in LV end-diastolic pressure, which subsequently causes elevations in left atrium (LA) pressures and an increase in lung capillary pressure. This elevated pressure in the lungs forces fluid out of the pulmonary capillaries and leads to pulmonary congestion in and around the lungs and the major clinical symptoms of dyspnea, cough and wheezing (**Figure 3**).

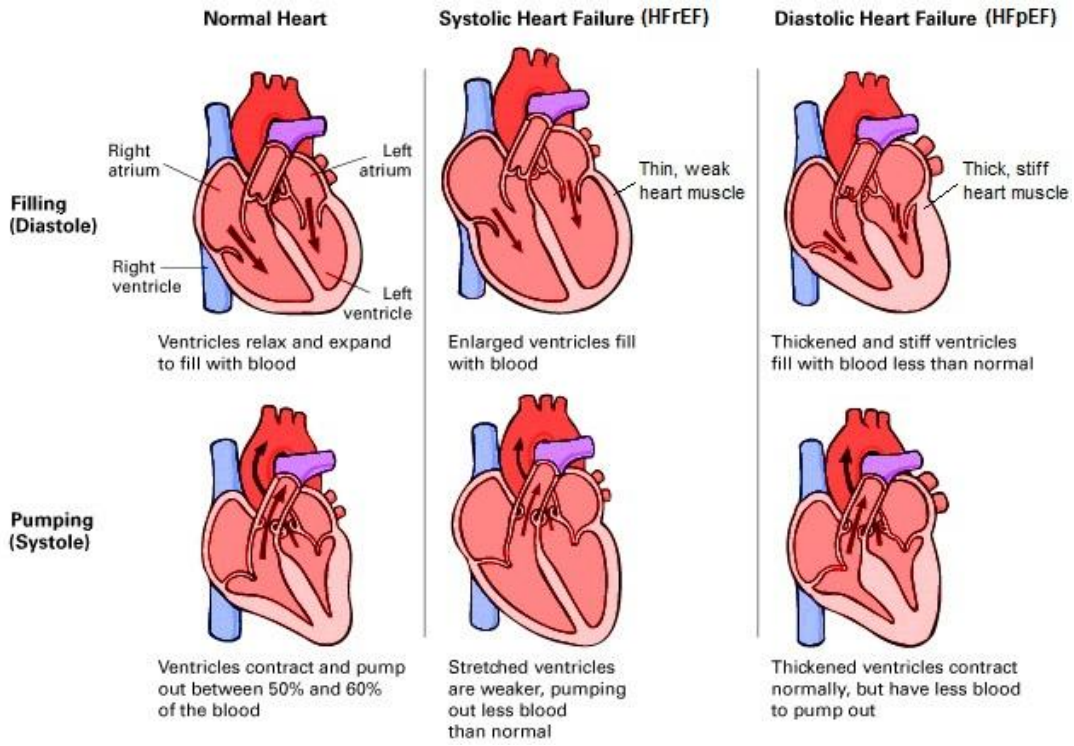

Figure 2: *Normal heart function versus systolic (HFrEF) and diastolic dysfunction (HFpEF). Adapted from* (6).

Heart failure with preserved ejection fraction

Diastolic HF (or HF with preserved ejection fraction, HFpEF) on the other hand, refers to an impaired ventricular relaxation and filling, in which the heart muscle is stiffened and cannot relax properly (**Figure 2**). Due to the decreased compliance of the ventricle, diastolic filling pressures become elevated, which makes it difficult for the blood to enter from the LA. As a result, these elevated pressures are transmitted retrograde to the pulmonary venous system, and lead to pulmonary congestion and signs and symptoms similar to HFrEF. Clinically it is very difficult to distinguish between HFrEF and HFpEF so the diagnosis is often only made by echocardiography during which a proper assessment of systolic and diastolic properties of the LV can be made. Additionally, most patients with HFrEF often have diastolic abnormalities as well and vice versa.

Right-sided heart failure

Right ventricle (RV) HF (or right sided HF) is most often the result of left sided HF, with secondary pulmonary hypertension and therefore increased RV afterload. As the RV fails, there is a similar increase in the amount of blood in the ventricle as with left sided HF, which in turn leads to elevated right atrial pressures and increased systemic venous pressure, and which impairs venous drainage from the body. This leads to increased pressure in the bowel and the lower extremities and to the clinical signs and symptoms of abdominal congestion (with ascites), hepatic congestion and peripheral edema in legs, ankles and feet (**Figure 3**). Fatigue is common as the failing heart cannot sustain enough CO to meet the body's metabolic needs, with conserved blood flow to the heart and brain. Nausea and lack of appetite may also occur as blood is shifted from the gastrointestinal tract to the more vital organs.

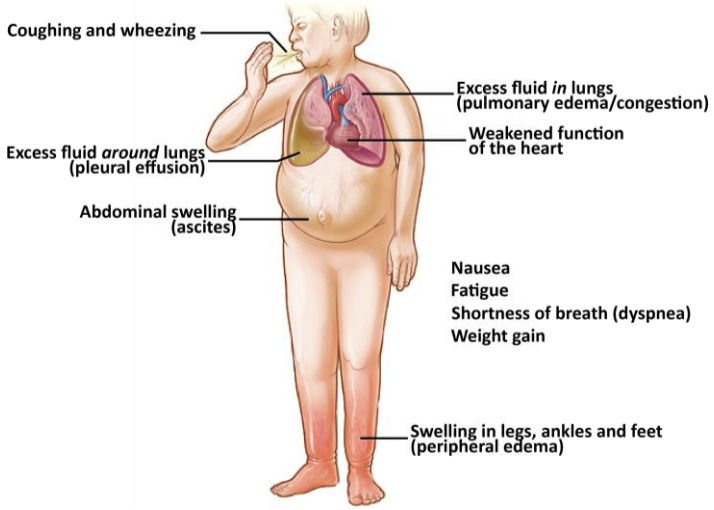

Figure 3: *Typical heart failure signs and symptoms. – Left sided: pulmonary edema, pleural effusion, coughing and wheezing. Right sided HF: ascites, peripheral edema. Common: weakened function of the heart, nausea, fatigue, dyspnea and weight gain. Adapted from* (7).

The neurohumoral system in heart failure: a detrimental vicious cycle

In HF, the body tries to maintain adequate tissue perfusion and activates several compensatory mechanisms, including the Frank–Starling mechanism, neurohumoral activation, and ventricular remodeling. As described by the law of Frank-Starling, the heart may try to increase its preload to maintain its CO in the face of impaired contractility. Neurohumoral systems on their turn, are activated in an effort to retain sodium and water, to restore adequate organ perfusion: the sympathetic nervous system (SNS), the renin-angiotensin system (RAS) and the production of antidiuretic hormone. The neurohumoral mechanisms that are activated in a response to the failing heart are actually identical to those that are triggered in situations like intense physical exercise. In such circumstances, the neurohumoral mechanisms are successful at reversing these temporary hemodynamic alterations and their activity eventually subsides. However in HF, these neurohumoral mechanisms are constantly activated in an attempt to compensate for the failing heart's inability to maintain normal cardiovascular homeostasis. The chronic secretion of these circulating neurohormones exacerbates the hemodynamic abnormalities already present in HF, which encourages further remodeling and neurohormone release, further hemodynamic deterioration and reduced systemic blood flow. In this final phase, the body maximizes all of its vasoconstrictive mechanisms in an attempt to redirect blood flow to critical organ systems, which only adds to the hemodynamic burden of the failing heart. Eventually, a vicious cycle develops whose end result is progressive ventricular dysfunction, terminal HF and in long-term possible death. When compensating mechanisms are exhausted, inadequate pump function and lack of efficient venous return brings about the typical clinical symptoms and signs of HF such as shortness of breath (dyspnea), lung congestion (build-up of fluid outside the lung blood vessels), gravity dependent (lower extremities and bowel) edema, weight gain and fatigue (**Figure 3**) (8).

1.3. Heart failure treatment

Life style modifications and pharmacological treatment

Based upon the international guidelines, the general treatment measures in both patients with HFrEF or HFpEF include lifestyle modifications (e.g. lose excess weight, abstain from smoking and alcohol use, improve physical condition, etc.) as well as medical therapies (9, 10). Pharmacological treatments for HFrEF include many medications that were designed to counteract the deleterious effects of the body's chronically activated compensatory mechanisms. Several randomized clinical trials have demonstrated the benefit of neurohumoral modulation to improve mortality rate and the number of HFrEF hospitalizations. These neurohumoral treatments for HFrEF patients include angiotensin-converting enzyme inhibitors (ACE-I) (11) angiotensin II-receptor blockers (ARB) (12), β-

blockers (13) and mineralocorticoid receptor antagonists (MRA) (14). ACE-I are among the most important drugs for treating patients with HF. ACE-I act on the RAS and block the conversion of angiotensin I to angiotensin II, by inhibiting the angiotensin-converting enzyme. Its action decreases the elevated sympathetic activity, water and salt retention and arteriolar resistance. This leads to positive effects on CO, stroke volume, blood pressure and signs of congestion. ARB have a similar function, but are used in patients that do not tolerate ACE-I therapy. ARB directly block the angiotensin receptors that are the final downstream target of the RAS. β-blockers inhibit the action of the endogenous SNS neurohormones, adrenaline and noradrenaline by targeting the β-adrenergic receptors. β-blockers are able to reduce heart rate (generating a more efficient contraction), increase vasodilatation and influence the RAS by decreasing the renin secretion and eventually reducing blood pressure. MRA (or aldosterone antagonists) have a diuretic function and antagonize the action of aldosterone at the mineralocorticoid receptors. This leads to an inhibited sodium resorption in the kidneys and increases the diuresis. MRA are often used as an adjunctive diuretic therapy, to reduce edema and the cardiac workload. Pharmacological therapy of patients with HFpEF mainly focuses on prevention of disease deterioration, via an adequate treatment of hypertension. But in clinical practice, HFpEF patients are also often treated with neurohumoral blockers. However, neurohumoral blockers have no proven beneficial effect on morbidity, mortality or diastolic function in these patients (9, 15).

Yet, despite neurohumoral blockage, both HFrEF and HFpEF patients continue to be readmitted to the hospital, with signs of hemodynamic alterations, such as congestion and/or reduced CO (16). For these patients, treatment mainly focuses on the alleviation of symptoms as they are most often treated with loop diuretics (LD). LD are used to address the signs of congestion by inhibiting the sodium and chloride resorption in the kidneys, increasing the diuresis, decreasing the blood volume and ameliorating edema.

Cardiac devices

As HF worsens, the implemented lifestyle changes and optimal pharmacological therapy may no longer be sufficient to control the symptoms. Some patients might benefit from the implantation of a cardiac device, such as an implantable cardioverter-defibrillator (ICD) or a cardiac resynchronization therapy (CRT) device.

