Heart failure in primary care with special emphasis on costs and benefits of a disease management programme

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Nothing is impossible. The impossible just takes a little longer.

Winston Churchill
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ABSTRACT

Background and aim. Heart failure (HF) is a common condition associated with poor quality of life (QoL), high morbidity and mortality and is frequently occurring in primary health care (PHC). It involves a substantial economic burden on the health care expenditure. There are modern pharmacological treatments with evident impact on QoL, morbidity, mortality, and proved to be cost-effective. Despite this knowledge, the treatment of HF is considered somewhat insufficient. There are several HF management programmes (HFMP) showing beneficial effects but these studies is predominantly based in hospital care (HC).

The first aim of this thesis was to describe patients with HF in the PHC regarding gender differences, diagnosis, treatment and health related costs (I, II).The second aim was to evaluate whether HFMP have beneficial effects in the PHC regarding cardiac function, quality of life, health care utilization and health care-related costs (III,IV).

Methods. The initial study involved retrospective collection of data from 256 patients with symptomatic HF in PHC (I). The data collected were gender, age, diagnostics and ongoing treatment. The second study was an economic calculation performed on 115 patients (II). The economic data was retrospectively retrieved as the number of hospital days, visits to nurses and physicians in HC and PHC, prescribed cardiovascular drugs and performed investigation during retrospectively for one year. The third and fourth study was based on a randomized, prospective, open-label study which was subsequently performed (III,IV). The study enrolled 160 patients with systolic HF who were randomized to either an intervention or a control group. The patients in the intervention group retrieved follow-up of HF qualified nurses and physicians in the PHC, involving education about HF and furthermore, optimizing the treatment according to guidelines if possible. The patients in the control group had a follow-up performed by their regular general practitioner (GP) receiving customary management according to local routines but there was no contact with HF nurses. The primary endpoint of the study was a composite endpoint consisting of changes in survival, hospitalization, heart function and quality of life (QoL) and to compare differences in resource utilization and costs (III,IV).

Results. In the first study, the prevalence was 2% and the average age was 78 years (I). The most frequent cause of HF was IHD followed o hypertension. The diagnosis in the study population was based on clinical criteria and only 31% had been subjected to echocardiography. The most common treatment was diuretics (84%) and angiotensin converting enzyme inhibitors (ACEI) were used in 56% of patients. In the following prospective study, the intervention group had significant improvements in composite endpoints. There were in the intervention group more patients with reduced levels of NT-proBNP (p=0.012) and improved cardiac function (p=0.03). No significant changes were found in New York Heart Association (NYHA) functional class or QoL. The intervention involved less health care contacts (p=0.04), less emergency ward visits (p=0.002) and hospitalizations (p=0.03). The total cost for HC and PHC was EUR 4471 in the intervention group and EUR 6638 in the control group which implies a cost reduction of EUR 2167 (33%).

Conclusions. HF is common in PHC with a prevalence of 2% the study population had an average age of 78 years. Only 31% of the HF patients have performed an echocardiographic investigation. Treatment with ACEI occurred in 56%. Differences were found between genders since women had performed significantly fewer echocardiographic investigations and, had less treatment with ACEI. When implementing HFMP in PHC, beneficial effects were found regarding cardiac function and health care-related costs in patients with systolic HF. These findings indicate that HFMP might be used even in PHC.
LIST OF PAPERS

This thesis is based on four original articles which are listed beneath. The articles are numbered in Roman numerals which are used when the text are referred to the article in question.


ABBREVIATIONS

ACE-I  Angiotensin Converting Enzyme Inhibitor
AF    Atrial fibrillation
AMI   Acute Myocardial Infarction
ARB   Angiotensin Receptor Blockers
BP    Blood pressure
BNP   Brain natriuretic peptide
CE    Clinical examination
CI    Confidence Interval
COPD  Chronic Obstructive Pulmonary Disease
CABG  Coronary Artery Bypass Grafting
ECG   Electrocardiogram
EF    Ejection Fraction
ESC   European Society of Cardiology
EQ-5D EuroQual 5D
EUR   Euro
GP    General Practitioner
ICD-10 International Classification of Diseases and Related Health Problems 10th version
IHD   Ischemic Heart Disease
IQR   Interquartile Range
HC    Hospital Care
HF    Heart Failure
HFMP  Heart Failure Management Programme
KCCQ  Kansas City Cardiomyopathy Questionnaire
MRA   Mineralocorticoid receptor antagonist
MLHF  Minnesota Living with Heart Failure
NP    Natriuretic Peptide
NT-proBNP N-terminal pro brain natriuretic peptide
NYHA class New York Heart Association Classification
PHC   Primary healthcare
RAS   Renin-Angiotensin system
QoL   Quality of Life
SEK   Swedish krona
SD    Standard deviation
SF-36  Short Form 36
TLV   Swedish Dental and Pharmaceutical Benefits Agency
INTRODUCTION

It has been suggested that there is room for improvement regarding the management of heart failure (HF) patients in the primary healthcare (PHC), and there are indications that most of the research performed on HF patients has been based on hospitalised patients and the research concerning the management of HF in the PHC is sparse. HF patients arriving in the emergency ward of a hospital are generally suffering from a more unstable and severe form of HF while in the PHC the HF patients are usually in a more stable condition and usually have mild to moderate HF. Despite the latter situation of HF patients in the PHC, there is room for improvement regarding diagnostics, treatment and management.

Background

Definition of heart failure

There are many definitions of HF but a simplified definition is that there is a functional or structural impairment in the heart, reducing its ability to deliver oxygenated blood corresponding to the requirements of the metabolizing tissues of the body. In combination with reduced cardiac function a neuroendocrine activation occurs, including the Renin-Angiotensin system (RAS). The haemodynamic consequences of these disturbances may explain symptoms (dyspnoea, fatigue) and findings (peripheral oedema) typical for HF. It is important to state that HF is not a disease but a clinical syndrome.

Aetiology and comorbidity

The most common causes of HF are ischemic heart disease (IHD) and hypertension, which explain about 80% of all cases of HF (1-5). Other causes are cardiomyopathies, valvular heart diseases and arrhythmias such as atrial fibrillation (AF), which explain the remaining 15-20% of cases.

There is a considerable comorbidity among HF patients such as IHD (59%) and hypertension (57%), while diabetes and chronic obstructive pulmonary disease (COPD) occur in approximately 25% of patients with HF, and other conditions include anaemia and hypothyrosis (6,7).

Epidemiology

The prevalence of HF is estimated to be about 2-3%, which means that approximately 180,000 to 270,000 individuals in Sweden suffer from it (5,8,9). A relatively large proportion of the population has reduced cardiac function without knowing it (10). The prevalence is approximately 1% in 40-year-old individuals, and increases to 10% in individuals older than 75 years (5). The incidence of HF has declined during the past decade, probably due to improved management and modern treatment, which in large controlled studies have been shown to improve mortality as well as morbidity and quality of life (QoL) (11). The average age is approximately 75-83 years for HF in a PHC-based population (6,7,12). However, the mean age of the population has increased due to survival benefits, and that means that the number of patients living with HF has increased, since HF is more common in the elderly.

Prognosis

According to previous studies, HF is associated with a poor prognosis, and the one year mortality is approximately 20% while the 5-year mortality is approximately 50-65% in population-based studies (13-15). HF has a higher mortality than many of the common...
malignancies (16). The long-term mortality after the first hospitalization for HF has decreased in Sweden during the past two decades (17). These results have been most apparent in younger patients, in men, and more for ischemic than for non-ischemic HF, but the mortality remains high, especially in patients in need of hospital care (HC). The annual mortality found in the Swedish HF registry is about 15% for hospital-based patients with symptomatic HF but only about 6% for HF patients managed in the PHC (18). This difference in mortality implies that HF patients in the PHC probably have a more stable and mild form of HF.

**Diagnostics of heart failure**

The diagnosis of HF is important but can be difficult in reality. In order to obtain the diagnosis of HF there are three criteria that have to be fulfilled. First of all, there must be symptoms that are typical of HF. Secondly, it is necessary to have clinical signs typical of HF and finally, it is necessary to verify impaired cardiac function. Even though these criteria are concrete and explicit, it can still be challenging to make the diagnosis properly.

**Symptoms and clinical signs**

When patients visit the PHC centre with symptoms such as shortness of breath, fatigue and weight gain, the suspicion of HF will arise. The most common clinical signs occurring in HF are peripheral oedema, dyspnoea at exertion, and pulmonary rales (19,20). The diagnosis of HF can be difficult since symptoms and clinical findings typical of HF are non-specific and this is probably more apparent in the PHC (21-24). In particular, it is difficult to interpret symptoms in elderly patients with obesity or chronic lung disease (25-27). The symptoms have usually been bothering the patient for several weeks to months and have been insidious. The patients experiencing a rapid deterioration in HF, on the other hand, usually have more obvious symptoms which often result in an urgent visit to a hospital emergency ward and they are unlikely to appear in the PHC.

**Laboratory blood tests**

In cases when suspicion of HF arises, it is important to take blood samples. The routine blood tests recommended according to European guidelines are, haemoglobin, leukocytes, glucose, thyroid stimulating hormone, liver enzymes, creatinine and electrolytes. These recommended routine laboratory tests do not describe the heart function but are helpful in excluding other diseases which might also explain the symptoms.

**Natriuretic peptides**

The natriuretic peptides (NP) consist mainly of brain natriuretic peptide (BNP), which is the active ingredient, and N-terminal pro brain natriuretic peptide (NT-proBNP), whose function is so far unknown. The secretion of NP is increased when the cardiomyocytes are exposed to tension. NP is secreted mainly from the ventricles of the heart. BNP increases natriuresis, diuresis, and peripheral vasodilation and inhibits RAS (28,29).

BNP and NT-proBNP are markers for HF with high sensitivity and specificity, which is useful in the PHC and the emergency ward when HF is suspected (30-33). An elevated level of NP implies that HF is likely, especially in an untreated patient. However, there are factors other than HF causing elevated levels of NP (34-36). When the cardiomyocytes are exposed to increased volumes, filling volumes, stiffness, ischemia and when there is decreased elimination, the levels of NP will increase. Factors which can elevate NP are atrial fibrillation (AF), pulmonary embolism, renal dysfunction, increasing age, unstable angina pectoris, acute myocardial infarction, valvular heart disease and moreover, women have slightly higher
values than men (37-39). Factors which involve lower NP levels can be obesity and, more commonly, pharmaceutical treatment used in HF (27,40). Consequently, normal levels of BNP and NT-proBNP exclude HF in an untreated patient but elevated levels need to be investigated further with echocardiography (41).

There has been research to determine whether NP can be used to guide HF therapy (42,43). Some studies have shown that monitoring of HF therapy with natriuretic peptides was successful (44-47). On the other hand, there are studies that have not achieved the same results (48-52).

NP is a strong prognostic predictor, whereas patients with higher levels of NP have a worse prognosis compared to patients with lower levels of NP (4,53-57).

