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# Evaluation and improvement of integrated cardiac care: efficient and effective care in patients with chronic coronary artery disease and chronic heart failure

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# CHAPTER 5

# TERTIARY HEART FAILURE CARE IN THE NETHERLANDS: WHAT IS THE ADDED VALUE?

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## ABSTRACT

**Objective:** Ideally, heart failure (HF) care is provided in a multi-professional manner with a seamless transition across primary, secondary and tertiary care. It is essential that the added value of each part of the HF-care chain is clear. The current study aimed to evaluate the added value of a dedicated HF-management program in a tertiary hospital.

**Design and methods**: HF-patients with a reduced left ventricular ejection fraction (LVEF) referred by a cardiologist to a tertiary HF-outpatient clinic in order to evaluate their HF-treatment options between 2011-2017. Treatment options were assessed systematically and clinical outcome and hospital admissions were evaluated up to 1 year follow-up.

**Results**: A total of 603 patients (64 years (95%CI 63–65), 70% male) were included. Additional treatment options were identified in 69% of patients, comprising optimisation of medication in 52%, invasive/surgical treatment in 39% and cardiac rehabilitation in 34%. At 1 year, New York Heart Association (NYHA) class improved from 2.3 (95%CI 2.3–2.4) to 1.9 (95% CI 1.8–2.0;P<0.001) and LVEF increased from 30% (95%CI 29–31%) to 35% (95%CI 34–36%;P<0.001). The percentage of patients admitted for decompensated HF decreased from 31% in the 6 months before referral to 13% (P<0.001) in the first 6 months and to 12% (P<0.001) in the 6-12 months period after referral.

**Conclusion**: A dedicated tertiary HF-management program is of added value since additional treatment options can be identified in the majority of patients paralleled by an improved clinical outcome and reduction in hospital admissions for decompensated HF.

## INTRODUCTION

Worldwide, the amount of patients with heart failure (HF) increases due to the ageing population and the prolonged survival of HF patients.(1) Advances in pharmacological treatment as well as percutaneous and surgical therapies have improved survival. In addition, the prevalence of risk factors like diabetes, obesity and hypertension, with a major contribution in developing heart failure still increases.(2, 3) Together these factors ensure HF continues to be a serious burden on the healthcare system which underlines the need to optimise the organization of HF care.

In 2011 the European Society of Cardiology emphasized the need to deliver HF care in a multi-disciplinary manner as this reduces mortality and HF hospitalizations.(4) Nowadays, most hospitals have dedicated HF outpatient clinics. The more recent attention for delivering "the right care at the right place" forces HF cardiologists in secondary and tertiary referral hospitals to improve co-operation with each other and with general practitioners.(5) Ultimately, this co-operation will result in a seamless transition of HF care across primary, secondary and tertiary centers.(6) However, for this to succeed it is essential that the added value of each part of the HF care chain is clear and that opportunities for improved HF management are identified.

The aim of the current study was to evaluate the added value of a tertiary HF management program. This program is especially designed for complex HF patients referred by a cardiologist in a general hospital in order to evaluate additional HF treatment options. The current study describes which treatment possibilities were identified and the subsequent course of symptoms, cardiac function and hospital admissions.

## DESIGN AND METHODS

### Recruitment

All HF patients referred by a cardiologist to our tertiary HF outpatient clinic in order to evaluate and optimize their HF treatment options were included (n=603). The inclusion period was from 2011-2017. The main criteria for inclusion of patients of the current study were HF patients with a left ventricular ejection fraction <40%. Patients referred by their general practitioner (for example because of new/recent-onset HF) and patients who were referred by a cardiologist for a particular HF intervention were not included in the current analysis. All patients were evaluated and treated according to the institutional MISSION!HF-program.(7)