HF patients with severe systolic dysfunction (LVEF ≤35%) and persistent mild to severe HF symptoms (NYHA II to IV), who are at high risk for sudden cardiac death caused by ventricular tachyarrhythmia, may benefit from an ICD implantation (17). This device continuously monitors the heart rhythm and delivers an electrical shock to the heart muscle when it detects an arrhythmia. In such, the ICD is able

to prevent and irregular heart rhythms to cause a cardiac arrest and eventually a sudden cardiac death (18).

HF patients with an interventricular conduction delay (widened QRS interval of ≥120ms), severe LV systolic dysfunction (LVEF ≤35%) and persistent moderate to severe HF symptoms (NYHA III to IV) may benefit from CRT, through the implantation of a biventricular CRT pacemaker device (17). CRT seeks to normalize the ventricle's depolarization to improve the efficiency of ventricular contraction and septal motion, to decrease mitral valve regurgitation and increase the diastolic filling time (19). The CRT device simultaneously stimulates the LV and RV, which restores a coordinated and synchronous pumping action. Some HF patients who are a candidate for CRT are also at high risk of sudden cardiac death from ventricular tachyarrhythmia. For these patients, a CRT with incorporated defibrillator function is available. Several trials have already illustrated the beneficial effects of CRT in HF patients, by demonstrating an improved all-cause mortality and a reduction in cardiovascular related hospitalizations (20, 21).

1.4. Heart failure readmissions: an important problem

Despite the technical and therapeutic innovations in cardiology medicine that increase the life expectancy of cardiac patients, HF remains an important cause of morbidity and mortality worldwide and a leading contributor to hospitalizations. HF affects 2 to 3% of the population of developed countries, with a marked rise in those aged over 65 (and up to 20% in the 70-80 year old) (22, 23). It has been established that about 15 (out of 900) million Europeans suffer from HF, figures very similar to the 5.8 (out of 300) million US Americans (23, 24). Also, because the incidence of HF increases with age, its prevalence will rise with as our population ages. On top of that, multinational studies conclude that HF is consuming about 2,5% of the health care budget, with 60-70% of this spent on acute decompensated HF (ADHF) hospitalizations (25, 26). Patients with ADHF continue to have 60-day mortality and readmission rates of 15% and 30%, respectively (27). Projections also show that by 2030, the total cost of HF will increase almost 120% to $70 billion from the 2013 estimated total cost of $32 billion in the USA, with comparable outcome expected in Europe (28).

1.5. Study objectives

Many questions still remain concerning the optimal care of HF patients, both pharmacologically and via elaborate disease management strategies, to effectively reduce the high readmission rates. In clinical practice, both HFrEF and HFpEF patients are generally treated with neurohumoral blockers. Despite the proven benefit of neurohumoral blockers in the treatment of patients with HFrEF, none of these blockers have yet been able to show a convincingly reduction in morbidity or mortality in HFpEF patients. Additionally, no definite answer exists on how to uptitrate neurohumoral blockers in HF patients after hospitalization.

Therefore, the first study in this thesis investigated the gap of evidence regarding the uptitration of the neurohumoral RAS and β-blockers during and after a HF hospitalization. We assessed the impact of optimization of these pharmacological treatments in HF patients, to improve clinical outcome and reduce HF readmissions. This observational study, performed at Ziekenhuis Oost-Limburg (ZOL; Genk, Belgium) followed both HFrEF and HFpEF patients over time and registered changes in RAS and β-blockers dosage, to compare the effects on patients who received uptitration to those who did not.

Another important deficit in contemporary HF treatment is thought to be the traditional model of care delivery, also called "usual care", which is considered to be an important contributor to the frequent rehospitalizations in HF (29). In usual care, treatment of HF patients generally consists of appointments with the primary physician or cardiologist, with often little attention paid to the common, modifiable factors that precipitate many HF hospitalizations. Due to their often high cardiac and non-cardiac comorbidity burden, HF patients also present themselves at hospital wards or medical services without HF expertise. Recognizing the deficiencies in usual care and the complex nature of HF, has led to the testing of interdisciplinary disease management models of care that have successfully been implemented and recommended by international guidelines. However, HF disease management programs are often organized in a single specialized ward and implement their care in a one-size-fits-all approach, negating the individual needs of the HF patient.

To address this problem, our second study investigated the feasibility and impact of an ambitious new treatment strategy developed in ZOL. This quality of care improvement program focuses on an individually tailored HF care, with implementation beyond the boundaries of the cardiology ward and with a central role for the specialized HF caregiver. We hypothesized that such an elaborate disease management follow-up program is able to effectively reduce ADHF and all-cause readmissions and improve the clinical outcome of these HF patients.

2. Methods

2.1. Gathering data for the Ziekenhuis Oost-Limburg heart failure database

To set up an initial working population, the hospital's database was screened for patients with a diagnosis of advanced HF in their electronic health record. The electronic health record of patients admitted to the cardiology ward of ZOL is registered using AGFA Healthcare (Mortsel, Belgium) medAr software. This includes a complete listing of the patient's clinical background and each outpatient consultation, hospitalization, telephone contact and medical device follow-up. These data are also integrated in the hospital-wide used web-based software MediWeb Resultserver from AGFA Healthcare. MediWeb Resultserver allows to access the complete medical register of each specific patient, with data from all hospital wards and also external patient information. For each patient an index hospitalization was defined at which they were included in the hospital's HF follow-up program. Demographics, clinical characteristics, echocardiography data and medical therapy at the time of inclusion were obtained for all patients, searching their electronic health records in both medAr and MediWeb Resultserver. Information up to one year before index hospitalization and up until study censoring or death was also gathered when needed. Long-term follow-up data were collected for all patients up to March 2013.

The next two chapters in this thesis are the results of my scientific studies which have been submitted for publication. Both articles focus on patients admitted with signs of advanced HF at ZOL. However, because different subpopulations of patients are considered, each article is listed separately. A flowchart was created and supplied in **Supplemental figure 1** for a general overview of patient subdivision into both studies. Yet, a general conclusion is provided.

3. Uptitration of Neurohumoral Blockers in Hospitalized Heart Failure Patients with Reduced versus Preserved Ejection Fraction

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Background: In ambulatory patients with HF and HFrEF, RAS and β-blockers at guideline-recommended target dose reduce all-cause mortality and readmissions. Benefits in HF with HFpEF, as well as uptitration after a hospitalization, remain uncertain.

Methods and Results: In consecutive patients (209/108 HFrEF/HFpEF), RAS and β-blocker dose changes were followed during 6 months after an index HF hospitalization. Patients with RAS and β-blocker dose increase ≥10% of the recommended target dose were compared to patients without uptitration. Patients who received uptitration were significantly younger, with a higher heart rate and better renal function. Both RAS and β-blocker uptitration were associated with significant reductions in the composite end-point of all-cause mortality or HF readmission in HFrEF [HR(95%CI)=0.36(0.22-0.60) and 0.51(0.32-0.81), respectively]. After correction for age, heart rate, blood pressure and renal function, this association remained significant for RAS blockers [HR(95%CI)=0.54(0.31-0.93); P-value=0.025], but not for β-blockers [HR(95%CI)=0.65(0.40-1.07); P-value=0.093]. No benefit of RAS or β-blocker uptitration was observed in HFpEF.

Conclusions: Uptitration of neurohumoral blockers after a HF hospitalization is more feasible in younger patients with low co-morbidity burden. RAS blocker uptitration independently predicts clinical outcome in HFrEF but not HFpEF patients.

KEY WORDS:
β-blockers; medication dose; outcome; renin-angiotensin system

Author contributions: *: Equally contributed authors
JD: Gathering of study data, study data analysis, writing of paper versions
FHV: Correction of paper versions and finalization

3.1. Introduction

Multiple randomized clinical trials have demonstrated that RAS blockers and β-blockers reduce all-cause mortality and HF admissions in *ambulatory* patients with chronic HF and HFrEF (5, 11-13, 30-34). Therefore, treatment with both these medications at dosages used by the same trials is recommended by current HF guidelines with the strongest level of evidence (10, 35). Despite these recommendations, only about a third of HFrEF patients in clinical practice receive RAS blockers at the guideline-recommended target dose, and even less reach this target dose for β-blockers (36). Improving adherence to guideline-recommended dosing might be an important strategy to reduce HF morbidity and mortality as cross-sectional studies show an association between RAS blocker or β-blocker dose and clinical outcome in HFrEF patients (37-39).

In contrast, no single pharmacological treatment– including RAS blockers – has proven to reduce either mortality or hospital admissions in randomized clinical trials of HFpEF (40-42). Despite this observation, most HFpEF patients receive similar drugs compared to HFrEF patients (43). Interestingly, in a recent observational study including 6,658 HFpEF patients, RAS blocker use was associated with a highly significant 15% risk reduction of all-cause mortality in patients who took the guideline-recommended dose for HFrEF, while no benefit was observed with a lower dose (44).

Importantly, there is a lack of longitudinal data regarding RAS blocker and β-blocker uptitration in individual HFrEF and HFpEF patients, especially during and following a HF hospitalization. Therefore, we followed a contemporary cohort of HF patients – with either HFrEF (ejection fraction <40%) or HFpEF (ejection fraction ≥40%) – over time after an index hospitalization during which HF was a primary or secondary diagnosis. We registered dose changes of RAS blockers and β-blockers serially over a period of 6 months and compared patients who received uptitration with patients who did not. We searched for determinants of non-uptitration and compared clinical outcome of these patients with those who did receive uptitration.

3.2. Methods

3.2.1. Study design

In this cohort study, all consecutive patients who were hospitalized between April, 2010, and January, 2011 at the Cardiology Department of ZOL and received a diagnosis of HF were included. Patients who were discharged during the first 24 h after admission were excluded. The study was conducted in accordance with the Declaration of Helsinki. The locally appointed ethics committee approved the study protocol and waived the need for informed consent as the study was only observational. All authors had full access to the data and contributed to the writing of the manuscript. Together, they take responsibility for the integrity of the data and agree to the report as written.

3.2.2. Baseline characteristics

For each patient, demographics, clinical data and medical therapy at the moment of admission were collected. Dosages of RAS blockers and β-blockers were expressed as percentages of the recommended target dose to account for differences between pharmacological agents. A conversion table is provided as **Supplemental table 1**. Comprehensive two-dimensional echocardiography exams were available for each patient at the time of the index hospitalization and performed by experienced sonographers using a commercially available system (Philips Healthcare, iE33®). Images were acquired in left lateral decubitus position, triggered to QRS complex and digitally stored in cine loops in DICOM format. For study purpose, a single experienced investigator, who was blinded to clinical data, reanalyzed the images offline. LVEF was obtained by Simpson's biplane or Teicholz-method, as recommended by the American Society of Echocardiography (45). Mitral valve regurgitation was semi-quantitatively assessed by color Doppler flow mapping (46). Serum creatinine at the time of admission was available in all patients and glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (47). Baseline plasma NT-proBNP was available in 177 patients (56%).