Electrocardiography

Electrocardiography (ECG) is an important investigation in patients with HF since it can provide important information regarding damage to the myocardium, or if there is rhythm disturbances. A normal ECG means that the probability of HF is low in patients with acute HF < 2% and in chronic HF < 10-14% (21,58-60).

Chest X-ray

When diagnosing HF, a chest X-ray is frequently conducted even though it provides little information about the cardiac function (61,62). A chest X-ray can be normal even if the patient has impaired cardiac function. Even though the x-ray may show elements of stasis, pulmonary congestion or increased heart size, the cardiac function may be normal. The investigation is still useful but mainly to rule out other explanations, particularly diseases of the respiratory system (63).

Cardiac function

When diagnosing systolic HF, it is crucial to evaluate the cardiac function and confirm that there is impaired cardiac function. The clinical criteria (symptoms, clinical signs, ECG and chest X-ray) are not reliable when evaluating the cardiac function (19,64). There are several methods to determine the cardiac function but the investigation that is most used and accessible is echocardiography (65-67). Echocardiography can be used to determine left ventricular function and estimate ejection fraction (EF). Moreover, it can detect structural changes such as cardiac hypertrophy, and visualize the wall motion and the valvular function.

Treatment of Heart Failure

When treating HF, there are different approaches. These include non-pharmacologic treatment, medications, and of course device treatment. The device treatment is strictly managed at departments of cardiology and not in the PHC and of that reason not further described. The main purpose of the treatment is to reduce symptoms, increase QoL, reduce hospital admissions and improve survival.

Non-pharmacologic treatment

Non-pharmacological treatment includes information of appropriate diets, salt and fluid intake and the importance of exercise in order to improve patient’s skill and self-care behaviours. Most commonly, the information to the patient and their family is provided as a patient education so the patients understand the cause of HF and why symptoms occur. The education
involves observing symptoms so the patient can recognize signs and symptoms of HF. The patients are advised to record their weight repeatedly and recognize weight gain. The patient receives information about self-care including knowledge when and how to reach health care provider and how to use flexible diuretic therapy when necessary. The non-pharmacological treatment involves understanding indications, dosing, effects and possible side-effects for each HF drug. Important components are also to understand the importance of following treatment recommendation, avoid excessive fluid consumption and to exercise regularly. It also includes the importance of smoking cessation, reducing alcohol consumption, and recommendations regarding vaccinations.

**Angiotensin-converting-enzyme inhibitor**

Treatment with angiotensin-converting enzyme inhibitors (ACEI) reduces morbidity and mortality and improves QoL in HF (68-71). Studies have shown that ACEI have the best effect when optimized doses are used (72). ACEI has a remarkable effect on the left ventricular remodelling, and is recommended in treatment of all HF patients.

**Angiotensin receptor blocker**

The effect of angiotensin receptor blockers (ARB) in HF is equivalent to ACEI. ARB is recommended when there are adverse reactions to ACEI (73-75). There are also studies that have shown that ARBs may be used in addition to ACEI in HF patients with EF <40% (76).

**Beta blockers**

Beta blockers have been shown to reduce morbidity and mortality, and improve QoL (77-81). These are additional positive effects that occur even if the patient has previously been treated with ACEI or ARB. Beta blockers have an effect on left ventricular remodelling. In addition, they have an important role in treating IHD, which commonly occurs in HF. It has been shown that beta blockers reduce sudden cardiac death in HF (77,78). Beta blockers are recommended in combination with ACEI or ARB in HF but should be given only to HF patients who are in a stable condition and should be used cautiously with a decompensated HF patient (82,83).

**Mineralocorticoid receptor antagonists**

A drug that blocks aldosterone receptors is mineralocorticoid receptor antagonist (MRA), and this has a well-documented effect on survival and morbidity in patients with systolic HF (84,85). MRA is recommended in treatment of HF patients who still have symptoms despite having already been treated with ACEI/ARB and beta blockers. It also has additional effect in patients with acute myocardial infarction (84). Although MRA has a good effect in HF there is a risk, particularly in elderly patients, of the development of impaired renal function with hyperkalaemia and hypotension. In the treatment there is reason to carefully monitor electrolytes and kidney function.

**Digoxin**

Digoxin has beneficial effects in HF regarding symptoms, QoL and physical function (86,87). Digoxin increases the cardiac contractility and decreases the heart frequency, mainly due to blocking in the atrioventricular node. It is mainly used when there is a need to reduce the heart rate in AF and beta blockers are not tolerated. However, digoxin can be used to increase cardiac contractility in HF with sinus rhythm, but other treatments are preferred.
Diuretics

Loop diuretics are useful in HF when there is fluid retention. The apparent advantage of loop diuretics is the rapid effect of increasing diuresis (88-90). The thiazides increase the diuresis but do not have the same rapid diuretic effect and therefore are more suited for HF combined with hypertension. Despite the evident effect of loop diuretics on diuresis and in reducing HF symptoms, there is no documentation on if diuretics affect morbidity or mortality.

Heart failure in primary healthcare

PHC in Sweden is organized by primary healthcare (PHC) centres in each county council. Each PHC center has team-based management, with general practitioners GPs collaborating with nurses, physiotherapists, occupational therapists, chiropodists, dieticians and sometimes psychological counsellors. There are usually nurses specializing in blood pressure, diabetes, asthma and COPD. There are also district nurses who see patients at PHC centres but who also carry out home visits. There are few PHC centres in Sweden that offer organized management of HF. When patients are diagnosed with HF, they are usually first admitted to hospital. After being stabilized and receiving treatment for HF, they are discharged from the hospital and referred to the PHC. If there is an HF clinic available at the hospital, the patients might have participated in a heart failure management programme (HFMP). Younger and male patients tend to continue their supervision and treatment at the hospital's outpatient clinic, but the elderly and women tend to be referred to the PHC (18). There are many patients diagnosed with HF in the PHC and consequently this has an important role in identifying HF (91). There are nevertheless shortcomings in the HF diagnostics, and the cardiac impairment is often not confirmed (64,92,93).

The diagnosis of HF in the PHC has a relatively low sensitivity of 66% but diabetes and hypertension have a fairly high sensitivity of 83-89% (94). In the PHC there are in general nurse managements of diabetes and hypertension which probably affects the registration of these diagnoses. In the PHC, patients with HF are older, more often women and it is more common that they have hypertension and COPD, while IHD is more unusual in the PHC than in a hospital population (18,25).

Patients with HF have several physician visits, irrespective of whether they are referred to the PHC for follow-up or if they have their continued outpatient follow-up at the hospital. A survey in Germany showed that patients have annually approximately six visits per year to their GP and 1.7 outpatient visits to an HC-based cardiologist (95). Studies in primary care show that a higher accessibility to a GP reduces the number of hospitalizations (96). Studies have shown that there is limited use in the PHC of medication recommended for HF, and when it is used, it is in sub-optimal dosages (7,97).

Heart Failure Management Programme

There are several studies reporting favourable results of an HFMP in reducing mortality and hospitalization (98,99). These studies are mostly hospital-based and the interventions carried out by hospital-based personnel. The comparison of HFMPs is difficult since they are heterogeneous in terms of the models of care. The most common is that used by multi-professional HF clinics but there are also HFMPs by telephone contact and others that are home-based or even in few cases PHC-based. Hospital-based studies have mainly enrolled patients when hospitalized due to HF and it can be assumed these patients had an unstable and
more severe HF. The patients attending an HFMP at an HF clinic after being admitted have after one year better adherence to medication (100). A Swedish hospital-based study investigating the benefits of an HFMP showed that the intervention led to a reduction in mortality, and fewer hospital admissions and days in hospital (101). The intervention in this Swedish study was led by specially educated cardiac nurses and consisted of follow-up 2–3 weeks after discharge. At each visit, there was an evaluation of clinical status, supervision of the HF treatment, provision of individualized education about HF and social support to patients together with family. Furthermore, the HF clinic personnel were reachable by telephone if the patients' HF symptoms worsened. There was a similar intervention in the COACH-study which did not show a reduction in mortality or hospitalization (102). In COACH study, the patients were randomized to a control group and a basic support or intensive support group. The control group had a follow-up by a cardiologist twice a year without involvement of the PHC, which can be considered as an advance follow-up and explain the outcome. However, the basic support group had as many as 13 outpatient visits (at hospital and home visits) after discharge and the intensive support group 25 outpatient visits (at hospital, in home visits and by telephone). It can therefore be assumed that the intervention itself is effective and not the frequency of the follow-up.

A Danish study compared HF patients discharged from hospital receiving an HFMP with extended follow-up period of 2.5 years by an HF clinic or having usual care in the PHC (103). The intervention involved follow-up with outpatient visits and telephone contact entailing symptom control, providing information of HF. Moreover, the patients had free access to nurses at the HF clinic. Both groups in this study had a high level of treatment concerning ACEI and beta blockers already at discharge and there were no benefits of long term follow-up at the HF clinic. A PHC-based German study consisting of follow-up by telephone and home visits with analogous intervention showed no improved health outcomes or healthcare utilization (104). However, at baseline there was already intense treatment with ACEI and beta blockers, giving little room for improvement. An Australian study comparing HFMP follow-up at an HF clinic with a home-based follow-up found there were lower healthcare costs due to fewer days of hospitalization (105). The patients were enrolled when hospitalized and randomized to either a follow-up consisting of outpatient HF clinic visits or home visits by a trained HF nurse. The intervention was the same in both groups and similar to the other mentioned studies. This difference might be caused of the accessibility to admissions when the patients were visiting the HC.

These studies all have a similar intervention programme consisting of a mixture of outpatient visits, home-based visits or telephone contact. The purpose should be to optimize the HF medication, offer adequate information about HF to increase the adherence regarding treatment and symptoms, self-care and symptom monitoring and flexible use of diuretics. The HFMP should also offer easy access to healthcare when HF worsens.

**Healthcare utilization of heart failure**

HF is a severe condition that consumes considerable healthcare resources, which implies that HF constitutes a major burden on healthcare economy (106). Previous studies have shown that the healthcare cost of HF is approximately 2% of the total national healthcare budget in developed countries (107-109). A Swedish study indicated that HF constituted a healthcare cost for Sweden of 3 billion SEK (107). This study used price tariffs from 1995 and patients were recruited from a hospital diagnose register covering all discharges and all bed-days for HF during 1995. The register in this study was probably insufficient concerning capturing data from PHC at that time since the recording of diagnoses in the PHC were not as rigorous.
and possible to apprehend. Consequently, the cost of hospital care dominated and was as high as 70% while the proportion of PHC was 6%. In more recent Swedish studies the average cost per HF patient was EUR 5700-7610 (110,111). A German study showed a yearly cost for HF of EUR 4681 per patient (95).

The COACH study was a comparison of basic support (intervention with nine visits to hospital and home visits) with intensive support (intervention involving 25 outpatient visits to hospital, home visits and telephone contact) which did not show a reduced cost (112). This study enrolled patients when they were hospitalized due to deteriorated HF. The explanation might be that there were intensive follow-ups in both groups. It is the hospitalization which in particular affects healthcare costs for HF (113). Almost 50% of the patients that have recently been hospitalized for HF are re-admitted within six months, which has a profound effect on hospital resource utilization (114,115). An intervention which can entail a reduction in hospital admissions and also a reduction in the number of days admitted to hospital would probably result in decreased healthcare costs. The number of days at hospital has previously been high, and in 1987 the average was 65 days at hospital per patient per year (116). Over the years, this number has declined markedly and in 1996 it was 10.7 days at hospital on average per year. More recent Swedish studies have shown a reduction in the number of days to 6.7 days in hospital (110,111).