### Study procedure

The MISSION!HF program is based on the European Society of Cardiology guidelines for acute and chronic heart failure and is systematically updated after the release of a new guideline version.(8-10) Data acquired during the baseline out-patient visit included New York Heart Association (NYHA) functional classification, heart rate and blood pressure as well as serum creatinine and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels and co-morbidities. Also quality of life was assessed with the Minnesota Living with HF questionnaire. HF medication and hospital admissions due to decompensated HF in the 6 months before referral and any previous cardiac interventions were recorded. Baseline transthoracic echocardiography was performed to assess biventricular function and the presence of valvular heart disease.(11) In patients with HF and known coronary artery disease and in patients with anginal complaints dobutamine stress echocardiography was performed to evaluate the presence of ischemia and viability.(12, 13)

After the initial visit all patients were discussed in the multi-disciplinary HF team consisting of HF-cardiologists, HF-nurses, imaging cardiologists, interventional cardiologists, electrophysiologists and cardiac surgeons. Potential treatment options and the possibility for initiation or up-titration of HF medication were considered. In patients using optimal HF medication the need for revascularisation, valve surgery, surgical left ventricular (LV) restoration, and/or cardiac resynchronisation therapy was determined in line with the guidelines.(8, 14, 15) Patients who remained in NYHA class IIIb/ IV despite optimal HF medication and who were ineligible for surgery and/or cardiac resynchronization therapy were considered for heart transplant or implantation of an left ventricular assist device (LVAD) as destination therapy. Additionally, a cardiac rehabilitation program was offered.

Follow-up, at 6 and 12 months, consisted of a clinical re-assessment, laboratory testing and echocardiography. Furthermore, admissions for decompensated HF were noted.

Patients were referred back to their original cardiologist if no additional HF treatment could be identified.

### Data Collection

Clinical and readmission data were collected from the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Centre, The Netherlands). Mortality data were collected using municipal civil registries in December 2018.

### Statistical Analysis

Statistical analyses were performed using IBM SPSS for Windows (version 23.0, Chicago, Illinois). Continuous variables are presented as mean ± standard deviation when normally distributed. Categorical variables were presented as frequencies and percentages. Log transformation was used in NT-pro BNP for all analyses to reduce the skewed distributions and make the data more interpretable. Mortality data and data on readmissions were available for all patients. For the other remaining clinical parameters, missing values were replaced by predictive mean matching using multiple imputation which was repeated a hundred times. For all clinical parameters, the rate of missing data was <10%. Baseline NYHA functional class, creatinin levels, NT-proBNP level, LVEF, admission rate, heart rate, blood pressure and BMI were used as predictors in the model for multiple imputation. The pooled data was used for analysis. The generalized estimating equations (GEE) model, utilizing an independent working correlation structure, was performed to analyze the clinical characteristics and laboratory results over time. The GEE model took into account the correlations between repeated measurements within the same subject. P-values<0.05 were considered statistically significant.



## RESULTS

### Study population

Between 2011–2017, 603 HF patients were referred to the MISSION!HF outpatient clinic in order to assess their additional HF treatment options. The demographic and clinical characteristics of the patient population are shown in Table 1. Mean age was 64 (95%CI 63–65) years and 70% of the patient population was male. Mean time between the diagnosis of heart failure and referral to the MISSION!HF outpatient clinic was 3.1 (95%CI 2.7–3.4) years. At baseline, NYHA class was 2.3 (95%CI 2.3–2.4) and LVEF 30% (95%CI 29–31%). In the 6 months before referral to the MISSION!HF outpatient clinic, 31% of patients were admitted due to of decompensated HF.

### Risk factors for heart failure

Almost half of the study population had an ischemic etiology of heart failure (49%). Table 1 includes important risk factors for developing heart failure. Mean Body Mass Index (BMI) was 27 kg/m2 (95% CI 26 – 28). Almost half of the patients had a history of

hypertension (47%) and one third an history of hypercholesterolemia (33%). Diabetes Mellitus was also present in nearly a third (28%) of the study population. A total of 40% smoked in their past and 9% was a current smoker. Furthermore, anaemia was present in 30% of the HF patients.