3.2.3. Population stratification and study groups

The study population was stratified in 2 groups according to a diagnosis of HFpEF versus HFrEF. Patients with a LVEF ≥40% were considered to suffer from HFpEF. Dosages of RAS blockers and β-blockers were again collected in all patients at discharge and after 6 months of follow-up. If the patient had been deceased (n=14, 4%) or lost during follow-up (n=12, 4%), the last observation available was considered. We assessed the impact of RAS blocker and β-blocker uptitration on the study end-points. RAS blocker and β-blocker uptitration were defined as a dose increase ≥10% of the recommended target dose after 6 months. Patients who were already treated at the recommended

target dose at the moment of inclusion and continued to receive this dose after 6 months were considered to be in the uptitration group.

3.2.4. Study end-points

The prespecified primary study end-point was a composite of death or HF admission. Secondary end-points were the separate components of the primary end-point. A HF admission was defined as a hospitalization ≥24 h because of dyspnea, signs of systemic congestion or low CO during which diuretics, inotropics or intravenous vasodilators were administered.

3.2.5. Statistical analysis

Continuous variables were expressed as mean±standard deviation (SD), if normally distributed, or otherwise by median interquartile range (IQR). Normality was assessed by the Shapiro-Wilk statistic. Data were compared using the independent samples student's *t*-test or Mann-Whitney *U* test, when appropriate. Categorical data were expressed as percentages and compared with the Pearson Chi-Square test. Statistical significance was set at a two-tailed probability level of α<0.05. Cumulative, actuarial survival rates were calculated according to the Kaplan–Meier method, and groups were compared with the log-rank test. The Cox proportional hazards model was used to calculate the hazard ratio (HR) with corresponding 95% confidence interval (CI) for the primary and secondary end-points. Baseline characteristics with a statistically significant different distribution among groups were entered as covariates. All statistics were performed using IBM SPSS (Chicago, Illinois, USA) (version 20.0) for Windows.

3.3. Results

3.3.1. Study population

During the study period, 354 patients received a diagnosis of HF while admitted at the study tertiary care center, ZOL. Thirty-six patients were excluded because they were not hospitalized ≥24 h. One patient was excluded because LVEF could not be reliably assessed. The remainder of patients formed the study population (n=317) and were admitted for a median (IQR) of 5 days (3-9 days) during their index hospitalization. The reason of the index hospitalization was a primary diagnosis of ADHF in 49%. Another 34% of patients were electively admitted for advanced HF therapy (e.g., placement of a cardiac device, performance of a catheterization procedure). Finally, in the remaining patients, HF was a secondary diagnosis with the primary diagnosis being an acute coronary syndrome in 7%, arrhythmia in 4% or a miscellaneous reason in 6%. Baseline characteristics of the study population are summarized in **Table 1**. Patients who received uptitration of either RAS blockers or β-blockers

were significantly younger with a higher heart rate and better preserved renal function. Patients with β-blocker uptitration also had a significantly lower LVEF, while patients who were uptitrated with RAS blockers had a significantly higher baseline blood pressure. Prescribed dosages of neurohumoral blockers at baseline, index hospital discharge and after 6 months of follow-up are presented in **Figure 4**. During the course of the study, 102 patients (32%) received a CRT device. The proportion of patients receiving CRT was similar in patients with versus without RAS blocker uptitration (34% versus 30%; P-value=0.520), but more patients who were uptitrated with β-blockers received CRT (37% versus 24% in patients who were not uptitrated; P-value=0.014).

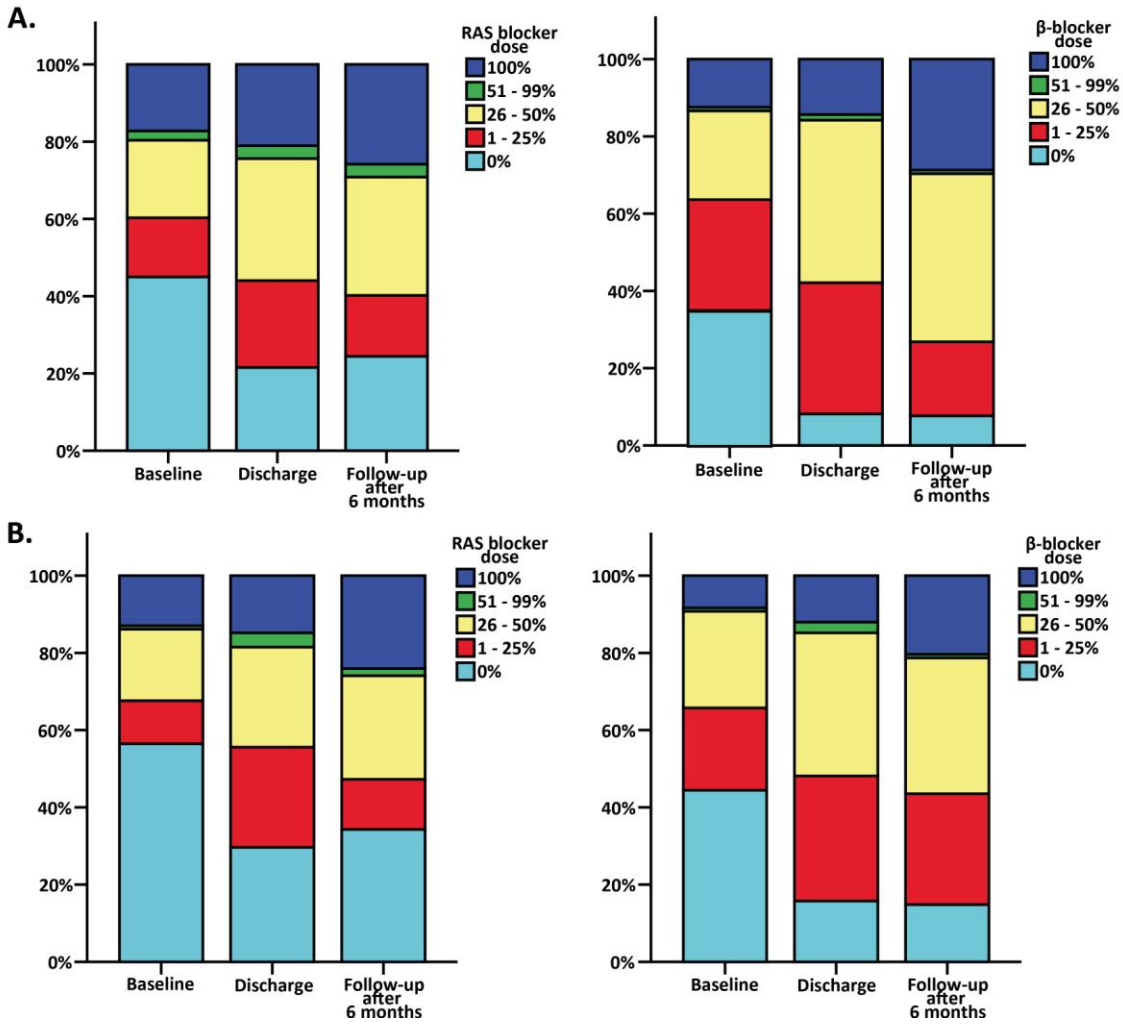

Figure 4: *Prescribed dosages of renin-angiotensin system (RAS) blockers and β-blockers at baseline, index hospital discharge and after 6 months of follow-up –* ***(A)*** *Heart failure patients with reduced ejection fraction (n=209);* ***(B)*** *heart failure patients with preserved ejection fraction (n=108).*

Table 1: *Baseline characteristics of the study population (n=317)*

	RAS blocker			β-blocker		
	Uptitration (n=160)	**No Uptitration (n=158)**	**P-value**	**Uptitration (N=187)**	**No Uptitration (n=131)**	**P-value**
Age (years)	67±12	73±10	<0.001	68±12	73±11	<0.001
Gender			0.387			1.000
Male	69%	73%		71%	71%	
Female	31%	27%		29%	29%	
Heart rate (bpm)	77 (65-96)	71 (61-86)	0.010	77 (64-95)	72 (61-85)	0.025
Arterial blood pressure (mmHg)						
Systolic	134±26	128±23	0.025	132±25	130±24	0.442
Diastolic	76±14	72±15	0.025	75±15	73±13	0.228
Body mass index (kg/m²)	28±5	28±5	0.552	28±6	28±5	0.989
NYHA class at moment of admission			0.537			0.453
I	6%	3%		4%	5%	
II	34%	32%		32%	35%	
III	52%	55%		57%	49%	
IV	8%	9%		7%	11%	
LVEF (%)	33±14	35±13	0.183	32±13	37±13	0.002
Mitral valve regurgitation ≥2	36%	41%	0.419	43%	32%	0.061
History of PCI	28%	31%	0.624	30%	30%	1.000
Diabetes mellitus	25%	33%	0.139	29%	29%	1.000
COPD	23%	29%	0.201	22%	31%	0.069
eGFR (mL/min/1.73m²)	74±24	56±27	<0.001	69±26	59±28	0.003
NT-proBNP (pg/mL)	2,354 (1,082-5,145)	3,243 (1,290-8,370)	0.070	2,624 (1,127-6,948)	2,924 (1,379-6,048)	0.629

COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RAS, renin-angiotensin system

3.3.2. Heart failure with reduced ejection fraction

From the patients who fulfilled study criteria for HFrEF (n=209), RAS blocker uptitration was performed in 106 of cases (51%), while β-blocker uptitration was done in 132 (63%). In 26 HFrEF patients (12%) who already took a RAS blocker at baseline, the dose had to be decreased because of intolerable side effects (n=15) or the medication completely withdrawn (n=11) because of an emerging contraindication (e.g. severe renal insufficiency or symptomatic hypotension). Similarly, β-blocker dose was decreased in 14 HFrEF patients (7%) with the prescription halted in 5 patients (2%). Reasons for decreasing β-blocker dosages were bradycardia and hypotension. During mean±SD follow-up of 23±11 months, 32 HFrEF patients died (15%), 53 were readmitted for HF (25%), while 138 (66%) had an event-free survival. The incidence of the primary end-point (i.e. all-cause mortality or HF admission) was significantly lower in HFrEF patients who received RAS blocker uptitration compared to patients who were not uptitrated (**Figure 5A**). Similarly, β-blocker uptitration was associated with a longer event-free survival (**Figure 5B**). After correction for age, heart rate, mean arterial blood pressure and estimated glomerular filtration rate, the primary study end-point remained significantly correlated to RAS blocker uptitration, while the association with β-blocker uptitration was no longer significant **Table 2**.