Patients with HF have a high utilization of PHC resources as well, but the results from various studies differ widely. A Swedish study showed that an HF patient in Sweden has 1.2 visits to GP (110). However, a German PHC-based study showed that a patient with HF had six visits to their GP. Meanwhile, in an English study, there were nine visits to the GP (95,117). These divergent findings possibly illustrate that PHC differs in European countries and that these studies had somewhat different populations.
AIMS OF THE STUDY

General aim

The general aim was to explore how patients with HF in a community area were diagnosed and treated, to calculate the healthcare costs and to elucidate if HF management with increased patient education of HF, accessibility to staff and intensified treatment of these patients could improve survival, hospitalization and healthcare costs.

Specific aims

- To describe patients diagnosed and treated for HF in a defined geographic area in primary healthcare in regard to factors such as diagnostic procedures, aetiologic diseases, and management, and to evaluate whether there was a difference between genders (I).
- To calculate the costs for patients with heart failure in a primary healthcare setting (II).
- To evaluate if the use of HFMPs also has beneficial effects on heart failure patients in primary healthcare in terms of improved cardiac function and QoL, reduced NT-proBNP levels, and lower utilization of healthcare services and mortality (III).
- To evaluate resource utilization and the cost implications of implementing a heart failure management programme in primary healthcare (III).

POPULATIONS AND METHODS

This research is based on four articles where the data was obtained from various populations.

- Retrospective collection of data from 256 patients treated for symptomatic HF at a PHC centre with a total population of 12,400 inhabitants. (I).
- Retrospectively retrieved data from 115 patients diagnosed with HF in two PHC centres with a total population of 19,400 inhabitants (II).
- Prospective randomized open-label study of 160 patients with systolic heart failure in five different PHC centres (III,IV).

Population (I)

The study was performed in the Åtvidaberg community located in south-eastern Sweden, with a population of 12,400 inhabitants. In the community, there were two PHC centres. There was one PHC centre with five GPs who supported approximately 10,000 inhabitants, and one PHC centre with a single GP who supported approximately 2400 inhabitants. Both of these PHC centres had computerized medical record documentation.

Inclusion criteria

Patients with a diagnosis of HF or being treated for HF, living in the Åtvidaberg community.

Exclusion criteria

Patients were excluded if the diagnosis of HF was evidently incorrect and was revoked according to medical record documentation.
Population (II)
The study included 115 patients diagnosed with heart failure at two PHC centres in southeastern Sweden, one in Ätvidaberg community and one PHC centre in Linköping community, with a total population of 19,400 people. These PHC centres had computerized health record documentation. The patients were included during the time period from 1999 to 2000.

Inclusion criteria
Patients diagnosed with HF (I50 and I42) according to ICD-10 coding in the PHC centre medical healthcare record documentation were included.

Exclusion criteria
Patients with dementia, malignancy or suspected malignancy were excluded from the study.

Population (III,IV)
The study included 160 patients with systolic HF from five PHC centres in south-eastern Sweden. These PHC centres were located in Vimmerby, Ätvidaberg and Linköping community.

Inclusion criteria
Patients with systolic HF, defined as an EF <50%, and who were >18 years of age with New York Heart Association (NYHA) functional class I-IV were included in the study. All patients had met the European Society of Cardiology (ESC) clinical practice guidelines diagnostic criteria in order to be in the study.

Exclusion criteria
Patients excluded from the study were those with a normal EF, haemodynamically unstable patients on the waiting list for cardiac surgery (cardiac transplantation, revascularization, or heart valve surgery), patients with an acute myocardial infarction (AMI) within three months, patients with impaired renal (serum creatinine >250 mikromol/L) or liver function (liver enzymes more than three times the normal value), patients with severe COPD (treated continuously with oral steroids and/or oxygen treatment), patients with diseases with an expected survival of less than one year, and patients unable to give informed consent due to diminished cognitive function (caused by dementia or cerebrovascular insult) or participating in another trial.

Methods (I)
This was a descriptive retrospective study in which medical health records of all patients with diagnoses of HF, hypertension, IHD, history of previous AMI or AF were examined in order to find all patients treated for HF. All the medical healthcare records in the PHC centres and the nearby hospital were carefully scrutinized. Data was documented regarding age, gender, concomitant diseases, how the diagnosis of HF was verified, and current treatment. The NYHA class for each patient was evaluated based on the medical healthcare record documentation and the extent of the medication. The concomitant diseases recorded were
IHD, history of AMI, diabetes mellitus, dilated cardiomyopathy, valvular heart disease, COPD and AF. The diagnosis process was reviewed and separated into four different investigation categories: 1) clinical examination (CE), 2) CE with an ECG, 3) chest x-ray and 4) echocardiography. The pharmaceutical treatments were separated into digitalis, diuretics and ACEI. Treatment with ACEI was further scrutinized regarding the treatment dose of the ACEI which was recorded and categorized in three different dosage levels. In order to compare these drugs, a percentage of dose level for each drug was calculated. A dosage level that was 100% signified a daily treatment with captopril 100 mg, ramipril 10 mg, enalapril and lisinopril 20 mg, according to local guidelines at that time. No other ACE inhibitor was used and the use of ARBs was negligible.

Methods (II)

Data collection

When accepted for the study, all patients were given an echocardiographic examination to assess their cardiac function. The computerized healthcare records in the PHC centres and the HC were carefully scrutinized retrospectively for one year before the date the patient was included in the study. The patient’s age, gender, NYHA class and concomitant diseases were collected. The number of visits to the GP, nurses, occupational therapist, physiotherapist and chiropodist in the PHC were also registered. The nurses serving in the PHC centres are assigned different tasks and were therefore categorized as regular PHC nurses, specialized PHC nurses (hypertension, diabetes and asthma/COPD nurse) and district nurses. The medical healthcare records from the Department of Cardiology, Internal Medicine, Surgery and Orthopaedics were reviewed and the number of days in hospital and number of visits to physicians and specialized nurses at the hospital were collected. All X-rays (such as chest X-rays, coronary angiography, skeletal X-ray and computed tomography scanning) and physiological investigations (such as echocardiography, ultrasound of blood vessels, scintigraphies and exercise tests) conducted during the study period according to the PHC and HC medical healthcare records were retrieved. In the same way, data on the medication that was prescribed during the study period were retrieved. The dosages and number of days on treatment were registered. The use of medications was separated into medication for cardiovascular diseases (beta blockers, calcium inhibitors, ACE inhibitors, Angiotensin II inhibitors, digoxin, diuretics, and statins), diabetes and COPD.

Resource utilization

From the collected data, the patient’s average number of days hospitalized (inpatient care), and visits to physicians and nurses (outpatient care) at HC was calculated. The average number of visits to a GP, nurses, district nurses and paramedical staff in the PHC as well as the average number of days at a nursing home was calculated. The price list for PHC was retrieved from the Ödeshög study to allow calculation of the patient costs (118). The prices representing inpatient and outpatient care for HC were retrieved from the County Council of Östergötland’s price tariffs for healthcare utilization for 2003. The costs for HC and PHC used are presented in Table I.
Table I. Cost per different unit of healthcare resources.

<table>
<thead>
<tr>
<th>Unit</th>
<th>SEK/unit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital care</strong></td>
<td></td>
</tr>
<tr>
<td>Inpatient care</td>
<td></td>
</tr>
<tr>
<td>Stay/day in an intensive care unit</td>
<td>6200</td>
</tr>
<tr>
<td>Stay/day in a hospital ward</td>
<td>3300</td>
</tr>
<tr>
<td>Outpatient care</td>
<td></td>
</tr>
<tr>
<td>Visit to a physician</td>
<td>2459</td>
</tr>
<tr>
<td>Visit to a heart failure nurse</td>
<td>930</td>
</tr>
<tr>
<td><strong>Primary healthcare</strong></td>
<td></td>
</tr>
<tr>
<td><em>Cost related to general practitioner</em></td>
<td></td>
</tr>
<tr>
<td>Visit</td>
<td>977</td>
</tr>
<tr>
<td>Home visit</td>
<td>1040</td>
</tr>
<tr>
<td>Telephone contact</td>
<td>14</td>
</tr>
<tr>
<td>Prescription of drugs</td>
<td>16</td>
</tr>
<tr>
<td><em>Cost related to nurses</em></td>
<td></td>
</tr>
<tr>
<td>Visit (regular nurse)</td>
<td>202</td>
</tr>
<tr>
<td>Visit to an asthma nurse</td>
<td>438</td>
</tr>
<tr>
<td>Visit to a diabetic nurse</td>
<td>415</td>
</tr>
<tr>
<td>Visit to a hypertension nurse</td>
<td>300</td>
</tr>
<tr>
<td><em>Cost related to district nurse</em></td>
<td></td>
</tr>
<tr>
<td>Visit</td>
<td>211</td>
</tr>
<tr>
<td>Home visit</td>
<td>299</td>
</tr>
<tr>
<td><em>Cost related to paramedical staff</em></td>
<td></td>
</tr>
<tr>
<td>Occupational therapist</td>
<td>509</td>
</tr>
<tr>
<td>Physiotherapist</td>
<td>257</td>
</tr>
<tr>
<td>Chiropodist</td>
<td>410</td>
</tr>
<tr>
<td><em>Costs related to other resources</em></td>
<td></td>
</tr>
<tr>
<td>Stay/day in a nursing home</td>
<td>417</td>
</tr>
</tbody>
</table>

SEK=Swedish kronor.

The price lists for X-ray and physiological examinations were derived from the Departments of Radiology and Clinical Physiology. The cost of medication was based on the Swedish Dental and Pharmaceutical Benefits Agency (TLV) price list for 2003. The costs were calculated as mean and median values for each patient. These were summarized in total but also subdivided to show PHC, HC, pharmaceutical and examination costs. All the costs were calculated and presented in Swedish krona (SEK).

The baseline characteristics and the cost calculation were presented in total, normal systolic cardiac function and impaired systolic function (according to the echocardiography performed at inclusion of the study). Patients with EF <50% were considered to have a reduced systolic cardiac function and patients with EF >50% were perceived as having normal systolic cardiac function.

**Method (III,IV)**

The study was prospective, randomized open-label and the study period was one year. All patients with HF were initially subjected to echocardiography and patients that met the inclusion criteria and none of the exclusion criteria were enrolled in the study.
Stratification

In order to avoid a skewed distribution between study arms, there was a stratification based on age (> 80 or <80 years of age) and treatment of furosemide (> 80 or <80 mg per day). Randomization of patients was in 12 blocks within each PHC centre and randomization carried out in the main centre before patient was included in the study. All information about the randomization was enclosed in a sealed envelope which was opened when randomization was pursued.