**Table 1.** Baseline characteristics of the study population

| | Mean / n (%) | 95% CI |
|---|---|---|
| Age (years) | 64 | 62 - 65 |
| Male sex | 422 (70%) | |
| HF aetiology, n (%) | | |
| Ischemic cardiomyopathy | 294 (49%) | |
| Non-ischemic cardiomyopathy | 309 (51%) | |
| Cardiac history | | |
| Myocardial infarction | 250 (42%) | |
| Revascularisation | 286 (47%) | |
| Prior valve surgery | 70 (12%) | |
| Prior device implantation | | |
| CRT-D | 122 (20%) | |
| ICD | 126 (21%) | |
| PM | 14 (2%) | |
| Mean time diagnosis HF and referral (years) | 3 | 3 - 3 |
| NYHA functional class | | |
| I | 72 (12%) | |
| II | 289 (48%) | |
| III | 199 (33%) | |
| IV | 28 (5%) | |
| N/A | 15 (2%) | |
| Heart rate (/min) | 74 | 73 - 76 |
| Systolic blood pressure (mmHg) | 114 | 113 - 116 |
| Diastolic blood pressure (mmHg) | 69 | 68 - 70 |
| BMI (kg/m2) | 27 | 26 - 28 |
| Laboratory assessment | | |
| Creatinine (umol/L) | 119 | 114 - 124 |
| NT-proBNP (ng/L) | 4222 | 3560-4885 |
| Electrocardiogram | | |
| Sinus rhythm | 438 (73%) | |

**Table 1.** Continued

| | Mean / n (%) | 95% CI |
|---|---|---|
| Atrial fibrillation/flutter | 127 (21%) | |
| Other rhythm | 38 (6%) | |
| QRS duration (ms) | 131 | 128-134 |
| LBTB configuration | 108 (18%) | |
| Echocardiography | | |
| Left Ventricular Ejection fraction (%) | 29 | 29 – 30 |
| Severe valve disease (AS, AR, MR, TR) | 69 (11%) | |
| Comorbidities | | |
| Hypertension | 282 (47%) | |
| Hypercholesterolemia | 197 (33%) | |
| Diabetes Mellitus | 167 (28%) | |
| History of CVA | 81 (14%) | |
| History of malignancy | 79 (13%) | |
| COPD | 56 (9%) | |
| Anaemia | 178 (30%) | |
| Peripheral vascular disease | 72 (13%) | |
| Smoking | | |
| Current | 55 (9%) | |
| Past | 241 (40%) | |

Continuous data are presented as mean (SD). Categorical data are presented as numbers (%). HF = heart failure; CRT-D = Cardiac resynchronization therapy defibrillator; ICD = implantable cardioverter defibrillator; PM = Pacemaker; NYHA =New York Heart Association; NT-pro BNP = N-terminal pro B type natriuretic peptide; AS = Aortic Stenosis; AR = Aortic regurgitation; MR = Mitral regurgitation, TR = Tricuspid regurgitation. Anaemia is defined as a haemoglobin concentration of 13.0 g/dL in men and 12.0 g/dL in women.



## HF treatment

At referral, HF medication comprised beta-blockers in 78%, ACE inhibitors or angiotensin receptor blockers (ARB) in 82% and mineralocorticoid receptor antagonists (MRA) in 51% patients. A total of 7% (N=42) of the patients received 100% of the target dose of BB at referral. A target dose of 100% of ACE or ARB and MRA was received by 11% (N=66) and 7% (N=40) of the patients, respectively. A target dose of 50% of BB was received by 19% (N=113) of the patients. And 20% (N=118) and 27% (N=162) of the patients received a target dose of 50% of ACE/ARB and MRA, respectively. Prognosis-improving HF medication could be optimised in 52% of the patients (Figure 1). As shown in Figure 2, optimisation of prognosis-improving HF medication consisted of initiation or up-titration of beta-blockers in 6% resp. 17%, initiation or up-titration of ACE inhibitors/

ARBs in 8% resp. 14% and initiation or up-titration of MRA in 13% resp. 4% of patients. Of interest, in 10% of patients loop diuretics were initiated and in 3% of patients the dosage was optimised.