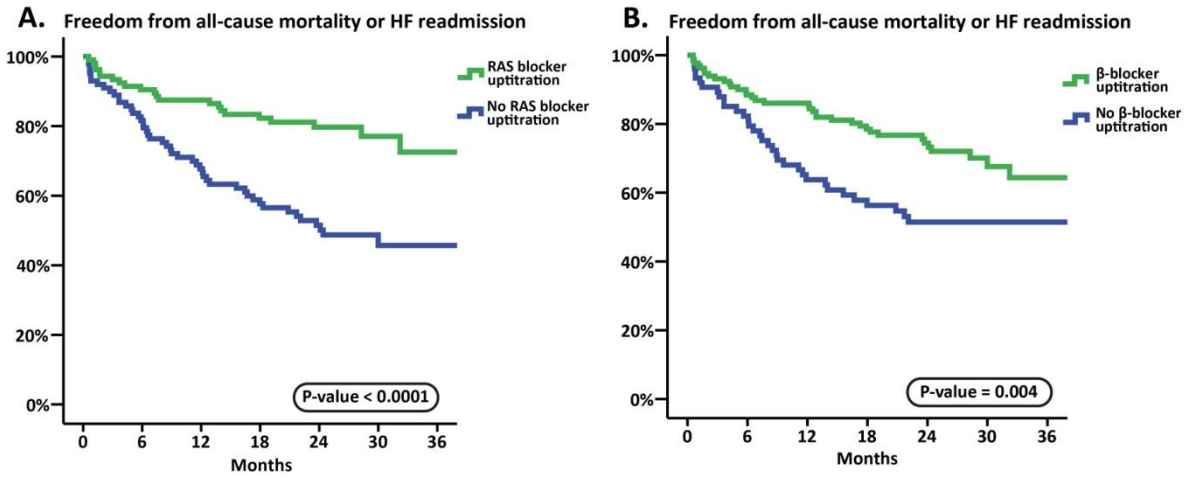

Figure 5: *Primary study end-point – Freedom from all-cause mortality or heart failure admission in heart failure patients with reduced ejection fraction according to uptitration of neurohumoral blockers. HF, heart failure; RAS, renin-angiotensin system.*

Table 2: *Primary and secondary end-points in HFrEF patients (n=209)*

	Unadjusted HR (95%CI)	P-value	Adjusted* HR (95%CI)	P-value
RAS blocker uptitration:				
All-cause mortality or HF admission	0.36 (0.22-0.60)	<0.001	0.54 (0.31-0.93)	0.025
All-cause mortality	0.24 (0.10-0.55)	0.001	0.38 (0.15-0.92)	0.032
HF admission	0.35 (0.19-0.63)	<0.001	0.47 (0.25-0.89)	0.021
β-blocker uptitration:				
All-cause mortality or HF admission	0.51 (0.32-0.81)	0.005	0.65 (0.40-1.07)	0.093
All-cause mortality	0.40 (0.20-0.81)	0.010	0.49 (0.23-1.04)	0.062
HF admission	0.51 (0.30-0.88)	0.016	0.68 (0.39-1.22)	0.196

*Adjusted for age, heart rate, mean arterial blood pressure, left ventricular ejection fraction and estimated glomerular filtration rate at baseline
CI, confidence interval; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; RAS, renin-angiotensin system

3.3.3. Heart failure with preserved ejection fraction

From the patients who fulfilled study criteria for HFpEF (n=108), RAS blocker uptitration was performed in 53 of cases (49%), while β-blocker uptitration was done in 54 (50%). In 13 HFpEF patients (12%) who already took a RAS blocker at baseline, the dose had to be decreased because of intolerable side effects (n=4) or the medication completely withdrawn (n=9) because of an emerging contraindication. Similarly, β-blocker dose was decreased in 10 HFpEF patients (9%) with the prescription halted in 4 patients (4%). Reasons for decreasing or stopping neurohumoral blockers were the same as in HFrEF patients. During mean±SD follow-up of 22±9 months, 22 HFpEF patients died (20%), 39 were admitted for HF (36%), while 54 (50%) had an event-free survival. The incidence of the primary end-point (i.e. all-cause mortality or HF admission) was similar whether HFpEF patients received neurohumoral blocker uptitration or not (**Figure 6**). No benefits with uptitration could be demonstrated for either of the secondary end-points (**Table 3**).

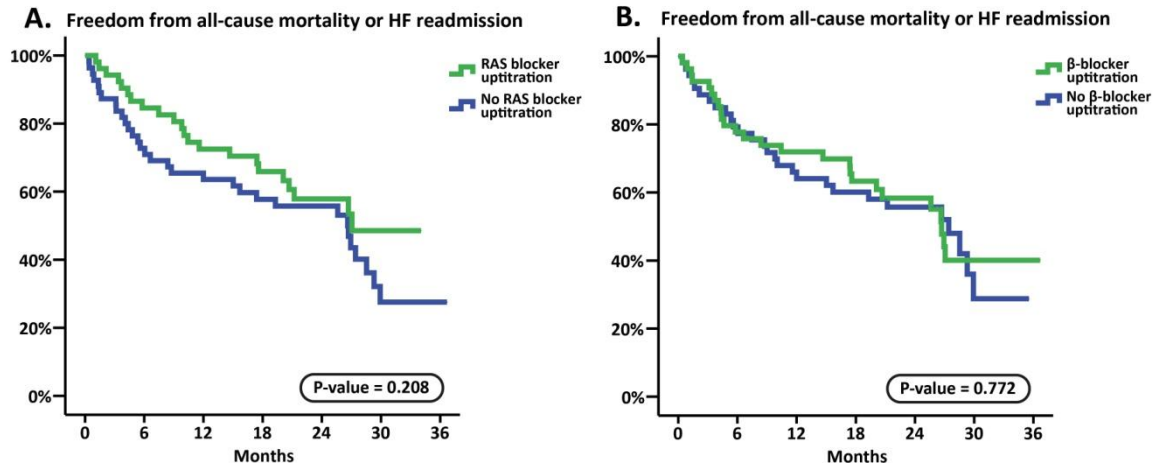

Figure 6: *Primary study end-point – Freedom from all-cause mortality or heart failure admission in heart failure patients with preserved ejection fraction according to uptitration of neurohumoral blockers. HF, heart failure; RAS, renin-angiotensin system.*

Table 3: *Primary and secondary end-points in HFpEF patients (n=108)*

	Unadjusted HR (95%CI)	P-value	Adjusted* HR (95%CI)	P-value
RAS blocker uptitration:				
All-cause mortality or HF admission	0.71 (0.41-1.22)	0.211	1.17 (0.62-2.20)	0.624
All-cause mortality	1.06 (0.45-2.46)	0.901	1.45 (0.57-3.74)	0.437
HF admission	0.57 (0.30-1.10)	0.095	1.06 (0.50-2.27)	0.879
β-blocker uptitration:				
All-cause mortality or HF admission	0.92 (0.54-1.58)	0.772	1.13 (0.65-1.96)	0.674
All-cause mortality	0.87 (0.38-2.02)	0.746	1.01 (0.43-2.39)	0.978
HF admission	1.04 (0.56-1.95)	0.897	1.33 (0.69-2.55)	0.393

*Adjusted for age, heart rate, mean arterial blood pressure, left ventricular ejection fraction and estimated glomerular filtration rate at baseline

CI, confidence interval; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; RAS, renin-angiotensin system

3.4. Discussion

Our study fills the important gap of evidence regarding uptitration of neurohumoral blockers during and immediately after a HF hospitalization in HFrEF and HFpEF patients, as changes in RAS blocker and β-blocker therapy were assessed serially over time in a cohort of 317 consecutive patients. Our results confirm that uptitration to guideline-recommended target dosages is more feasible in younger patients with less co-morbidity. Nevertheless, after correction for baseline characteristics including age, heart rate, arterial blood pressure, and renal function, RAS blocker uptitration remained a very strong predictor of improved clinical outcome in HFrEF patients, being associated with a 46% reduction of the combined end-point of all-cause mortality or admission for HF. β-blocker uptitration was also associated with a lower incidence of this combined study end-point, but after adjustment, the 35% relative risk reduction was no longer statistically significant. No benefits of neurohumoral blocker uptitration were observed in HFpEF patients.

Although treatment of chronic HFrEF patients with a RAS blocker at the target dose used in randomized clinical trials has a class I recommendation (Level of evidence: A) in current HF guidelines, there is surprisingly sparse evidence regarding a differential "dose effect" with this medication (10, 35). In the Assessment of Treatment with Lisinopril and Survival (ATLAS) study, 3,164 patients were randomized to (very) low-dose (2.5-5 mg) versus high-dose (32.5-35 mg) lisinopril (48). The primary study end-point of all-cause mortality differed not significantly among groups, but a benefit of high-dose lisinopril was suggested by a 12% reduction in the risk of death or hospital admission (a prespecified secondary end-point) and a 15% reduction in the risk of death or hospital admission for HF (a post-hoc end-point). High-dose lisinopril was associated with a higher incidence of hypotension, worsening renal function and hyperkalemia, but withdrawal of medication was needed in only 4% of patients. Another smaller study (n=248) compared an intermediate dose of enalapril (mean dose achieved: 18 mg) with a high dose (mean dose achieved: 42 mg) (49). No differences were observed in reverse LV remodeling, functional status improvement assessed by NYHA functional class or clinical outcome after one year. Importantly, the latter study included very young patients with mean age around 55 years, and half of them were NYHA functional class II, resulting in an event rate of only 18%, which causes some concerns about the statistical power of the study. The Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan (HEAAL) study is the third randomized trial available directly comparing high- versus low-dose RAS blockade in HFrEF patients (50). In this study (n=3846), 150 mg losartan was superior to 50 mg to reduce all-cause mortality or HF admissions. Again, renal impairment, hyperkalemia and hypotension were more frequent in the high-dose group, but did not lead to more treatment discontinuation. In the light of these somewhat contradicting results, our observational study provides further insight as dynamic

changes in RAS blocker dose were assessed serially over time. Moreover, we specifically included patients only during a hospitalization in which HF was a primary or secondary diagnosis, as especially in this vulnerable high-risk population, data are lacking to support uptitration. An important consequence was that the majority of patients included in our study (62%) were in NYHA functional class III/IV in contrast to for instance the HEAAL study which included mainly (70%) of patients in NYHA functional class II (50). In addition, our patients were slightly older with more impaired renal function. Our results confirm that uptitration of the RAS blocker dose in such HFrEF patients, started in hospital, is not only safe and feasible, but also improves all-cause mortality (RRR=62%; NNT=6) and HF readmissions (RRR=53%; NNT=6). Importantly, this effect could be demonstrated in a rather small population of 209 HFrEF patients, in contrast with the randomized clinical trials that needed around 4,000 patients to provide a relative risk reduction of 10%.