The intervention

At each PHC centre, there was an HF-trained nurse along with GPs interested in HF, who was responsible for the intervention. These nurses were educated about HF disease and were also educated regarding management and monitoring of HF medication. The HF nurses were therefore capable of optimizing the HF medication and of offering adequate information about HF in order to increase the patient’s adherence to treatment, self-care, symptom monitoring and flexible use of diuretics. The patients had open direct access to the HF nurses at the PHC centre when experiencing worsening HF. An alliance between the HF nurses in the PHC centres and nurses at the special HF clinics in hospitals was established to allow consultation and support in complex situations.

When the patients were randomized to the intervention group, they had an initial consultation with the GP, followed by a visit to an HF-educated nurse. The HF nurses presented oral and written information about HF and also information from a validated computer-based information programme (119). There was an overview of each patient’s medication and clinical status in order to optimize the medication. The HF nurses had a mandatory follow-up examination within six weeks with the objective to ensure that medical treatment was optimized according to recognized guidelines. The HF nurse contacted the patients by telephone within one month and after six months to ensure the patients had maintained their status and adherence to their HF medication. Additional contacts were scheduled only if the patient had a clinical need. The basic treatment with ACEI or ARB and beta blockers was introduced if missing, and was optimized. For patients having adverse reactions to the medication, such as hypotension, renal dysfunction or bradycardia, a reduction in dosage and suboptimal treatment doses were accepted. MRA or an ARB was added if the patient still had symptomatic HF after this basic treatment.

The study process

A flow chart illustrating the study process is presented in Figure 1. Before entering the study, all patients were given an echocardiographic examination in order to verify a systolic dysfunction. The patients had a visit at inclusion to a physician and an HF nurse, and were randomized to either the intervention or control group. The physician-based NYHA functional class, physical examination, and quality of life (QoL) were assessed and blood samples for routine laboratory analyses and NT-proBNP were obtained. All patients included in the study had been given a chest X-ray. The patients randomized to the intervention group participated in the intervention while the patients in the control group were managed by their ordinary GP according to clinical routines. The length of the follow-up period was 12 months for all participants. At the end of the study period all patients made a final visit to a physician and all examinations performed at the start of the study were repeated, with the exception of the chest X-ray.
Figure 1. Illustrates the study design.

**Echocardiography**

The Doppler echocardiographic examinations (Vingmed System Five) were carried out with the patient lying in a left lateral position, and both M-mode and 2D methodology were applied in the examination. Semi-quantitative levels were applied when defining the systolic left ventricular function. The left ventricular function was normal when EF ≥ 50%, a mild systolic dysfunction was EF 40-49%, a moderate dysfunction EF 30-39%, and a severe dysfunction of the systolic left ventricular function signified an EF <30%. This method has been validated against the modified Simpson algorithm (120,121).

**Blood sampling and NT-proBNP measurement**

Blood sampling was conducted after the patient had been resting for 30 minutes. The samples were collected in pre-chilled plastic tubes containing EDTA (Terumo EDTA K-3), and then preserved in ice and centrifuged at 3000 g for 10 minutes at a temperature of +4 ° Celsius. The samples were subsequently immediately frozen and deposited at a temperature of -70 until subsequent analysis. No sample was thawed and liquefied before analysis. NT-proBNP was analysed by using an electrochemiluminescence immunoassay (Elecsys 2010, Roche Diagnostics, Mannheim, Germany), a method that had previously been validated (122). The total coefficient of variation was 4.8% at the level of 217 ng/L and 2.1% at the level of 4261 ng/L in our laboratory.
Measurements of quality of life and functional capacity

Quality of life (QoL) was evaluated with the SF-36 which is a validated QoL instrument (123). The evaluation of SF 36 was self-assessed by the patients. SF-36 evaluates eight different dimensions: physical function (PF), role physical (RP), body pain (BP), general health (GH), vitality (VT), social function (SF), role emotional (RE), and mental health (MH).

The NYHA classification was used to evaluate the functional capacity. NYHA is separated into four functional levels. The patients in NYHA class I have no HF symptoms, in NYHA class II there are HF symptoms during physical exertion, in NYHA class III there is a restricted life with HF symptoms even with minor effort and in NYHA class IV there are HF symptoms even at rest.

Evaluation of composite endpoints

Composite endpoints were valued by using a score system from a previous study (125). A composite endpoint was assessed from the changes in survival, hospitalization, heart function and QoL which is illustrated in Table II. The survival was based on the mortality versus survival at the end of the study, and the hospitalization was based on the first hospitalization for cardiovascular disease. The heart functions were based on EF at echocardiography and NT-proBNP which could be improved, unchanged or worsened. The QoL was based on a physical component scale and a mental component scale.

Table II. The allocation of scores for evaluation of composite endpoints.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survival</strong></td>
<td></td>
</tr>
<tr>
<td>Death (at any time during the trial)</td>
<td>-3</td>
</tr>
<tr>
<td>Survival to the end of the trial</td>
<td>0</td>
</tr>
<tr>
<td><strong>Hospitalization</strong></td>
<td></td>
</tr>
<tr>
<td>First hospitalization for cardiovascular disease</td>
<td>-1</td>
</tr>
<tr>
<td>No hospitalization</td>
<td>0</td>
</tr>
<tr>
<td><strong>Heart Function</strong></td>
<td></td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
</tr>
<tr>
<td>Improved EF</td>
<td>+1</td>
</tr>
<tr>
<td>Unchanged EF</td>
<td>0</td>
</tr>
<tr>
<td>Worsened EF</td>
<td>-1</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td></td>
</tr>
<tr>
<td>Decreased ≥500</td>
<td>+2</td>
</tr>
<tr>
<td>Decreased &lt;500</td>
<td>+1</td>
</tr>
<tr>
<td>Unchanged</td>
<td>0</td>
</tr>
<tr>
<td>Increased &lt;500</td>
<td>-1</td>
</tr>
<tr>
<td>Increased ≥500</td>
<td>-2</td>
</tr>
<tr>
<td><strong>Quality of Life/SF 36</strong></td>
<td></td>
</tr>
<tr>
<td>Physical Component Scale and Mental Component Scale</td>
<td></td>
</tr>
<tr>
<td>Increased ≥5</td>
<td>+2</td>
</tr>
<tr>
<td>Increased 1-4</td>
<td>+1</td>
</tr>
<tr>
<td>Unchanged</td>
<td>0</td>
</tr>
<tr>
<td>Decreased 1-4</td>
<td>-1</td>
</tr>
<tr>
<td>Decreased ≥5</td>
<td>-2</td>
</tr>
<tr>
<td><strong>Possible score</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-11 to +8</td>
</tr>
</tbody>
</table>

Note: EF, ejection fraction; NT-proBNP, N-terminal pro brain natriuretic peptide; SF-36, Short Form 36.
Assessed resource utilization

During the study period all healthcare contacts with HC and PHC were registered. This record included the number of visits to physicians, various nurses, and paramedical personnel. The number of inpatient days of hospitalization in Department of Internal Medicine or Geriatric was also recorded. The unit costs for 2012 are illustrated in Table III. Admissions, inpatient days in the Department of Neurology, Orthopaedics, Surgery and other surgery were not recorded since such care was considered to have little relation to heart disease. There was a separate registration of nurse visits, which included cardiovascular and haemodynamic monitoring during the initial six weeks of the study period. These cardiovascular nurse visits were summarized, whereas other visits to nurses that did not include haemodynamic monitoring were excluded. Investigations such as chest X-ray, coronary angiography, echocardiography, and physiological tests were also collected. Unit costs were derived from the County Council of Östergötland’s price tariffs for healthcare utilization for 2012. These tariffs for healthcare utilization are applied in the south-eastern region of Sweden and have been used to estimate patient costs in HC and PHC in the present study.

Table III. Official prices for each cost item in South-East of Sweden in 2012.

<table>
<thead>
<tr>
<th>Hospital Care</th>
<th>Price (EUR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient care</td>
<td></td>
</tr>
<tr>
<td>Stay/day in hospital ward</td>
<td>724</td>
</tr>
<tr>
<td>Outpatient care</td>
<td></td>
</tr>
<tr>
<td>Emergency ward</td>
<td>535</td>
</tr>
<tr>
<td>Visit to physician</td>
<td>377</td>
</tr>
<tr>
<td>Visit to a heart failure nurse</td>
<td>143</td>
</tr>
<tr>
<td>Primary Healthcare</td>
<td></td>
</tr>
<tr>
<td>Cost related to general practitioner</td>
<td></td>
</tr>
<tr>
<td>Visit</td>
<td>220</td>
</tr>
<tr>
<td>Administrative (prescription/telephone)</td>
<td>36</td>
</tr>
<tr>
<td>Cost related to nurses</td>
<td></td>
</tr>
<tr>
<td>Visit to specialized nurse</td>
<td>74</td>
</tr>
<tr>
<td>Cost related to district nurse</td>
<td></td>
</tr>
<tr>
<td>Visit</td>
<td>74</td>
</tr>
<tr>
<td>Home visit</td>
<td>74</td>
</tr>
<tr>
<td>Cost related to paramedical staff</td>
<td></td>
</tr>
<tr>
<td>Paramedicine</td>
<td>91</td>
</tr>
</tbody>
</table>

EUR 1 = SEK 8.7

The ongoing medication, dosages, and number of days on treatment were registered according to HC and PHC medical health records. Compilation of the treatment was conducted to explore how many patients were treated with RAS blockade and beta blockers at entry and at the end of the study. There were also calculations of the percentage average dosage of the recommended optimal dosage for RAS blockade and beta blockers. In order to compare the dosage of the ACEI, ARB and beta-blockers, a percentage of the recommended dosages were calculated. These recommended dosages for these medications were those according to local routine recommendations. The dosages which were considered as 100% of recommended dosage for ACEI was captopril 100 mg/day, enalapril 20 mg/day, ramipril 10 mg/day and lisinopril 20 mg/day. For ARB, the recommended dosages was candesartan 32 mg/day, losartan 100 mg/day, valsartan 160 mg/day and for beta-blockers the dosages considered as
100 % were bisoprolol 10 mg/day, metoprolol 200 mg/day, carvedilol 50 mg/day and atenolol 100 mg/day.

The cost of medication was based on the Swedish Dental and Pharmaceutical Benefits Agency (TLV) price list for 2012. The price tariffs were converted from Swedish kronor (SEK) to Euro EUR. The exchange rate was calculated from the average value of the EUR for the year 2012 (Exchange rate: 1 EUR = SEK 8.7).

Statistics

Continuous variables are presented as mean ±SD and median (interquartile range (IQR)) for baseline measures and as mean ±SD for costs, since the average cost is the key statistic for economic outcomes (I-IV). Differences in the distribution of continuous variables between intervention groups were tested using the nonparametric Mann-Whitney U-test, whereas the chi-squared test was used for discrete variables (I-IV). A multiple regression analysis was carried out to exclude the possibility that the variables of gender, age, NYHA class, cardiovascular diseases, and cardiac function had affected the cost (II). The analysis of NT-proBNP at baseline and the end of the study between the intervention group and the control group involved the use of three different tests using both T-tests between groups of both untransformed as well transformed variables of the difference between inclusion and termination plasma concentration of NT-proBNP, and also by use of the Mann-Whitney U test (III).