After optimisation of HF medication, structured analysis revealed potential for invasive/surgical treatment in 39% of patients (Figure 1). Invasive or surgical HF treatment consisted of revascularisation (9%), valve surgery (13%), LV restoration (6%), cardiac resynchronisation therapy (21%) and ICD implantation (18%). In total one patient was accepted for heart transplant and in 3% a LVAD was implanted as destination therapy. A cardiac rehabilitation program was completely fulfilled by 34% of the patients (Figure 1). No additional HF treatment options could be identified in 31% of the patients. These patients were referred back to their original cardiologist.

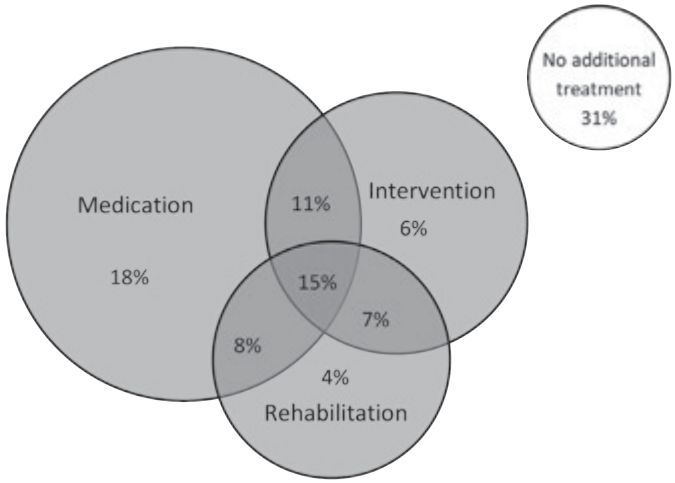


**Figure 1.** The additional treatment options as identified during the program

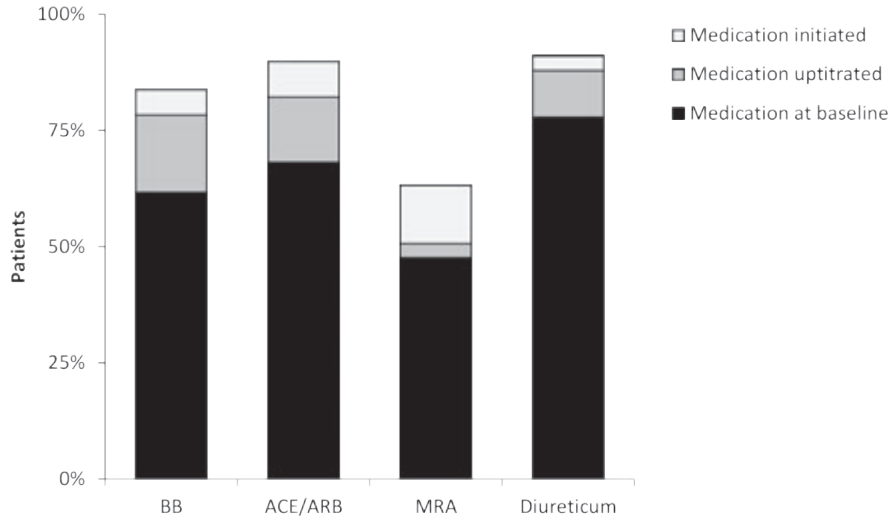


**Figure 2.** Heart failure medication use. At referral 78% of the patients used a beta blocker (BB), 82% used angiotensin-converting-enzyme inhibitor (ACE) or (ARB) and 51% used a mineral corticoid antagonist (MRA). BBs could be up-titrated in 17%, ACE/ARBs in 14% and MRAs in 4%. There was an initiation of BBs in 6%, of ACE/ARBs in 8% and of MRAs in 13% of the patients.
ACE = angiotensin-converting-enzyme; ARB = Angiotensin II Receptor Blockers; BB = beta blocker; MRA = mineral corticoid antagonist