No randomized clinical trial has compared high-dose with low-dose β-blocker in HFrEF patients. However, in a subanalysis from Heart Failure: A Controlled Trial Investigation Outcomes of Exercise Training (HF-ACTION), there was a significant inverse relationship between baseline β-blocker dose and the end-point of all-cause death or all-cause hospitalization (51). In this study, 2,331 well-treated HFrEF patients were analyzed, and after adjustment for baseline characteristics, each 10 mg increase in carvedilol dose equivalents was associated with a 4% reduction of the combined end-point. In contrast, 3 retrospective studies, encompassing more than 1,000 patients together, have demonstrated that after correction for heart rate reduction, β-blocker dose was no longer significantly associated with better clinical outcome (52-54). In addition, a subanalysis of the Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT) has demonstrated that the magnitude of heart rate reduction by β-blockers combined with ivabradine primarily influences clinical outcome, irrespective of background β-blocker dose (55). Our results confirm that the effect of β-blocker uptitration on clinical outcome is less robust compared to RAS blocker uptitration. In the Cardiac Insufficiency Bisoprolol Study III (CIBIS-III), 1010 HFrEF patients were randomized to uptitration of enalapril first versus bisoprolol first, before switching to a combination (56). Overall, clinical outcome was similar in both strategies. Moreover, the agent that was initiated first was significantly more likely to be uptitrated to guideline-recommended dose (57). Therefore, our results suggest that after start of both drugs, it might be wise to preferentially uptitrate RAS blockers first.

Finally, our results suggest that uptitration after a HF hospitalization is not associated with better clinical outcome in HFpEF patients. This may seem to contradict the much larger retrospective study of Lund et al. (44). Using the Swedish Heart Failure Registry, it was showed in 7,941 propensity-matched patients that high-dose (≥50% of the recommended target dose for HFrEF), but not low-dose RAS blockade was significantly associated with lower all-cause mortality. However,

important differences in the study designs should be noted when interpreting the results. It is well known that even with propensity-matching of a predefined set of baseline characteristics, residual confounding by indication remains likely. An important strength of our study in this respect is the serial assessment of dose changes over time instead of a cross-sectional study design. Therefore, our study design allowed us to specifically answer the question whether uptitration of RAS blockers and β-blockers, started during a hospitalization for HF impacts on clinical outcome. Importantly, both our study and the study by Lund et al. used the same somewhat arbitrary definition of HFpEF, i.e., a LVEF of ≥40%. Probably, by applying this definition, some HFrEF patients with only modest systolic dysfunction are misclassified as HFpEF. Because the study of Lund et al. included more than 20 times as many patients as our study, this might have confounded their results more. Indeed, the positive effects on clinical outcome were most evident in patients with a 40-49% LVEF. Our study was underpowered for a subanalysis of patients with a 40-49% LVEF versus ≥50%, but no heterogeneity was observed (results not shown). Indeed, our results of serially obtained dose changes of RAS blockers in HFpEF patients demonstrate that the small trend towards better outcome with uptitration disappeared completely after adjusting for baseline characteristics including LVEF. Similarly, no benefits of β-blocker uptitration were found in HFpEF patients.

Study limitations

Some limitations should be acknowledged when interpreting the study results. First, it is clear from our results that patients who received neurohumoral blocker uptitration were younger with lower co-morbidity burden. This might create concerns that the observed benefit on clinical outcome in patients who received uptitration was entirely due to ascertainment bias of less sick patients. Indeed, the magnitude of the benefit with uptitration of both RAS and β-blockers decreased in similar proportion after adjustments for baseline characteristics. Yet even after adjustment, RAS blocker uptitration remained associated with a highly significant 46% relative risk reduction of the combined end-point of all-cause mortality or HF admission. Second, our study had a limited sample size, resulting in relatively wide CI. Indeed, the adjusted 35% relative risk reduction of the combined end-point with β-blocker uptitration was not statistically significant, which was possibly due to a lack of power. Third, a substantial number of patients received CRT during the course of the study (32%), a treatment that has been demonstrated to have major impact in HFrEF patients. However, the proportion of patients who received CRT was similar in patients whether they received RAS uptitration or not. Yet more patients who were uptitrated with β-blockers also received CRT, which might be expected to overestimate the beneficial effect of β-blocker uptitration. Finally, our 40% LVEF cut-off to define HFpEF is somewhat arbitrarily but based on current guidelines (10, 35). Therefore, some HFrEF patients might have been classified incorrectly as HFpEF.

4. Implementation of Transmural Disease Management in Patients Admitted with Advanced Heart Failure

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Objectives: To assess the feasibility and impact on readmissions of transmural disease management in patients admitted for advanced HF.

Background: HF is a complex syndrome characterized by cardiac and non-cardiac morbidity, with optimal treatment requiring an individually tailored approach.

Methods: Consecutive patients, readmitted within one year for advanced HF therapy by a dedicated HF specialist (n=55), were followed after implementation of a hospital-wide transmural disease management strategy. Participants received a tag in their electronic health record, triggering a HF caregiver contact, with subsequent guideline-recommended protocol-driven care on each cardiac or non-cardiac hospitalization as well as outpatient evaluation. Upon transition to outpatient follow-up, patients were instructed to call the dedicated caregiver with any question at low threshold. Readmission rates were prospectively collected.

Results: Despite receiving adequate treatment with neurohumoral blockers, patients (71±11 years; LVEF of 35±13%) had spent 4% (2-7%) of the year preceding study inclusion in hospital, with 73% admitted once, 20% twice, and 7% more for ADHF. During the study period, patients were exposed to 6±4 dedicated HF caregiver contacts. Participation in device telemonitoring increased from 31% to 92%, with 1 (0-3) additional phone contacts per patient-year of follow-up in this subgroup (n=24). All-cause mortality and readmission rates for ADHF were 10% and 25% after one year, and 19% and 39% after 2 years, respectively (P-value<0.001). Follow-up time spent in hospital decreased significantly to 2% (1-6%) (P-value=0.047).

Conclusions: Follow-up of advanced HF patients through transmural disease management is associated with favorable clinical outcome.

KEY WORDS:

Disease management; heart failure; hospitalizations; outcome; quality of care; transmural

4.1. Introduction

Improvements in pharmacotherapy and innovations in cardiac devices have led to an increased life expectancy and better quality of life in HF patients (5, 11-13, 30-34, 58-64). Yet despite these advances, HF remains an important cause of morbidity and mortality worldwide. It affects 2-3% of the total population in developed countries, with a prevalence as high as 20% in octogenarians (28, 35). ADHF is the leading cause of hospital admissions in patients >65 years of age, with 60-day mortality and repeat readmission rates close to 15% and 30%, respectively (27). Moreover, HF is a major contributor to healthcare costs, consuming about 2.5% of the total budget, with 60-70% spent on hospitalizations for ADHF (25, 65). Therefore, major societies like the Heart Failure Society of America (HFSA), American Heart Association (AHA), American College of Cardiology (ACC) and European Society of Cardiology (ESC) have engaged themselves in trying to reduce HF readmission rates by implementing better current evidence-based treatments and guidelines (10, 35).

Regrettably, disease management strategies implemented only at a single specialized HF ward using a one-fits-all approach have failed to improve ADHF readmission rates (66). Moreover, it is important to acknowledge that HF is not one specific disease, but rather a complex clinical condition, characterized by diverse cardiac and non-cardiac diseases. Indeed, co-morbid conditions like renal dysfunction, diabetes, or lung disease are very prevalent, and have a major impact on morbidity and mortality (67). As a result, HF patients frequently present at non-cardiac wards or medical services (i.e., extramural) (68). Therefore, care for HF patients ideally comprises an individually tailored approach which should be delivered in a systematic way with each hospitalization (or outpatient contact), irrespectively of the reason for admission, and thus also including non-cardiac hospitalizations (i.e. transmural care). Such a quality of care improvement initiative, focusing on individually tailored HF disease management with transmural care delivery and a central role for the paramedical HF caregiver, was implemented at our center for advanced HF patients with repeated readmissions. Here we report outcome data for patients who were followed by this strategy. More specifically, we assessed the impact of the program on readmission rates and clinical outcome.

4.2. Methods

4.2.1. Study population

From May, 2009, until March, 2011, we included consecutive patients admitted to our tertiary care center ZOL with a diagnosis of advanced HF, who were referred to one of the dedicated HF specialists for further therapy. Additionally, patients had to be admitted for ADHF at least once during the preceding year. ADHF hospitalizations were defined as hospital admissions because of signs and/or symptoms of congestion and/or low CO, during which diuretics, inotropics and/or intravenous vasodilators were administered. The study complied with the declaration of Helsinki and the locally appointed ethics committee approved the study protocol. As the study was only observational, the need for informed consent was waived.

4.2.2. Study efforts to deliver transmural individually tailored care

Identifying the patient throughout the hospital

What sets the transmural disease management strategy of our study apart from other multidisciplinary programs is that real efforts were made to deliver individually tailored HF care across the classical borders of the cardiology ward and even across the hospital (i.e., transmural). Therefore, upon inclusion in the study, all patients received a special tag in their electronic health record, which became subsequently activated with each hospital readmission or outpatient evaluation and triggered a paramedical HF caregiver contact. Consequently, irrespectively of the reason for readmission or location of the patient inside or outside of the cardiology ward, a HF caregiver was notified, and did visit and evaluate the patient.

Central role for the dedicated paramedical heart failure caregiver

A dedicated team of HF caregivers, all nurses trained in HF pathophysiology, echocardiography, and cardiac devices, played a central role in our disease management strategy. Importantly, these HF caregivers remained at the center of HF care during and after transition to outpatient follow-up, irrespective of the physician level treating the patient: 1) specialized care by the dedicated HF cardiologist; 2) general cardiology care by the patient's personal cardiologist; and 3) non-cardiac care including the general practitioner of the patient. Patients were explicitly instructed to contact their HF caregiver for any question at low threshold, during hospitalization (cardiac and non-cardiac) as well after discharge.

Transmural care delivery during hospital admission

At any time when a patient was visited by the HF caregiver, disease education was provided tailored to patient's individual needs and condition. Compliance with medications and dietary sodium

restriction was always evaluated, as instructed by the guidelines (35). Notes were made in the electronic health record of the patient about different aspects of education provided. Generally, patients received 6 education moments within the first year after a hospital admission for ADHF: two elaborated education session, preferably with the patient's close relatives (ca. 30 min); two short education sessions focusing on key points of medications and dietary sodium restriction (ca. 8 min) and two telephone contacts 2 weeks and 6 months after discharge. Importantly, as the paramedical HF caregiver team had a thorough insight into HF pathophysiology, echocardiography and devices, individually tailored care and education could be provided. Furthermore, the HF caregiver was instructed to check if HFrEF patients were receiving optimal medical therapy including an ACE-I or ARB, a β-blocker and a MRA at guideline-recommended tolerated target dosages. If pharmacological treatment might be improved, the HF caregiver would inform the patient's general cardiologist or treating physician in order to increase the dose if appropriate. Similarly, indications for advanced HF therapies could be suggested by the HF caregiver.