The p-value under the null hypothesis of no difference in total cost between intervention groups was the primary test of the intervention’s impact on the total cost of healthcare (IV). To explore the strength of the outcome, two sensitivity analyses were performed. One was a comparison of total healthcare costs adjusted for potential differences in baseline characteristics between groups (IV). The other was a comparison of healthcare costs accounting for potential differences in follow-up time between groups. For these, log-normal regression models were used with adjustment for age, sex, ischemic heart disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, NYHA functional class, heart rate, systolic and diastolic blood pressure, and creatinine values encountered at baseline (125). The second model also included time in study as an offset term. Continuous variables were modelled as psplines with four degrees of freedom (126). Model fit was assessed by normal qq-plots of the residuals. Inference was based on the p-value for the intervention-group coefficient. A p-value of less than 0.05 was regarded as a statistically significant difference.

The statistical analyses were carried out using three different and commercially available statistical software package programs. The commercial statistical software program StatView (SAS Institute Inc.) was used in paper I while SPSS v 15.0 (IBM SPSS Statistics) was used in paper II. The statistical processing of papers III and IV was conducted with the assistance of the commercially available statistical software-package Statistica v. 10.0 (Statsoft Inc., Tulsa, OK USA) (III,IV).

Ethics

The Ethics Committee at the University Hospital of Linköping approved the study.
RESULTS

Result I

Distribution of age

In the initial descriptive retrospective study there were 256 patients with a diagnosis of HF. The average age was 78 years in total, and the average age for women was 80 years and for men 76 years (p<0.05). The age distribution is described in Figure 2.

Figure 2. Age distribution, totally and divided by sex.

Etiological factors and concomitant diseases

IHD was the most common aetiology, followed by hypertension, which is illustrated in Table IV (I). Compared to women, men had IHD significantly more often (p<0.05).

Table IV. Etiological factors, chronic diseases associated with HF and NYHA functional classes totally and divided by sex.

<table>
<thead>
<tr>
<th>Chronic diseases</th>
<th>Total</th>
<th>Women</th>
<th>Men</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aetiology of HF (main reason)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>142 (55)</td>
<td>50 (46)</td>
<td>92 (62)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>46 (18)</td>
<td>23 (21)</td>
<td>23 (16)</td>
<td>NS</td>
</tr>
<tr>
<td>VOC</td>
<td>6 (2)</td>
<td>2 (2)</td>
<td>4 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>Unknown</td>
<td>62 (24)</td>
<td>33 (31)</td>
<td>29 (19)</td>
<td>NS</td>
</tr>
<tr>
<td>Chronic diseases associated with HF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>64 (25)</td>
<td>23 (21)</td>
<td>41 (28)</td>
<td>NS</td>
</tr>
<tr>
<td>Chronic obstructive lung disease</td>
<td>35 (14)</td>
<td>13 (12)</td>
<td>22 (15)</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>97 (38)</td>
<td>43 (40)</td>
<td>54 (37)</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>44 (17)</td>
<td>20 (20)</td>
<td>22 (15)</td>
<td>NS</td>
</tr>
<tr>
<td>II</td>
<td>130 (51)</td>
<td>48 (48)</td>
<td>78 (53)</td>
<td>NS</td>
</tr>
<tr>
<td>III</td>
<td>78 (30)</td>
<td>30 (30)</td>
<td>46 (31)</td>
<td>NS</td>
</tr>
<tr>
<td>IV</td>
<td>4 (2)</td>
<td>2 (2)</td>
<td>2 (1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

A history of AMI occurred in 40% of all the patients and there was a significant difference between genders, whereas 49% of the men and 27% of the women had AMI (p<0.001).
Diagnostics of heart failure in primary healthcare

The diagnosis of HF was based on clinical criteria in 69% of the patients. Consequently it was found that 31% had undergone echocardiographic examination according to recommendations. The distribution regarding how the diagnosis of HF was determined is illustrated in Figure 3. There was a significant difference between genders since 20% of the women and 38% of the men had been subjected to echocardiographic examination (p<0.01).

![Figure 3. Diagnostic procedures used in the whole study population and divided by gender. The first group (CE) had diagnosis of heart failure based on a clinical examination (CE) and the second group (CE+ECG) also had an ECG in addition to the CE. The third group (X) had a CE, ECG and chest X-ray, and the fourth group had an echocardiographic investigation.](image)

Treatment of heart failure in primary healthcare

Treatment with diuretics had been given to 84% of the patients. ACEI was used in 56% and 40% of the patients had been treated with digoxin. There was no significant difference between the genders regarding treatment with diuretics and digitalis. However, there was a significant difference between the genders in treatment with ACEI, in which 64% of the men had an ACEI compared to 43% of the women (p<0.01). It was found that 52% of the patients treated with ACEI had an optimized dosage.

Results II

There were 294 patients with the diagnosis of HF (I50, according to the ICD-10 classification), and they were identified from the computerized healthcare records in the PHC centres. The patients not fulfilling the inclusion criteria were excluded and the remaining 174 were offered the opportunity to participate. Fifty-nine patients declined to participate mainly due to high age, declining health and cognitive impairment. Finally, 115 consecutive patients with a clinical diagnosis of HF were included. Of these, 52 (45%) were women and 63 (55%) were men. The average age was 77 (SD 8) years. The women had a mean age of 78 (SD 8) years and for the men it was 76 (SD 8).
Cardiac function according to echocardiography

There were 33 patients with HF diagnosis who had normal cardiac function, verified with echocardiography, and there were 82 patients with impaired cardiac function. Among the patients with impaired cardiac function, there were 26 (32%) with a mild systolic dysfunction, 41 (50%) with a moderate dysfunction, 10 (12%) with a severe dysfunction, and there were also five patients (6%) with a diastolic dysfunction.

Comorbidity in patients with HF in the PHC

The most common concomitant diseases in the patients who participated in this study were IHD and hypertension. There was a higher occurrence of IHD (83% versus 52%) among the patients with cardiac dysfunction. Among patients with impaired cardiac function there were more with a previous history of AMI, and coronary artery bypass grafting (CABG) surgery compared to patients with a normal cardiac function. However, there was no difference in the prevalence of diabetes mellitus, valvular heart disease and COPD between these groups.

The pharmacological treatment of heart failure

There was no significant difference in drug treatment regardless of cardiac function. The patients with a normal cardiac function had a higher proportion of beta blocker and diuretic use but a slightly lower proportion of ACEI and warfarin therapy. There were no differences in treatment in regard to calcium channel blockers, digitalis, statins, long-acting nitrates and antiplatelet agents.

The resource utilization for patients with heart failure

The average cost of a patient with the diagnosis of HF in the Swedish PHC was SEK 37,100 (median SEK 23,283) regardless of cardiac function or gender. The distribution of costs is illustrated in Table V. The distribution of costs in percentage showed that the most costly entity was the HC (47%). PHC was responsible for 22% of the costs, medication for 18%, nursing home for 5%, and X-rays and physiological examinations for 6%. On average, there were 4.3 days at hospital during the study period and there were 0.7 visits to physicians and 0.1 visits to the specialist nurse in HC. There were on average 4.6 visits to the GP in the PHC and a total of 8.5 visits to the district nurse, and 0.2 to 1.0 visits to specialized nurses in PHCs.

Results (III,IV)

Baseline characteristics

There were 301 patients with suspected HF who were given echocardiography, and 141 patients did not meet the inclusion criteria. In total, 160 patients were included in the study and the mean age was 75 years (SD 7.8). Four patients died in the intervention group and five patients died in the control group. The overall mortality was 6%.

In the baseline characteristics, there was no significant difference in follow-up time in the study, haemodynamics, NYHA-classes, renal function, concomitant diseases or medication, which is illustrated in Table V.
Table V. Baseline characteristics of the patients included in the two treatment groups in the study.

<table>
<thead>
<tr>
<th></th>
<th>Intervention Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n (%)</td>
<td>79 (49)</td>
<td>81 (51)</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>75 (8.6)</td>
<td>75 (7.1)</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>76.0 (74.0-80.0)</td>
<td>76.0 (69.5-80.0)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>21 (27)</td>
<td>28 (36)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>58 (73)</td>
<td>53 (64)</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time in study, days, mean (SD)</td>
<td>379 (38.1)</td>
<td>374 (45.8)</td>
</tr>
<tr>
<td>Time in study, days, median (IQR)</td>
<td>378 (360-413)</td>
<td>377 (364-392)</td>
</tr>
<tr>
<td>Number of deaths, n (%)</td>
<td>4 (6)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Number of drop outs, n (%)</td>
<td>1 (1)</td>
<td>3 (4)</td>
</tr>
<tr>
<td><strong>Haemodynamics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, mean bpm (SD)</td>
<td>70 (14)</td>
<td>70 (11.6)</td>
</tr>
<tr>
<td>Heart rate, median (IQR)</td>
<td>70 (60-77)</td>
<td>70 (58.5-77.5)</td>
</tr>
<tr>
<td>Systolic BP, mean mm Hg (SD) *</td>
<td>131 (19)</td>
<td>134 (22.2)</td>
</tr>
<tr>
<td>Systolic BP, median (IQR)</td>
<td>135 (115-148)</td>
<td>130 (120-140)</td>
</tr>
<tr>
<td>Diastolic BP, mean mm Hg (SD)</td>
<td>71 (10.8)</td>
<td>73 (12)</td>
</tr>
<tr>
<td>Diastolic BP, median (IQR)</td>
<td>72 (66-80)</td>
<td>75 (68-80)</td>
</tr>
<tr>
<td><strong>Renal function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-creatinine mean umol/L (SD)</td>
<td>110.5 (30.7)</td>
<td>111.4 (31.8)</td>
</tr>
<tr>
<td>S-creatinine median umol/L (IQR)</td>
<td>103 (87-128)</td>
<td>102 (91.5-118)</td>
</tr>
<tr>
<td><strong>Concomitant diseases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD, n (%)</td>
<td>64 (81)</td>
<td>69 (85)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>33 (42)</td>
<td>27 (33)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>17 (22)</td>
<td>26 (32)</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>15 (19)</td>
<td>16 (20)</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAS-blockade, n(%)</td>
<td>62 (78)</td>
<td>67 (83)</td>
</tr>
<tr>
<td>Beta blockers, n(%)</td>
<td>54 (68)</td>
<td>61 (75)</td>
</tr>
<tr>
<td>MRA, n(%)</td>
<td>14 (18)</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Furosemide, n(%)</td>
<td>55 (70)</td>
<td>51 (63)</td>
</tr>
<tr>
<td>Digoxin, n(%)</td>
<td>17 (22)</td>
<td>21 (26)</td>
</tr>
</tbody>
</table>

Note: n: numbers; SD: standard deviation; bpm: beats per minute; BP: blood pressure; IHD: ischemic heart disease; COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association functional class RAS-blockade: renin-angiotensin-system blockade. MRA: mineralocorticoid receptor antagonists

* There was missing data for one patient in the intervention group for systolic blood pressure

**Medication**

When entering the study, 78 % of the patients were being treated with RAS-blockade in the intervention group and 83 % in the control group (p=0.50). At the end of the study, 100 % of the patients were receiving RAS-blockade in the intervention group and in the control group it
was 84 % (p=0.002). The average dosage level (percentage average dosage of the optimal dosage) of RAS blockade was 63 % at baseline in both groups. At the end of the study, the average dosage level of RAS-blockade was 94 % in the intervention group and 69 % in the control group (p <0.0001). The same calculation was made for beta blockers, showing that 68% of patients in the intervention group had treatment with beta blockers and 75% in the control group (p=0.33). There were 73% of the patients in the intervention group and 78% in the control group who had beta blocker therapy at the end of the study (p=0.52). The average dosage level of beta blockades at baseline was 33% in both groups. At the end of the study, the average dosage level was increased to 46% in the intervention group and in the control group the dosage level was 36% (p=0.10).