## Follow-up

The survival rate at 6 and 12 months was 94% and 92% respectively. During 12 months follow-up, 51 patients died. The leading cause of death was progressive HF (39 patients, 75%). As shown in Figure 3, patients experienced a significant improvement in NYHA class from 2.3 (95%CI 2.3–2.4) at baseline to 2.0 (95%CI 1.9–2.0) at 6 months (P<0.001) and 1.9 (95%CI 1.8–2.0) at 12 months (P<0.001 vs. baseline) and an increase in LVEF from 30% (95%CI 29–31) at baseline to 34% (95%CI 33–35) at 6 months (P<0.001) and 35% (95%CI 34–36) at 12 months follow-up (P<0.001 vs. baseline). Table 2 demonstrates the improvements in NT-pro BNP levels and shows that optimisation of heart failure medication resulted in a significant decline in heart rate whereas blood pressures and renal function remained unchanged. Furthermore, patients experienced a higher quality of life based on the Minnesota Living with HF questionnaire. The percentage of patients admitted for decompensated HF declined from 31% in the 6 months prior to referral to 13% (P<0.001) in the first 6 months and 12% (P<0.001) in the period from 6-12 months after referral (Figure 4).

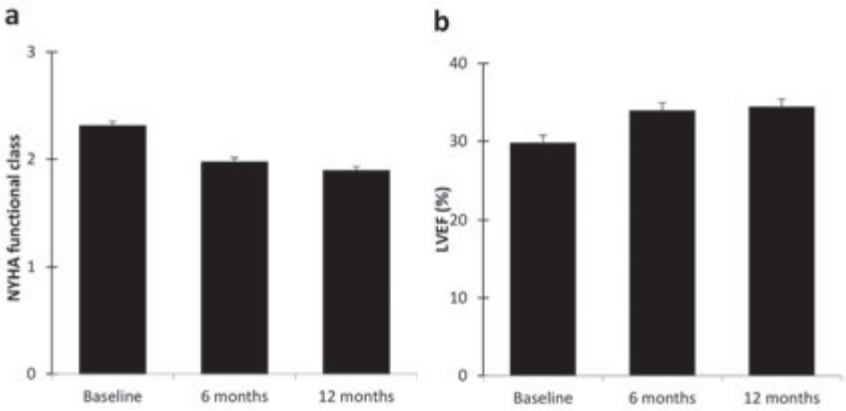


**Figure 3.** Clinical follow up. Panel a: Changes in NYHA class from baseline to 6 and 12 months follow-up. Panel b: Changes in LVEF from baseline to 6 and 12 months follow-up. Data are presented as mean±standard error of the mean. NYHA = New York Heart Association; LVEF = Left Ventricular Ejection Fraction

**Table 2**. Clinical outcome at baseline and 6- and 12 months follow up

| | **Baseline** | | **6 months** | | **12 months** | | **P-value*** |
|---|---|---|---|---|---|---|---|
| | | 95% CI | | 95% CI | | 95% CI | |
| Creatinin (umol/L) | 119 | 114 – 123 | 119 | 114 – 124 | 125 | 119 – 131 | 0.007 |
| NT-pro BNP (ng/L)** | 3.3 | 3.2 – 3.3 | 3.1 | 3.0 – 3.1 | 3.0 | 3.0 – 3.1 | <0.001 |
| Heart rate (/min) | 74 | 73 – 76 | 72 | 70 – 73 | 70 | 68 – 71 | <0.001 |
| SBP (mmHg) | 114 | 113 – 116 | 113 | 111 – 114 | 113 | 112 – 115 | 0.223 |
| DBP (mmHg) | 69 | 68 – 70 | 69 | 68 – 70 | 70 | 68 – 70 | 0.826 |
| Minnesota Living with HF score | 33 | 31 – 55 | 23 | 19 – 28 | 23 | 20 – 28 | <0.001 |

* P value of 12 months compared with baseline
** Estimated using log transform.
Continuous data are presented as mean (SD). Categorical data are presented as numbers (%). NT-pro BNP; N-terminal pro B type natriuretic peptide; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure

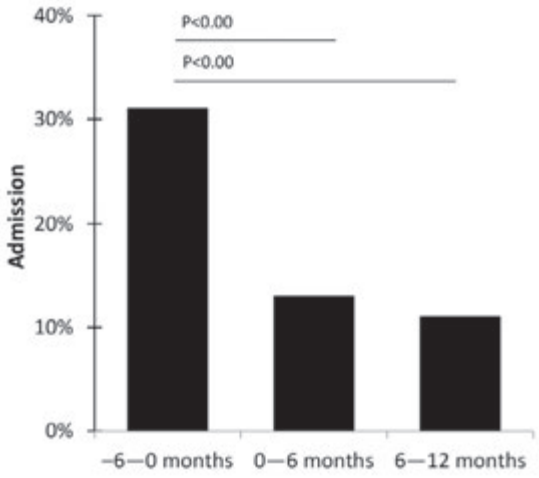


**Figure 4.** The percentage of patients that was admitted for decompensated HF in the 6 months before baseline and in the 0-6 and 6-12 months after baseline

Subgroup analysis of the 374 non-invasive optimised patients revealed that these patients also had a significant improvement in clinical outcome. In particular, NYHA class improved from 2.3 (95%CI 2.2–2.3) to 2.0 (95%CI 1.9–2.0) at 6 months (P<0.001) and 1.9 (95%CI 1.8–2.0) at 12 months (P<0.001 vs. baseline). The percentage of patients admitted for decompensated HF declined from 30% before referral to 10% (P<0.001) in the first 6 months and to 14% (P<0.001) in the period from 6-12 months after referral.

Subgroup analysis of the 552 survivors at 12 months showed similar results as in the entire study population. NYHA class improved from 2.3 (95%CI 2.2–2.3) to 1.9 (95%CI 1.9–2.0) at 6 months (P<0.001) and 1.9 (95%CI 1.8–1.9) at 12 months (P<0.001 vs. baseline). LVEF increased from 30% (95%CI 29–30) at baseline to 34% (95%CI 33–35) at 6 months (P<0.001) and 35% (95%CI 34–36) at 12 months (P<0.001 vs. baseline). The percentage of patients admitted for decompensated heart failure declined from 30% in the 6 months before referral to 11% (P<0.001) in the first 6 months and 11% (P<0.001 vs. baseline) in 6-12 months after referral.

## DISCUSSION

The key finding of the current study is that after referral by a cardiologist to a tertiary referral centre, a structured and multidisciplinary HF management program can identify additional treatment options in 69% of patients. This includes optimisation of HF medication (52%), invasive treatment (39%) and cardiac rehabilitation (34%). At 12 months follow-up, there was an improvement in clinical outcome and a decline in hospital admissions for decompensated heart failure.

**The MISSION!HF-program**

The current study describes the results of the MISSION!HF-program. This program was designed in response to the growing number of tertiary referred HF patients and the expanding treatment modalities for HF. It provides a structured and guideline-based framework for the treatment of complex HF patients. Typically, cardiologists in general hospitals refer patients to a tertiary care centre when symptoms persist despite optimised management and/or when multiple invasive treatment options are considered. The characteristics of the current patient population reflect this routine. Compared with other HF registries, patients in the current study were relatively young (64, 95%CI 63–65) and were treated quite extensively at baseline. (16-18) Despite this comprehensive treatment in the current population, 31% had a recent admission because of decompensated HF and 38% was in NYHA class III/IV. The observation that 62% of patients had a relatively low NYHA class might at first be somewhat striking. Importantly, however, the recently published "I Need Help" acronym indicates that not only NYHA class III or IV should be taken into account when considering patients with advanced heart failure for tertiary referral.(19) Indeed, renal failure (mean creatinine 119 umol/L), a very low ejection fraction (LVEF<20%: 19%), more than 1 hospitalisation for decompensated heart failure in the last 12 months (7%), and a systolic blood pressure <100 mmHg (30%) were common in the current study.