If a prolonged hospitalization was needed, the HF caregiver continued to visit the patient at least once every three days. Standardized instructions to measure daily weight changes, restrict the use of intravenous fluids and avoid non-steroidal anti-inflammatory drugs if possible were given to non-cardiac nursing teams caring for the patient. Finally, a structured questionnaire was performed to assess the need for further evaluation, and possibly advanced treatment by the dedicated HF specialist (**Figure 7**). Afterwards, the HF specialist would consider the need and strategy for decongestive therapy, advanced HF therapy, and check indications for cardiac devices. At ZOL, patients with cardiac devices are followed through cooperation between the HF specialist, electrophysiologist, cardiac imaging specialist, and dedicated nurses in a multidisciplinary clinic as described before (69-71).

Transition to outpatient care

Finally, when the patient was ready for discharge, the HF caregiver provided discharge notes with general information about HF, recommendations for life style adaptations, and a telephone number of the HF caregiver team, which could be contacted during working hours for trouble-shooting in case of questions or problems. In addition, the general practitioner was always informed electronically of any hospitalization or outpatient contact, and if needed instructed to check patient adherence to medication and/or life style adaptations. Patients with an implantable ICD or CRT defibrillator device were invited to participate in telemonitoring. Alarms which prompted action of the HF caregiver included lead/device problems, ventricular and supraventricular arrhythmias, drops in biventricular pacing <90% in case of CRT, sudden decreases in heart rate variability, and changes in

thoracic impedance in some devices. The dedicated HF caregiver interpreted the alarms daily, with transmissions during weekends read on Monday. Patients were contacted by telephone if alarms were considered to be relevant. The same structured questionnaire used by the HF caregiver for in-hospital evaluation was subsequently employed and HF education provided by phone (**Figure 7**). At each telephone contact, patients were encouraged to contact the HF caregiver team if there was any further change in clinical condition. It is important to state that there was a close collaboration between the HF caregiver team and the general practitioner of the patient, who was informed of every telemonitoring call to the patient, and instructed to closely follow-up on recommended treatment adaptations suggested.

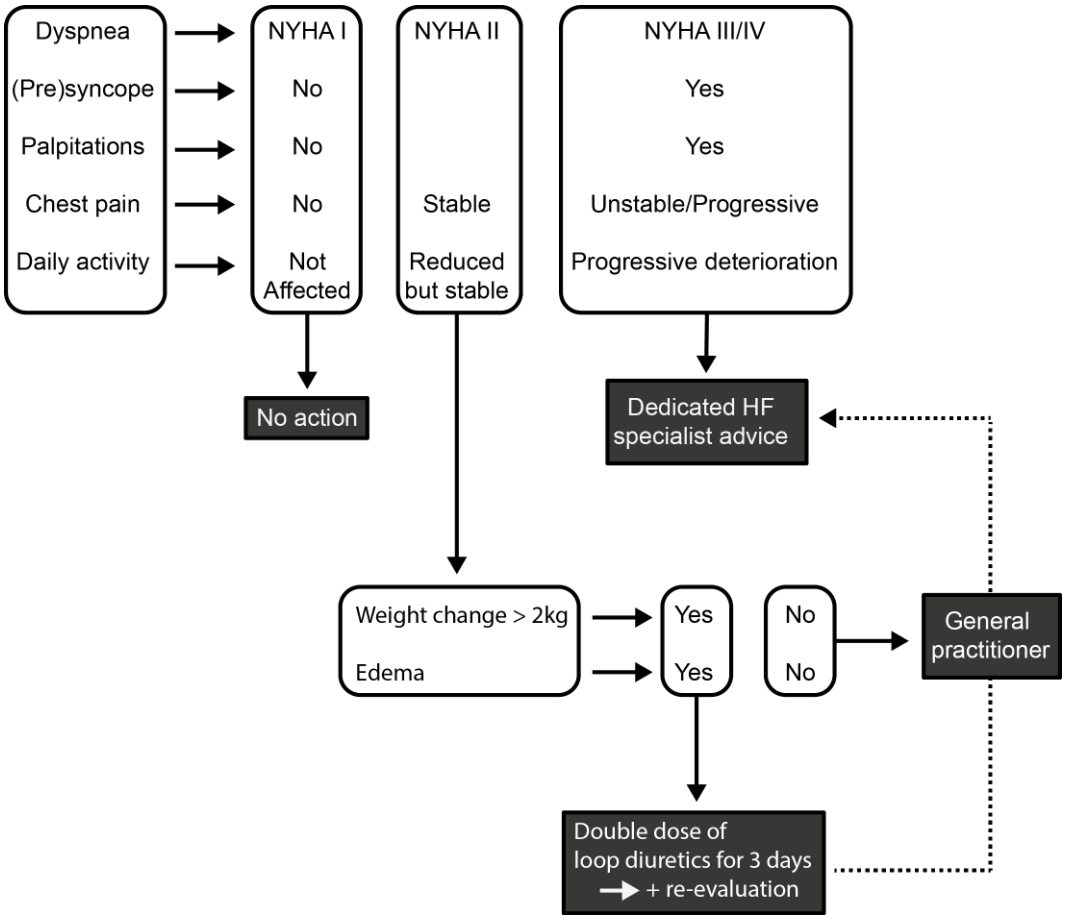

Figure 7: *Structured questionnaire used by the heart failure caregiver to evaluate the need for further evaluation by the dedicated HF specialist.*
HF, heart failure; NYHA, New York Heart Association.

4.2.3. Study end-points

Demographics, clinical data, medical therapy and admission cause were obtained at the time of the index hospitalization. Changes in medical therapy at hospital discharge and after 6 months of follow-up were registered. A comprehensive assessment was made of different treatment options

performed in each patient. Patients were followed until death, their last hospitalization, or their last outpatient evaluation, whatever came last. The primary end-point of the study was the readmission rate for ADHF after one year of follow-up, excluding elective rehospitalizations. Subsequently, we compared the ADHF readmission rate in each individual patient with the year preceding inclusion in the study. The secondary end-points were the total number of hospitalizations per year of follow-up and the percentage of follow-up time spent in hospital. Further, time to all-cause mortality was assessed. In addition, the absolute number and type of hospitalizations that occurred in the study population during follow-up were prospectively listed. ADHF hospitalizations were subdivided according to their presumed trigger: infection (e.g., respiratory infection), arrhythmia (e.g., atrial fibrillation), non-compliance which also included substance abuse or ADHF because of non-steroidal anti-inflammatory drugs use, or an unknown trigger. Acute cardiac hospitalizations were classified as an acute coronary syndrome, a primary diagnosis of arrhythmia, or a miscellaneous cause. Other non-elective hospitalizations were considered to be co-morbidity-related. Causes of elective hospitalizations included: implantation of a CRT device, implantation of a pacemaker or ICD, right heart catheterization with/without subsequent hemodynamic-guided therapy, an electrophysiological procedure (i.e., ablation, electrical reconversion or electrophysiological diagnostics), or another non-specified cause.

4.2.4. Statistical analysis

All continuous variables were expressed as mean±SD, if normally distributed, or otherwise as median (IQR). Categorical variables were expressed as percentages. The primary and secondary end-points were compared using the Wilcoxon signed rank test. Statistical significance was set at a two-tailed probability level of $\alpha<0.05$. Actuarial survival rates were calculated according to the Kaplan-Meier method. All statistical analyses were performed using IBM SPSS (version 20.0) for Windows. All authors had full access to the data, take responsibility for its integrity, have read and agree to the manuscript as written.

4.3. Results

4.3.1. Study population

Fifty-five patients fulfilled inclusion criteria and had at least one ADHF hospitalization during the year preceding the index hospitalization. Baseline characteristics of the study population are presented in **Table 4**. The median (IQR) length of index hospital stay was 7 days (4-10 days) and reasons for admission are presented in **Table 5**.

Table 4: *Baseline characteristics of the study population (n=55)*

Age (year)	**71 ± 11**
Gender	
Male	73%
Female	27%
Body mass index (kg/m²)	28 ± 6
Blood pressure (mmHg)	
Systolic	126 ± 22
Diastolic	70 ± 13
Heart rate (bpm)	82 ± 24
QRS width (ms)	129 ± 42
QRS width ≥150 ms	36%
LVEF (%)	35 ± 13
LVEF <40%	67%
Mitral valve regurgitation ≥2/4	46%
Tricuspid valve regurgitation ≥2/4	29%
Ischemic heart disease	59%
History of cardiac surgery	
Coronary artery bypass graft	22%
Valvular surgery	19%
History of atrial fibrillation	60%
Diabetes mellitus	31%
Chronic obstructive pulmonary disease	33%
NYHA functional class	
I	4%
II	29%
III	62%
IV	5%
Maximal aerobic capacity (mL/min/kg)	12.6 ± 2.9
Cardiac device	
Implantable cardioverter-defibrillator	42%
Cardiac resynchronization therapy	21%
Serum hemoglobin (g/L)	12.5 ± 2.0
eGFR (mL/min/1.73m²)	56 ± 25
Plasma NTpro-BNP (pg/mL)	3,655 (2,310-8,832)

eGFR, estimated glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association

4.3.2. Care strategies during follow-up

Patient education

During mean±SD follow-up of 22±10 months, the 55 study patients had a total of 570 HF education moments by dedicated caregivers resulting in 6±4 HF caregiver contacts per patient-year of follow-up. Forty-two percent of these contacts took place during a hospitalization (27% while being admitted at the cardiology ward, i.e. intramural; 15% extramural), while 58% were in an outpatient setting. The median (IQR) time spent by the HF caregiver on an education contact was 31 (12-39) minutes in case of an intramural hospitalization, 10 (5-10) minutes for an extramural hospitalization and 15 (10-15) minutes for an outpatient contact. An additional 30-minutes education session was provided to patients who received a cardiac device and were included in telemonitoring. Involvement of the treating physician was minimal and protocol-driven (**Figure 7**).

Table 5: *Reason for the index hospitalization*

ADHF	51%
Non-elective hospitalization not due to HF	
Cardiac arrhythmia	5%
Infectious disease	2%
Miscellaneous*	13%
Elective hospitalization	
CRT implantation	22%
Left- or right-sided cardiac catheterization	4%
Electrophysiological procedure (ablation, reconversion, diagnostics)	3%

* Pleural effusion, pacemaker erosion, chest pain
ADHF, acute decompensated heart failure; HF, heart failure; CRT, cardiac resynchronization therapy

Pharmacological therapy and hemodynamic-guided therapy

An overview of changes in pharmacological therapy during the index hospitalization and subsequent follow-up including the use of neurohumoral blockers and vasodilator therapy is provided in **Table 6**. Hemodynamic-guided therapy through guidance by pulmonary artery catheter measurements, with titration of sodium nitroprusside and intravenous diuretics to achieve a central venous pressure ≤8 mmHg and pulmonary capillary wedge pressure ≤15 mmHg as described before, was performed in 14 patients (25%) after inclusion (72, 73). In contrast, this treatment strategy was used in only 4 patients (7%) before inclusion in the study.