**Compilation of composite endpoints**

A summary of the composite endpoint consisting of survival, echocardiography, NT-proBNP, hospitalization and physical component scale and mental component scale was calculated to further highlight the effects of the intervention and is illustrated in Table VI. In this compilation, the most obvious impacts are in NT-proBNP (p=0.003) and in the QoL variable mental component scale (p=0.04). The summarized composite endpoints resulted in a significantly higher score in the intervention group.

Table VI. Composite endpoint calculation including survival, echocardiography, NT-proBNP concentration, hospital admission and two components of health-related quality of life within the intervention and the control group of the study population.

<table>
<thead>
<tr>
<th></th>
<th>Intervention group (points)</th>
<th>Control group (points)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>-12</td>
<td>-15</td>
<td>0.76</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>11</td>
<td>10</td>
<td>0.85</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>50</td>
<td>0</td>
<td>0.003</td>
</tr>
<tr>
<td>Hospital admission</td>
<td>-24</td>
<td>-32</td>
<td>0.23</td>
</tr>
<tr>
<td>Physical Component Scale</td>
<td>6</td>
<td>17</td>
<td>0.50</td>
</tr>
<tr>
<td>Mental Component Scale</td>
<td>10</td>
<td>-29</td>
<td>0.04</td>
</tr>
<tr>
<td>Summarized points</td>
<td>25</td>
<td>-37</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Note: The term ‘hospital admission’ refers to admissions caused by cardiovascular disease.

**NYHA functional classes**

There were no significant differences regarding NYHA functional classes between the groups at baseline or at the end of the study. The distribution of the NYHA classes is illustrated in Table VII. In the intervention group at baseline, there were slightly fewer patients in NYHA class I, more patients in NYHA-class II, and fewer patients in NYHA class III compared to the control group. There were no significant differences in NYHA classes between the groups at the end of the study. The number of patients in NYHA class I in the intervention group had increased from three to eight patients at the end of the study but was unchanged in the control group.
Table VII. Distribution of NYHA functional classes of the patients included in the study before and after the study period.

<table>
<thead>
<tr>
<th>NYHA-functional classes</th>
<th>Before Intervention</th>
<th>Before Control</th>
<th>p-value</th>
<th>After Intervention</th>
<th>After Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA I, n (%)</td>
<td>3 (4)</td>
<td>6 (7)</td>
<td>0.28</td>
<td>8 (10)</td>
<td>6 (7)</td>
<td>0.63</td>
</tr>
<tr>
<td>NYHA II, n (%)</td>
<td>51 (65)</td>
<td>43 (53)</td>
<td></td>
<td>37 (47)</td>
<td>33 (41)</td>
<td></td>
</tr>
<tr>
<td>NYHA III, n (%)</td>
<td>25 (32)</td>
<td>32 (40)</td>
<td></td>
<td>29 (37)</td>
<td>34 (42)</td>
<td></td>
</tr>
</tbody>
</table>

Cardiac function with echocardiography

A calculation was performed for patients with EF <40% according to echocardiography. It was not possible at baseline to detect a difference in the number of patients with EF <40% between the groups (39/71 vs. 44/70; χ²:0.91; p=0.34). At the end of the study, the intervention group had significantly fewer patients with EF <40% compared to the control group (33/71 vs. 45/70; χ²:4.88; p=0.03). All the results of echocardiography are specified in Table VIII.

Table VIII. All results of the echocardiographic examinations allocated in functional levels.

<table>
<thead>
<tr>
<th>Echocardiography</th>
<th>BEFORE</th>
<th>p-value</th>
<th>AFTER</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention Group</td>
<td>Control Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF &gt; 50 %, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>7 (9)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>EF 40-49 %, n (%)</td>
<td>32 (41)</td>
<td>27 (33)</td>
<td>32 (43)</td>
<td>17 (23)</td>
</tr>
<tr>
<td>EF 30-39 %, n (%)</td>
<td>37 (47)</td>
<td>35 (43)</td>
<td>25 (34)</td>
<td>32 (44)</td>
</tr>
<tr>
<td>EF &lt; 30 %, n (%)</td>
<td>10 (13)</td>
<td>19 (23)</td>
<td>8 (11)</td>
<td>13 (18)</td>
</tr>
<tr>
<td>Missing</td>
<td>2(3)</td>
<td>3(4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note; EF: ejection fraction; n: number; Missing, Not attend final echocardiography

Cardiac function assessed with natriuretic peptides

At the start of the study, there was no difference in NT-proBNP levels between the groups. The mean value in the intervention group was 1091 ng/L (median 1734 ng/L), while in the control group it was 588 ng/L (median 1137 ng/L) (p=0.07). The mean value of NT-proBNP at the end of the study was 895 ng/L (median 1354 ng/L) in the intervention group, and 671 ng/L (1234 ng/L) (p = 0.7) in the control group.

The assessment of health-related quality of life

The outcomes of the QoL measurements obtained in eight different dimensions according to SF-36 are demonstrated in Figure 4. None of the dimensions demonstrated a significant difference in QoL between the intervention group and the control group. However, the dimension “Role Emotional” displayed a p-value of 0.06 which was the most apparent difference of all analysed dimensions between the intervention and the control groups.
The utilization of healthcare resources

The utilization of healthcare contacts in the HC, PHC and in total is shown in Table IX. There was no significant difference in the number of contacts between the intervention group and the control group in HC or PHC contacts (p=0.13 and 0.51). However, there was a significant difference overall in the number of contacts, with the intervention group having a lower number of contacts (p=0.04).

An assessment of the number of visits to the emergency ward showed that the patients in the intervention group had 38 visits and patients in the control group had 62 visits (p=0.002). The patients in the intervention group had 36 admissions to hospital and in the control group there were 51 admissions (p=0.03). Subsequently, the intervention group had fewer patients who visited the emergency ward without subsequent hospitalization (two visits versus 11 visits (p=0.0001)). There were 24 patients in the intervention group who were admitted at least once, and in the control group there were 32 patients with at least one admission to hospital (p=0.06). Among patients who were admitted to hospital on any occasion, the number of hospital days on average was 8.3 days and there was no difference between groups.

Regarding the number of hospital days, the intervention group had an average of 3.4 days per patient and the control group had 5.2 hospital days on average, which was not a significant difference (p=0.16), and which is shown in detail in Table X. The intervention group had significantly fewer (0.4) visits to HC physicians, and in the control group there were 0.8 visits (p=0.01). In the intervention group, the number of outpatient visits to nurses was on average 0.1 visits, and in the control group 0.6 (p=0.004).

The healthcare utilization in the PHC is also illustrated in table X. The number of visits to the GP was 2.9 visits in the intervention group and 3.8 visits in the control group (p=0.02). Regarding visits to the district nurse, there were 4.4 visits in the intervention group and 7.8 in the control group (p = 0.14). The number of visits to specialized nurses in the PHC was 1.7 visits on average in the intervention group, and in the control group it was 1.6 (p=0.08). Furthermore, there were significantly more visits by the intervention group during the first six weeks (1.1 versus 0.2 visits (p=0.02)).
Table IX. Utilization of healthcare in the intervention group and control group. The utilization of hospital care, primary healthcare and total contact is illustrated both in total numbers and as mean values.

<table>
<thead>
<tr>
<th>Hospital Care</th>
<th>Intervetion Group</th>
<th>Control Group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of admissions</td>
<td>36</td>
<td>51</td>
<td>0.03</td>
</tr>
<tr>
<td>Number of days in a hospital ward; n</td>
<td>265</td>
<td>423</td>
<td></td>
</tr>
<tr>
<td>Emergency ward, n</td>
<td>2</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Visit to physician, n</td>
<td>34</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Visit to a heart failure nurse, n</td>
<td>7</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Total number of days for hospital care; n</td>
<td>308</td>
<td>550</td>
<td></td>
</tr>
<tr>
<td>Number of contacts/patients; mean (SD)</td>
<td>3.9 (10.3)</td>
<td>6.8 (13.6)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outpatient care</th>
<th>Intervetion Group</th>
<th>Control Group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visits related to general practitioner</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visits, n</td>
<td>227</td>
<td>311</td>
<td></td>
</tr>
<tr>
<td>Administrative (prescription/telephone), n</td>
<td>209</td>
<td>216</td>
<td></td>
</tr>
<tr>
<td>Visits related to nurses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit to specialized nurse, n</td>
<td>135</td>
<td>129</td>
<td></td>
</tr>
<tr>
<td>Visits related to district nurse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visits, n</td>
<td>347</td>
<td>633</td>
<td></td>
</tr>
<tr>
<td>Visits related to para medical staff</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paramedicine, n</td>
<td>65</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>Total number of contacts with PHC; n</td>
<td>983</td>
<td>1414</td>
<td></td>
</tr>
<tr>
<td>Total number of contacts/patient; mean (SD)</td>
<td>12.4 (12.0)</td>
<td>17.5 (19.4)</td>
<td>0.051</td>
</tr>
<tr>
<td>Total number of contacts with PHC &amp; HC; n</td>
<td>1291</td>
<td>1964</td>
<td></td>
</tr>
<tr>
<td>Total number of contacts/patient for PHC &amp; HC; mean (SD)</td>
<td>16.3 (18.0)</td>
<td>24.2 (28.7)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Note: n=number; SD, standard deviation; HC, Hospital Care; Paramedical staff, physiotherapist, occupational therapist, dietician, podiatrist; PHC, primary healthcare.

Calculations were made of the average cost for the variables HC, PHC, examinations, medication, and the total cost, all of which are illustrated in Table X. The cost of the HC was EUR 2698 in the intervention group and EUR 4331 in the control group (p=0.02). The cost for PHC was EUR 1254 in the intervention group and EUR 1777 in the control group (p=0.02). In total, the cost for the intervention group was EUR 4407 while in the control group it was EUR 6590 (p=0.01). This implies that the intervention resulted in a cost reduction of EUR 2183 per patient (33%).