The current study shows a significant decline in NT pro BNP levels. This biomarker is commonly used in the diagnosis and prognosis of HF.(20) The field of biomarkers is developing and besides NT pro BNP levels, other biomarkers like C-Reactive Protein (CRP), tumor necrosis factor-**α** and interleukins are contributing to the knowledge of HF pathophysiology. In the future to optimize HF management it would be helpful to use a multiple bio marker approach during follow-up.(21)

When a cardiologist refers a patient for advanced HF therapy, a pitfall could be solely focus on invasive treatment options. Numerous studies, however, emphasized that drug therapy is the cornerstone for the HF management.(10, 22) Even though the extensive medication use at referral, the MISSION!HF-program revealed the opportunity to even further optimise HF medication in 52% of patients. It might be assumed that this substantial optimisation in medication partially contributed to the relatively low percentage of patients in whom invasive treatment was indicated. Indeed, subgroup analysis in the non-invasively optimised patients revealed that these patients also had a reduction in HF symptoms and a decrease in hospital admissions. These results underline the importance of drug therapy for HF patients. Optimal patient selection and timing of invasive therapy in HF patients is a major challenge. A range of treatment options exist and cardiac surgery in severe HF patients is not without risk.(23) In the current study, 39% of patients were invasively treated. Previous publications of our centre described the effect of each individual treatment modality.(24-26) However, the focus of the current manuscript is on the results of the entire tertiary HF program,

since we feel that invasive treatment should be considered as an integral part of HF treatment.

Apart from drug and invasive treatment options, another important factor in optimizing the management of chronic HF care is to optimize the nutritional status of the patient. (27) Advanced heart failure is frequently paralleled with cardiac cachexia and chronic systemic inflammatory response, which influence the inadequate intake of nutrients. Malnutrition is associated with higher hospital admission rates and poor prognosis. (28) Future studies should evaluate the role of routine nutritional assessment during follow-up.

**Implications for the HF care chain**

The identification of additional treatment options and the observed reduction in symptoms and hospital admissions are good news for patients. However, the current data also suggest that the management of HF patients in the Netherlands should be optimised. Especially, the use of HF medication can be improved. In 18% of the patients medication optimisation was all that changed after referral. And, even after optimisation, the rate of MRA use was only 64%. Although numerous previous studies already stressed the importance of up-titrating HF medication, awareness on this topic remains to be accomplished.(6, 29, 30) Setting up a national HF registry could help to create transparency on medication-use in different hospitals and improve the quality of HF care. Sharing experience between general cardiologists and dedicated HF cardiologists on up-titrating HF medication could contribute in optimising the long-term management of HF care.



Furthermore, the referral pattern from general hospitals to tertiary referral hospitals can be optimized. Invasive treatment was performed in only 39% of patients. Education on the (contra)indications for novel invasive treatment modalities as well as accessible contact between cardiologists in general hospitals and in tertiary care hospitals may increase the efficiency of referring patients. And finally, more widespread use of cardiac rehabilitation seems reasonable, as only 34% of the patients in the current registry completed a cardiac rehabilitation program and there is a strong rationale for exercise in HF patients. (31, 32)

**Study limitations**

There are several limitations that have to be acknowledged. First, this is a retrospective observational single centre study. Consequently, it remains to be shown whether the observed clinical improvement and a reduction in hospital admissions for decompensated HF is directly related to tertiary heart failure care. To overcome this issue, ideally, a randomized study should be performed. However, we feel that to deny tertiary heart failure care from patients with progressive heart failure is unethical. Accordingly, in our opinion, the current study design is the only way to provide insight

in the added value of tertiary heart failure care. Secondly, the fact that the study population is a "real-world" population makes it quite heterogeneous especially with regard to HF treatment modalities. Thirdly, due to the retrospective character of the study, there are missing data during follow-up. To overcome this problem and to increase precision multiple imputation models were used.

**Conclusion**

A dedicated HF management program in a tertiary referral hospital is of added value in addition to regular heart failure care in general hospitals since additional treatment options can be identified in the majority of patients and may result in beneficial effects on heart failure symptoms and cardiac function paralleled by a reduction in decompensated heart failure hospital admissions.

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