Table 6: *Pharmacological therapy*

	Baseline	Discharge	After 6 months of follow-up
ACE-I	53%	49%	43%
Dose (% of the recommended target dose)	50 (25-63)	50 (50-100)	50 (50-100)
ARB	11%	16%	19%
Dose (% of the recommended target dose)	50 (25-50)	25 (19-50)	38 (25-50)
ACE-I or ARB	62%	64%	60%
Dose (% of the recommended target dose)	50 (25-50)	50 (25-75)	50 (28-100)
β-blocker	87%	91%	91%
Dose (% of the recommended target dose)	50 (25-94)	50 (25-56)	50 (25-100)
Mineralocorticoid receptor antagonist	51%	56%	58%
Loop diuretic	80%	89%	75%
Dose (mg furosemide eq.)	40 (40-80)	40 (36-80)	40 (40-80)
Hydralazine	20%	31%	26%
Dose (mg)	50 (38-200)	75 (50-200)	75 (38-113)
Nitrates	9%	13%	13%

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker

Elective hospitalizations

Thirteen patients (24%) had a total of 17 elective rehospitalizations (0.18 per patient-year of follow-up). A detailed description of the reasons for such hospitalizations is provided in **Table 7**.

Table 7: *Reason for elective rehospitalizations*

CRT implantation	12%
Pacemaker or ICD implantation	18%
Right heart catheterization	
Only diagnostics	6%
Including hemodynamic-guided therapy	12%
Electrophysiological procedure (ablation, reconversion, diagnostics)	35%
Miscellaneous*	18%

* Percutaneous transluminal aortic valvuloplasty, transcatheter aortic valve implantation
CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator

Telemonitoring

At the moment of the index hospitalization, 16 patients had an ICD or CRT defibrillator and only 5 were followed by telemonitoring (31%). After inclusion in the study, there was a clear increase of participation as all but one patient agreed to be followed within the telemonitoring program. Moreover, another 9 out of 10 patients who received an ICD or CRT defibrillator after inclusion participated as well, resulting in an eventual overall participation of 92%. The 24 patients that were followed with telemonitoring were contacted 95 times in total during the study period, resulting in 1 (0-3) phone contacts per patient-year of follow-up. A detailed description of the reasons for telemonitoring phone contacts and subsequent actions is presented in **Table 8**.

Table 8: *Reasons and actions for telemonitoring contact*

Thoracic impedance alarm	**70%**
Education provided, no further action necessary	45%
Outpatient evaluation by general practitioner and increased diuretics	31%
Outpatient evaluation by dedicated HF specialist	24%
Semi-urgent hospitalization	2%
Arrhythmia	**11%**
Education provided, no further action necessary	40%
Outpatient evaluation by general cardiologist	60%
Biventricular pacing <90%	**5%**
Education provided, no further action necessary	80%
Outpatient evaluation by dedicated HF specialist	20%
Lead- or device problem	**7%**
Education provided, no further action necessary	71%
Outpatient evaluation by electrophysiologist	29%
Patient initiative	**7%**
Outpatient evaluation by general practitioner	60%
Semi-urgent hospitalization	40%

HF, heart failure

4.3.3. Primary and secondary end-points

The readmission rate for ADHF after one year of follow-up was 19%. After two years, this figure increased to 39%. Compared to the year preceding inclusion, the median (IQR) number of ADHF hospitalizations per patient per year decreased significantly from 1 (1-2) to 0 (0-0.65) (P-value<0.001; **Figure 8**). However, patients who still experienced readmissions for ADHF had a substantial higher yearly hospitalization rate of 1.00 (0.63-2.04). The overall yearly all-cause hospitalization rate decreased significantly from 2 (2-3) before to 1 (0-3) after inclusion in the program (P-value=0.014). As a result, the percentage follow-up time spent in hospital also decreased significantly from 4% (2-7%) in the year before to 2% (1-6%) after inclusion (P-value=0.047). Freedom from all-cause mortality was 90% after 1 year and 81% after 2 years of follow-up.

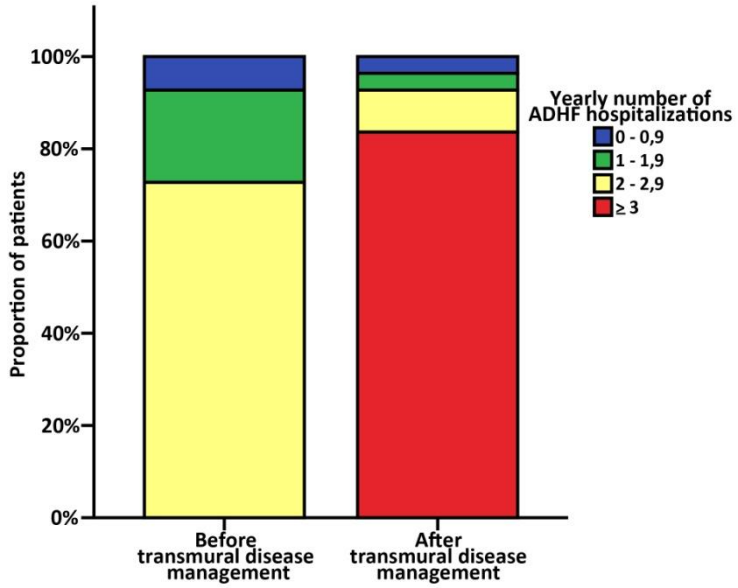

Figure 8: *Yearly number of hospital admissions for acute decompensated heart failure (ADHF) in the study population before and after transmural disease management.*

4.3.4. Hospitalization causes

ADHF hospitalizations accounted for 30% of all non-elective hospital readmissions. Triggers for ADHF were diverse, but in 55% no clear cause could be identified and non-compliance was carefully excluded in these cases (**Figure 9**). Acute cardiac hospitalizations accounted for 11% of non-elective hospital admissions (2% acute coronary syndrome; 6% arrhythmia; 3% miscellaneous). The remaining 59% of non-elective hospitalizations were comorbidity-related (22% within the cardiology ward; 37% outside of the cardiology ward).

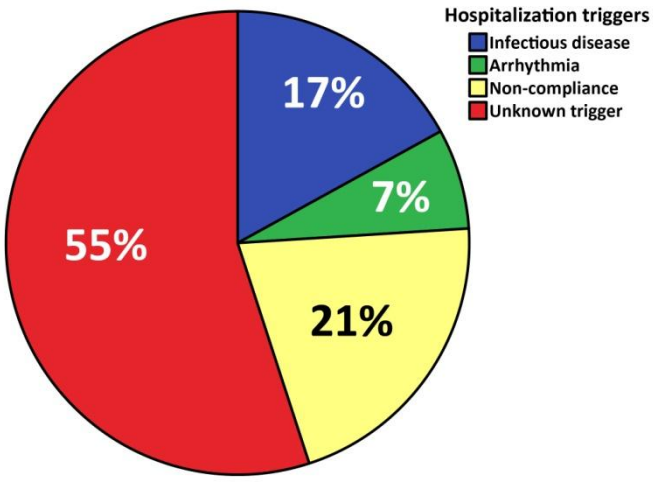

Figure 9: *Triggers for ADHF hospitalizations (n=42).*

4.4. Discussion

The primary finding of this study is that a transmural disease management program with individually tailored, supervised HF care across the borders of the cardiology department – within and outside of the hospital – is feasible in clinical practice without significant time investment of physicians. Moreover, the implementation of such a program, mainly provided by paramedical HF caregivers, resulted in an impressive decrease of ADHF readmissions in patients with advanced HF. Although hospital readmissions for ADHF still accounted for 30% of the remaining hospitalizations during follow-up, most of these readmissions were presumably not preventable as they were triggered by infection (17%) or lacked a clear trigger with non-compliance excluded as a cause (55%). Overall, survival was good in this population of very sick HF patients (90% after one year and 81% after two years) with only 2% follow-up time spent in hospital after implementation of the transmural care pathway. Our study strongly suggests that HF care should exceed beyond the boundaries of the cardiology ward. However, an engaged, educated and dedicated team of HF caregivers is pivotal to achieve this.

As HF is not a simple disease, but an often complex clinical syndrome, care for patients has evolved to comprehensive, integrated and interdisciplinary disease management strategies. The first randomized clinical trial that investigated such an approach reported a reduction in the readmission rate of elderly HF patients when comprehensive education of patient and family, dietary advice, review of the medication, social service consultation and discharge notes by HF nurses were implemented systematically (74). Subsequently, several large meta-analyses, have confirmed that multidisciplinary disease management strategies in HF patients are associated with a 30% reduction

in ADHF readmission rates and up to 18% decrease in the combined event of readmission or death (75, 76). Furthermore, multidisciplinary HF strategies were cost-efficient as the increased cost of organized HF care was offset by a reduction in readmissions (75-77). It is both reassuring and thought-provocative that the implementation of a transmural HF disease management strategy in our study was able to significantly reduce readmission rates, even in old and very sick patients with high co-morbidity burden.

However, an important limitation of randomized clinical trials and meta-analyses that evaluate disease management strategies for HF remains the substantial variation concerning the design and characteristics of these programs. Moreover, it is very difficult to assess which aspects of an integrated approach are essential for perceived benefits. Based on current knowledge, successful strategies probably include a multidisciplinary approach, including in-hospital care, intensive patient education, supportive self-care strategies, optimization of medical treatment, and continued surveillance during follow-up (77). It should be noted that these aspects were central in our transmural disease management program. Other key aspects described by others and central in our care strategy were the active involvement of dedicated caregivers and cardiologists specialized in HF, a close collaboration with the general practitioner, and prompt response on deterioration during follow-up, which was especially true in our patients who participated in telemonitoring. In addition, it should be stressed that HF caregivers in our study were thoroughly trained to have knowledge on HF hemodynamics (clinical assessment and echocardiography), medical therapy and device technology (diagnostics and optimization). These important insights allowed them to really deliver individualized HF care.