When estimating the cost for the intervention, it was assessed that the cost was EUR 332, which includes the cost of 222 EUR for nurse visits and EUR 110 for visits to the GP.
Table X. Mean healthcare costs, study visits and inpatient days per patient distributed in hospital, examinations, primary care and medication for patients allocated to the intervention group as well as the control group.

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>p-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visits or days</td>
<td>Cost (EUR)</td>
<td>Visits or days</td>
</tr>
<tr>
<td><strong>Hospital Care</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inpatient care</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stay/day in hospital ward, n</td>
<td>3.4</td>
<td>2429</td>
<td>5.2</td>
</tr>
<tr>
<td><strong>Outpatient care</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency ward, n</td>
<td>0.5</td>
<td>14</td>
<td>0.8</td>
</tr>
<tr>
<td>Visit to physician, n</td>
<td>0.4</td>
<td>162</td>
<td>0.8</td>
</tr>
<tr>
<td>Visit to a heart failure nurse, n</td>
<td>0.1</td>
<td>13</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Cost of examinations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examinations</td>
<td>34</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>X-ray</td>
<td>47</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td><strong>Total cost for hospital care</strong></td>
<td>2698</td>
<td></td>
<td>4331</td>
</tr>
<tr>
<td><strong>Primary Healthcare</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost related to general practitioner</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit, n</td>
<td>2.9</td>
<td>632</td>
<td>3.8</td>
</tr>
<tr>
<td>Administrative, n</td>
<td>2.6</td>
<td>95</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>Cost related to nurses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit to specialized nurse week 1-6</td>
<td>1.1</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Visit to specialized nurse week 7-52</td>
<td>0.6</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Visit to specialized nurse total, n</td>
<td>1.7</td>
<td>127</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>Cost related to district nurse</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit (including home visits), n</td>
<td>4.4</td>
<td>325</td>
<td>7.8</td>
</tr>
<tr>
<td>Paramedicine</td>
<td>0.8</td>
<td>75</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Total cost for primary healthcare</strong></td>
<td>1254</td>
<td></td>
<td>1777</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cardiovascular medication</td>
<td>116</td>
<td>156</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular medication</td>
<td>340</td>
<td>325</td>
<td></td>
</tr>
<tr>
<td><strong>Total cost for medication</strong></td>
<td>453</td>
<td>481</td>
<td></td>
</tr>
<tr>
<td><strong>Total cost of healthcare</strong></td>
<td>4407</td>
<td></td>
<td>6590</td>
</tr>
</tbody>
</table>

Note: n: numbers, Administrative: prescription/telephone, Non-parametric tests have been used in table X when comparing costs. * P-value under null hypothesis of no cost difference between the groups.

**DISCUSSION**

Studies on HFMPs have shown that they reduce mortality and hospitalization (99,101). These studies have been mainly Hospital-based with populations probably having more severe HF, and the enrolment to these studies was usually carried out when the patients were hospitalized and their HF condition had deteriorated. In the present study (III,IV), the enrolled patients were stable in their HF condition and the HF was considered as a mild form. Therefore, the results are not completely comparable due to a difference in population, and the present study had different results in resource utilization and not mortality. Two PHC-based HFMP studies with a similar design and population to the present study have been carried out. One was from New Zealand, which showed that HFMPs in PHC after discharge reduced hospitalization by 26%. The other was an American study, which showed a reduction by 40% in the number of visits to the hospital emergency ward. These results were similar to those found in the present study (127,128). This thesis has shown that the HF population in PHC is old, and the most common etiological factors are IHD and hypertension, and only 31% are diagnosed with echocardiography (I). When an HFMP intervention was implemented in PHC, there was reduction in health care utilisation and costs (III,IV). The intervention group had a significantly lower number of health care contacts and there was also a lower (36 versus 62) number of admittances to hospital as well (p=0.002). The cost of HC was EUR 2698 in the intervention group and EUR 4331 in the control group (p=0.02), and the costs for PHC were found to be similar since the intervention group had a cost of EUR 1254, while for the control
group it was EUR 1777 (p=0.02). In total, the intervention group had a cost of EUR 4407 and the control group EUR 6590 (p=0.01), which is a cost reduction of 33%. The intervention also resulted in a reduction of NT-proBNP and improved cardiac function but the mortality and QoL remained unchanged.

Population characteristics

The average age in the first study was 78 years and in comparison with other studies which were mainly population-based, this finding was well matched (I) (9,15,18,91,129). Furthermore, the average age for women was higher in the present study, 80 for women and 76 for men (p<0.05), which is also congruent with comparable studies (9,15,91). The reason why women were significantly older is probably that women have a later onset of HF and have their AMI 7-8 years later compared to men, probably because women have more hypertension with a later onset of HF. The prevalence of HF calculated in the population of the first study was 2% (I). There are similar findings when comparing with other studies (5,9). In the study population III-IV, there was a mortality rate of 6%. This is a low mortality rate since other studies have shown a mortality of 20-29 % for one year and a mortality that increases markedly with age (11,102,129). A Swedish register study showed mortality in an HC population of 21 % and a mortality of 6% in PHC-based patients (18). Presumably, the patients in the HC population have a more severe HF compared to the patients in the PHC and therefore, it can be difficult to compare results from HC to PHC.

Etiological factors and concomitant diseases in heart failure

The most common etiological factors in HF are IHD and hypertension. Valvular disease and cardiomyopathy are more unusual causes of HF in an HF population, and this was also found in the present study (I, II) (1-5). Other diseases occurring in this study population were diabetes in 25%, COPD in 14-20% and AF in 38%. Diabetes was present in 25 % of the patients in these populations (I-III). This is consistent with other studies and, consequently, diabetes is an important component in HF (7,9,18). There was an occurrence of AF in 30-40% of the patients in the present populations and this finding is comparable with other studies that have 40-45% of the patients with AF (I-III) (7,18).

Diagnostic considerations of heart failure in primary health care

In the first retrospective study, 69% of the patients had the diagnosis of HF based on clinical criteria and only 31% received it based on echocardiography (I). When HF is based on clinical criteria, basically 50% of the patients will have an incorrect diagnosis (4, 19,25,64). In comparison with other studies which are population- or PHC-based, echocardiography was applied in 8-30% of patients with the diagnosis of HF in the PHC (6,7,97). Consequently, there is a substantial risk that the diagnosis is incorrect and that patient will receive inappropriate treatment. Admittedly, this data is somewhat old and therefore it can be expected that there has been an improvement in recent years. Physicians in PHC might have been cautious about using echocardiography at that time, due to low availability and possibly with regard to the cost aspect.
The use of medication in heart failure

The retrospective study of the HF population demonstrated that treatment with RAS blockade occurred in 56% (I). However, diuretic therapy was used with 84% of the patients and was the most commonly used drug in HF (I). Digoxin was used in 40% of cases, which was roughly equivalent to the number of patients having AF, implying that digoxin was primarily used to regulate the heart rate. Treatment with beta blockers or MRA was not considered since it was not fully recognized therapy when planning the study. In other studies, 60-70% had treatment with RAS blockade (7,18,64). Treatment with beta blockers occurred in 30-50% of the patients, which could be regarded as an underuse of medication, and when used, it was often in suboptimal dosages (I) (18). There is overwhelming evidence that these drugs have positive effects on HF when used at recommended dosages (68-75,77-81).

In the prospective study, there were no significant differences at baseline between the intervention and the control group regarding the number of patients treated with RAS-blockade or beta blockers. However, a significantly higher number of patients were treated with RAS-blockade in the intervention group (100 vs. 84%) at the end of the study (p=0.002). The dosage levels were also significantly increased in the intervention group which had 94% of the optimized dosage compared to 69% in the control group (p=0.0001). These results for RAS-blockade were not found in the control group, nor were they found for beta blockers in either group. The increased usage and dosages of RAS-blockade should be a result of the intervention, which might be a factor contributing to the reduction of health care utilization and health care costs.

Functional capacity in heart failure

When analysing the NYHA functional classes in all the studies, it was evident that NYHA class II (41-51 %) was the most frequent functional class, followed by NYHA class III (30-40 %) (I-IV). NYHA class I occurred in approximately 10% (4-17%). Patients in NYHA class IV, however, were unusual and were only detected in 2% (I). When comparing with the COACH study, 50% of the patients were in NYHA-class II, 46% in NYHA class III and 4% in NYHA class IV. The presumption is that the COACH study had a more severe HF compared to the present studies, with a mortality which was 29% and therefore not completely comparable. In the PHC-based study illustrated, there was a distribution of NYHA classes (NYHA class I 19%, NYHA class II 41%, NYHA class III 24% and NYHA class IV (7%) and since this was a similar descriptive study as study I, these findings are considered to be comparable (7). In the present study, there were patients with NYHA class I, who would be non-symptomatic HF patients. The patients participating in the present prospective study were recruited when there had been no deterioration in HF but when they had shown impaired cardiac function in echocardiography. The explanation is that these patients previously had symptomatic HF, and after receiving HF treatment recovered to be in NYHA I.

Evaluation of the composite endpoints

Since the present study had a short intervention time and consisted of a small study population with a stable HF, it could not be expected to find significant differences in mortality and morbidity and therefore there was a calculation of composite endpoints consisting of the variables of survival, hospitalization, changes of NT-proBNP, echocardiography and QoL. However, the composite endpoints showed that the intervention group had significantly improved scores compared to the control group.
**Natriuretic peptides**

The NT-proBNP was significantly decreased in the intervention group during the study period, which was not observed in the control group (III). It can be presumed that the intervention caused an increased adherence to medications and furthermore resulted in enhanced dose optimization of HF-related medications. In the UPSTEP-study, which was a BNP-guided treatment study, there was a subgroup analysis comparing responders (a reduction of BNP >30%) with non-responders (52). This analysis illustrated significant differences in several outcomes and even in mortality. These findings should imply that the reduction of NP has an important role and has an impact on the heart failure prognosis. Furthermore, NP levels are prognostic factors (43,56,57). The SIGNAL-study, with NT-proBNP-guided management of HF patients in the PHC, did not result in improved treatment and was not able to show changes in mortality or morbidity (130). The study did not, however, have similar intervention as in present study (III). This study was not designed to evaluate NT-proBNP-guided management, but it appears that optimized medication and (probably) increased adherence to medication are important factors.

**Cardiac function**

The cardiac function was analysed with echocardiography and, at baseline, and there was no significant difference between the two groups (III) in the number of patients with EF <40%. After the intervention, there were significantly fewer patients with EF <40% in the intervention group. Even though this is a small study population with patients with milder forms of HF, it was possible to demonstrate an improvement in cardiac function. This indicates that it was possible to show improvement even in cardiac function assessed by echocardiography. When cardiac function was evaluated using echocardiographic examination, differences could be found in the number of patients with EF <40% after the intervention, with fewer patients in the intervention compared with the control group, even though no significant difference between the two groups could be found at the start of the intervention.