Yet, one of the largest randomized clinical trials evaluating a HF disease management strategy, the Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH) showed disappointing results (66). In the COACH study, 1049 HF patients were randomly assigned to usual care, an interventional group with basic support and an interventional group with intensive support. Patients in the basic support group received visits by a HF nurse at admission and with each outpatient contact. The nurse provided protocol-guided education and a contact address was given in case of clinical deterioration, HF signs or symptoms. Education materials included a patient diary, brochures on HF and its management and samples of sodium-restricted food seasonings. Patients in the intensive support group received the same interventions as the basic support group, but were scheduled for monthly HF nurse visits, weekly telephone contacts in the first month after discharge and were visited at home by a HF nurse. Furthermore, the intensive support also included extra telephone calls, two home visits, multidisciplinary advice given by a physiotherapist, dietician and

social worker and extra education in HF patient self-efficacy. During follow-up of 18 months, the study's first primary end-point of ADHF readmissions or all-cause mortality did not differ significantly between groups, nor did the second primary end-point of number of days lost because of death or hospitalization during follow-up. At first sight, the findings of this study seem in disagreement with previous evidence. However, the COACH study featured a one-size-fits-it-all approach for each individual patient in a specific group. Moreover, HF care delivery was provided only intramural, while our study clearly demonstrates that through the use of a HF tag incorporated in the electronic health record of the patient, transmural care delivery is probably more successful at reducing readmissions. This is illustrated by the fact that 63% of HF caregiver contacts took place outside the borders of the cardiology ward, and 58% of these even outside of the hospital. Moreover, the substantial proportion of patients who had an ICD or CRT defibrillator (n=24) and were followed with telemonitoring had an additional 1 (0-3) phone contacts per patient-year of follow-up. Indeed, the COACH investigators acknowledge that HF disease management programs should not be abandoned but rather refined. Our study, which describes in detail different treatment options performed and reasons for readmission in a population of very sick HF patients with repeated readmissions, is reassuring as it indicates that with transmurally delivered, individually tailored, multidisciplinary HF disease management programs, caregivers can actually dramatically reduce readmission rates.

Study limitations

Some limitations should be acknowledged when interpreting the results of this study. First, this was a single-center study in an experienced tertiary care center, which might create some concerns regarding external validity. However, as explained, we think the concept of transmural disease management is feasible in clinical practice with a simple tag in the electronic health record, even in less experienced centers, if a motivated team of dedicated and educated HF nurses is present. Second, the sample size of this study is rather small, implying that our findings are only hypothesis-generating and should be confirmed in larger studies. Yet it remains very difficult to rigorously perform a trial evaluating the impact of a multidisciplinary treatment strategy on clinical outcome. Importantly, our cross-over design ensures minimal intra-individual variability and the unequivocally positive results of the study in a selected group of very sick HF patients make a strong pledge towards efficacy of the disease management strategy. Third, the sample size of our study was too small to identify the relative effectiveness of different aspects within the disease management program to improve clinical outcome. Fourth, despite a strong focus on optimal medical treatment, the proportion of patients who took guideline-recommended neurohumoral blockers increased little during follow-up and the percentage of patients on renin-angiotensin system blockers might be considered low. However, patients were already diagnosed (and treated) for HF before inclusion in

the study. Moreover, they were very sick with a median NT-proBNP of 3,655 pg/mL and a lot of them suffering from chronic kidney disease and not tolerating further uptitration of these medications. Fifth, 25% of patients received a CRT device during follow-up, which has been shown to reduce readmissions for ADHF in similar populations as ours (61, 62). However, this effect of CRT in only a subset of patients is unlikely to account for large drop in ADHF readmissions observed in the population as a whole.

5. General conclusions

The goal of this thesis was to assess potential strategies to improve the clinical outcome of HF patients, thereby reducing HF morbidity, rehospitalizations and mortality. Two studies were performed, one to investigate the effect of neurohumoral uptitration in HFrEF and HFpEF patients after hospitalization, the other to improve the contemporary quality of care of patients with advanced HF and multiple ADHF readmissions.

The first study showed that neurohumoral blocker uptitration, started during a hospitalization for HF, is more feasible in younger patients, with less co-morbidity. The study also revealed that RAS blocker uptitration is an independent predictor of better clinical outcome in HFrEF. As the impact of β-blocker uptitration was less pronounced, it might be prudent to try and reach the guideline recommended dose of RAS blockers first. However, no benefits of neurohumoral blocker uptitration were observed in HFpEF patients.

The second study reports outcome data for a selected cohort of advanced HF patients with repeated readmissions for ADHF, after the implementation of a hospital-wide, transmural HF disease management strategy. Our data showed that when HF care is individually tailored and delivered beyond the borders of the cardiology ward, readmissions for ADHF and all-cause hospitalizations can be reduced dramatically, even in a population of very sick patients. Moreover, by giving a central role to dedicated HF caregivers, such strategy is feasible in clinical practice as patients are efficiently referred to the most appropriate level of care. This requires close collaboration between general practitioners and other caregivers including but not limited to cardiologists, with patients only referred to the dedicated HF specialist for advanced HF therapies.

Future directions

Both studies in this thesis were able to indicate that optimal care for patients with HF is ideally organized via an individually tailored approach. However, some directions for the future should be considered. First of all, a clear distinction between HFrEF and HFpEF oriented treatment should be implemented in the future. In current clinical practice, both patients groups are generally treated with neurohumoral blockers, however no beneficial effect is seen in HFpEF patients, also proven by our study. Future adaptations of international guidelines should consider these results and discourage the use of neurohormonal blockers in HFpEF patients and encourage the use of vasodilatory medication to augment the diastolic function of these patients and treat the signs of hypertension. Additionally, guidelines are safe to recommend uptitration of neurohumoral blockers in HFrEF patients, with priority to RAS blockers over β-blockers. Secondly, as proven by our study, a

HF disease management program, adapted to the needs of the individual patient, with boundary crossing action and a with central role for the dedicated HF caregiver shows markedly superior effects over usual care and even regular one-size-fits-all management approaches. Guidelines should definitely recommend the use of such elaborate disease management programs and pinpoint the need of investment in well-educated HF caregivers, and provide them with a pivotal and delegating role. A future study on the transmural disease management of ZOL should also include an economic perspective and investigate the economic impact of such an approach, although in general, disease management programs appear to be cost saving, as already commented in our discussion.

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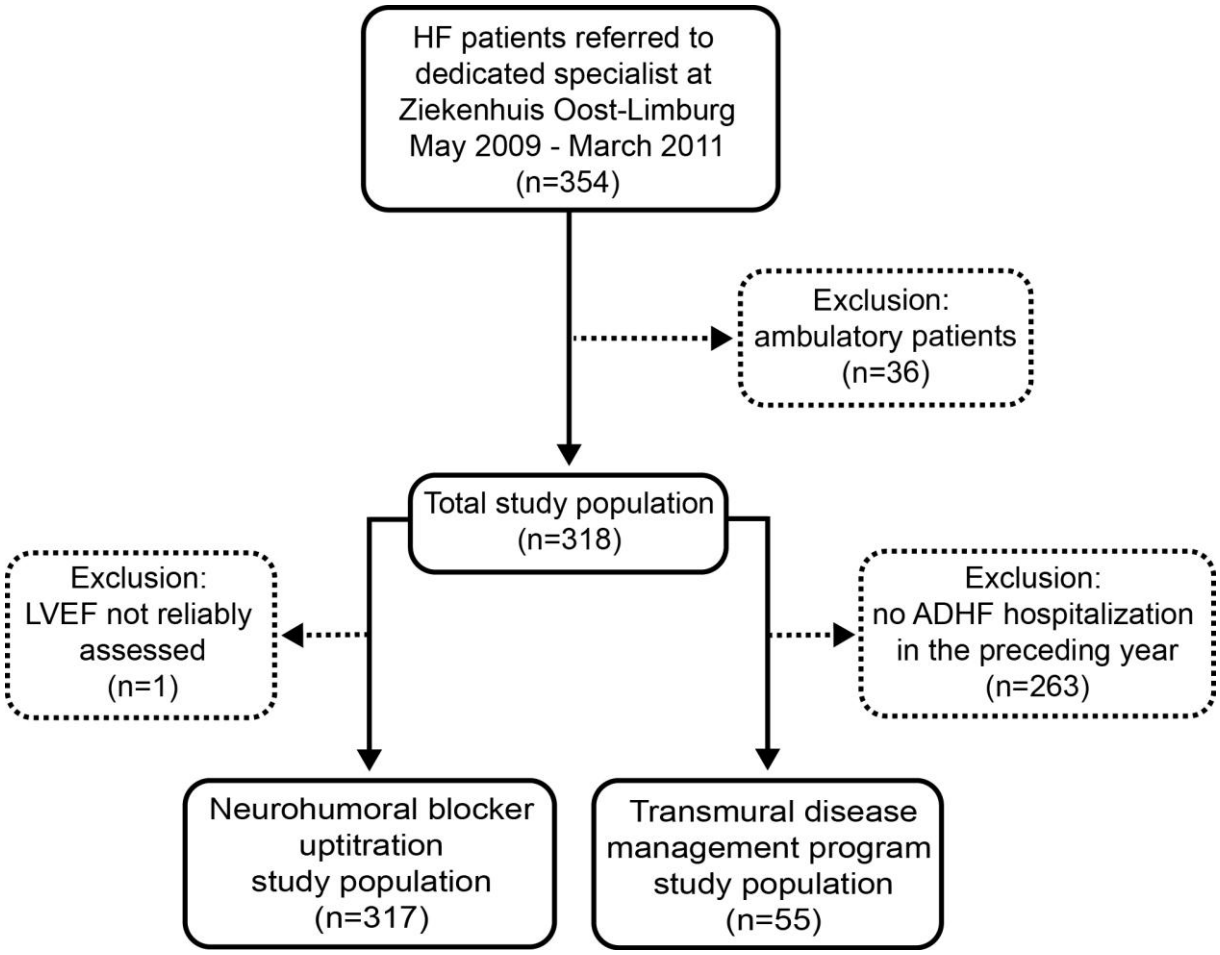
Addendum



Supplemental figure 1: *Overview flow-chart of both studies.*
ADHF, acute decompensated heart failure; HF, heart failure; LVEF, left ventricular ejection fraction.

Supplemental table 1: *Conversion table of recommended daily target dosages for renin-angiotensin system blockers and β-blockers*

Renin-angiotensin system blockers	Recommended target dose
Captopril	150 mg
Enalapril	40 mg
Lisinopril	40 mg
Perindopril	10/8 mg*
Quinapril	40 mg
Ramipril	10 mg
Candesartan	32 mg
Eprosartan	600 mg
Irbesartan	300 mg
Losartan	150 mg
Olmesartan	40 mg
Telmisartan	80 mg
Valsartan	320 mg
β-blockers	
Atenolol	100 mg
Bisoprolol	10 mg
Carvedilol	50 mg
Celiprolol	400 mg
Metoprolol	200 mg
Nebivolol	10 mg

*5 mg perindopril arginine = 4 mg perindopril tert-butylamine

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Richting: **master in de biomedische wetenschappen-klinische en moleculaire wetenschappen**
Jaar: **2013**

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Datum: **8/06/2013**