**Assessment of Quality of life**

There are several instruments used for measuring QoL. There are QoL instruments that are disease-specific, where Minnesota living with HF (MLHF) and Kansas City Cardiomyopathy Questionnaire (KCCQ) are frequently used instruments in HF. In the disease-specific QoL instruments, there is an emphasis on problems which are specific to HF. There are also generic QoL instruments which are broader and more extensive, which makes them more usable for patients with different characteristics and diseases. Such instruments are SF-36 and EQ-5D, but in this context, SF-36 was selected since it is a commonly used QoL instrument all over the world. Since there would be extensive comorbidity and an elderly population in the present study, the QoL instrument SF-36 would be more applicable in this study. SF-36 is a questionnaire which has been validated for HF (113,131). A comparative German study conducted in a PHC population using SF-36 revealed small differences in favour of the intervention in QoL regarding mental component scale and physical functioning scale, even though these were not significant (104). There was a significant change in the intervention for vitality scale but not in any of the other scales in SF-36. It is probably difficult to obtain enhancements in QoL in studies which are conducted in a PHC setting, especially when the patients have been enrolled when they had preserved health. QoL assessed with SF-36 revealed no statistical differences in any of the eight dimensions in the present study. There was a positive tendency in the intervention group, although it was not significant. In the control group, negative readings in six of eight dimensions were confirmed.
Meanwhile, in the intervention group, there were negative readings in two dimensions and positive readings in the remaining six.

**The resource utilization**

In the present study, there was decreased resource utilization in the intervention group regarding days in hospital, outpatient visits to HC and PHC (II-IV). Regarding the number of days in hospital, there were, on average, 4.4 days in hospital in study II. In the following prospective study, there were, on average, 5.2 days in hospital in the control group but in the intervention group, this was reduced to 3.4 days in hospital (III-IV). Although this difference is not significant, it indicates that the intervention had an impact on the hospitalization. In comparison, two Swedish studies had an average of 6.7 hospital days per year, which is higher than the control group in the present study (110,111). There are differences in these studies since one study had a higher number of hospitalizations and the other study recruited patients when hospitalized, which indicates that these patients possibly had more need of HC compared to those in the present study. In the present study, the intervention group had 36 hospital admissions compared with 62 (p=0.03) in the control group and there were a lower number of outpatients visits to physicians and nurses at the hospital. These results are reasonable since the intervention should have an influence on these variables. The healthcare utilization in PHC was also reduced in the intervention group regarding contacts with GP and district nurses, which would also be a consequence of the intervention (III,IV). The number of visits to a GP in the intervention group was 2.9 visits per year and in the control group it was 3.8 visits (p=0.02). When comparing to the retrospective study II, there were 4.6 visits to GP which was slightly higher compared to the result for the control group. Nevertheless, in comparison with a German PHC based study there were six visits to a GP (95). In a Swedish population-based cohort study, it was demonstrated that the HF patients had approximately two visits to physicians in HC and 1.2 visits to a GP. This study included patients when performing an echocardiography of some reason why these patients were probably in more need of HC in comparison to the present study (110).

The number of visits to specialized nurses in PHC for the whole study period was the same in both groups. The visits to the specialized nurses were distributed among the visits which took place during the first six weeks and the visits conducted from week 7 and until the study was terminated. It was demonstrated that the intervention group had significantly more visits in the first six-week period and that the number of visits decreased later on. This result was expected since there was an intervention in the initial six weeks which was regarded as an investment and which later on resulted in a reduced number of visits.

The intervention resulted in a statistically significantly reduced cost in total (IV). The most prominent cost reduction, which was 38%, occurred in the HC while the cost reduction was 29% in PHC. HC was consequently the most apparent cost driving factor which after all was remarkable since the intervention was executed in a PHC-based setting without directly focusing on HC. There are data showing that HFMPs in PHC is cost-effective compared to conventional standard care of HF (132).

The average cost per patient on a one-year basis was shown in the retrospective study to be SEK 37,100, equivalent to EUR 4264 (II). The prospective follow-up study was found to have a cost of EUR 6590 in the control group (IV). This discrepancy is basically because there are differences in the price tariffs, and to elucidate if the difference was due to the prize tariffs, there was a calculation using both price tariffs in the population in study II and the control.
group of study IV, and no significant difference was found. The intervention group had a lower cost of EUR 4407 which was a reduction of 33% (p=0.01). In two Swedish studies, the cost was EUR 5700-7610 and in a German study, there was a cost of EUR 4681 per year (95,110,111). These comparative costs are approximately at the same level as cost of EUR 6590 representing the control group in the present study. There are probably several reasons for these differences in costs, including differences in population and there could possibly be differences in the price tariffs. These factors are probably the reason for the difference found in the allocated costs in HC and PHC. In study II, HC accounted for half the cost and PHC accounted for 22% (II). In the prospective study IV, the HC was still the prominent cost driving factor, representing approximately 65% of the costs while the PHC accounted for about 28% of the costs, which is a higher proportion than previously described. These findings are obviously different from comparative studies where HC accounted for 70% or even 84% while PHC accounted for a minor proportion, confirming the differences between the studies (107,110,111). The studies illustrating that HC represents 70% of the costs are register studies from Stockholm. These registers were HC-based and PHC was not well represented. Furthermore, the results may have been influenced by the presence of a high number of private PHC facilities in Stockholm area with closed systems of medical health care records, and the PHC might not have been properly included in the registers. The included patients were in contact with HC which should result in differences in populations.

It was also found that the implementation of HFMPs in PHC resulted in a cost reduction of EUR 2183 (33%). The stipulated cost of the intervention was EUR 332 whereas the overall cost reduction was EUR 1851. This would result in a cost reduction in a population of 100 000 inhabitants of EUR 185 million.

Limitations of the research

This research might have been unsuccessful in including patients with severe HF. It is possible that HF patients with very serious conditions and needing advanced HC were not included in the present study since the population in this study were solely enrolled in the PHC. As the severely deteriorated patients with recurrent requirements of advanced HC, this may have affected the cost. During the study period, there were no patients included in the present study who were being considered for transplantation or devices such as ICD or CRT. These severe conditions would be more common in HC but would be very rare in a PHC population and should not have a substantial impact on the costs.

The study had a relatively short follow-up, which will cause difficulties in obtaining statistical outcomes on certain variables. At the same time, there was a relatively small study population which also might have made it difficult to find significance in some variables.

The study was carried out at several PHC centres and there could be a risk that the regular physicians, the GPs at the PHC centres, were influenced by the study. This may have prompted these physicians to provide enhanced management and treatment of patients in the control group.
Conclusions

- The average age was about 78 years (I). The diagnosis of HF in the PHC was preferably based on clinical criteria, and only 31% were subjected to echocardiography in order to determine cardiac dysfunction. Women had a slightly higher average age than men. In addition, women had to a lesser extent been subjected to examination with echocardiography, and were treated more often with diuretics and more rarely with RAS blockade.

- The cost for a patient with heart failure was SEK 37 100, which gives a total cost for HF in Sweden in the range of SEK 5.0-6.7 billion, much higher than previously known (II). There were no significant differences in cost concerning gender, NYHA class, age, or heart function assessed by echocardiography. PHC accounted for a greater part of the total costs than previously assumed.

- Implementation of an HFMP in the PHC resulted in improved cardiac function, reduction in NT-proBNP and reduction of health care utilization. I did show statistically unchanged QoL and had no effect on mortality (III).

- The intervention with an HFMP in PHC entailed a reduction of resource utilization and a reduction of health care costs by 33% (IV).

The research implications

The implementation of the research

These results imply that HFMPs can be recommended in PHC. However, there can be obstacles since the PHC centres are different in size, population, localisation and traditions. A small PHC centre with young population and located close to a hospital will probably have trouble finding enough patients to uphold sufficient HF experience. However, larger PHC centres, located far from the hospital and with an older population will probably experience a positive outcome with HFMP. A PHC centre with a functional HFMP would have improved management of patients being discharged from hospital after deterioration of HF. The contact with HF nurses in PHC would involve providing information about HF and treatment of HF which would increase adherence to treatment and self-management to avoid worsening of HF. It also involves optimizing treatment which entails an increased welfare and improved cardiac function. HFMP probably contributes to increasing the patient’s self-confidence and continuity of health care.

Future research

Forthcoming research should further investigate where the HF patients receive their health care from a much wider perspective. Recent implementation of data registers and integrated medical health care records make it possible to conduct research using more expanded and precise information regarding HC, PHC and investigations.

It would also be of interest to investigate the HFMP implementation in a larger population in order to confirm the positive outcomes.
This thesis did not elucidate what factor or factors influence the reduction of resource utilization and costs. Therefore, it would be interesting to elucidate such factors and how they affect the outcome. Further research should investigate if it is the improved medication, the efforts from the HF nurses or increased accessibility of health care that affect the outcome.

Detta forskningsarbetet omfattade fyra delarbeten och det inledande arbetet var en deskriptiv retrospektiv studie med 256 patienter som behandlades för hjärtsvikt i Åtvidabergs kommun (I). Syftet var att beskriva hjärtsvikt i primärvården beträffande förekomst, orsak till hjärtsvikt, handläggning av utredning, behandling samt värdera om det förelåg några könsskillnader. Resultatet var att ischemisk hjärt sjukdom följd av hypertoni är det den dominerande orsaken till hjärtsvikt. Behandlingen bestod av diuretika (84%), ACE-hämmare (56%) och digoxin (40%). Det var endast 31% som hade bekräftat diagnosen hjärtsvikt med ekokardiografi. Följaktligen var det 69% som fick sin hjärtsviktssmottagning baserad på kliniska kriterier (klinisk undersökning, EKG eller lungröntgen) trots att detta innebär många diagnoser blir felaktiga. Det fanns könsskillnader beträffande behandling och diagnostisering eftersom kvinnorna mer sällan fick behandling med ACE-hämmare och mer sällan fick genomgå ekokardiografi jämfört med männen.

Syftet med det andra delarbetet var att beräkna sjukvårdsutnyttjande, sjukvårdsrelaterade kostnader samt ta reda på om det förelåg könsskillnader (II). Detta var en retrospektiv undersökning genomförd vid två vårcentraler. Det samlades in 115 patienter med diagnosen hjärtsvikt som fick utföra ekokardiografi för att fastställa hjärtfunktionen. Därefter granskades journaler och data samlades in angående antal vårddagar på sjukhus, besök på sjukhus och vårcentral samt läkemedelsförbrukning och genomförda undersökningar. Resultatet blev att kostnaden för en patient med hjärtsvikt var i genomsnitt under ett år SEK 37 100. Det gick inte att påvisa någon kostnadsskillnad beträffande, kön, ålder, NYHA-klasser eller hjärtfunktion. Det var sjukhusvården som svarade för den största kostnaden som var 47%, primärvården 22%, läkemedelsbehandlingen 18%, sjukhem 5% och undersökningar stod för 6% av kostnaden.

De tredje och fjärde delarbetena som sedan genomfördes var en randomiserad, prospektivt, öppen studie med syftet att undersöka om intervention med hjärtsviktssmottagning i primärvården medför förbättrad hjärtfunktion, ökad livskvalitet och om det därigenom gör att påverka sjukvårdsutnyttjande och sjukvårdsrelaterade

Sammanfattningsvis är hjärtsvikt vanligt förekommande i primärvården och består av patienter med hög ålder. Det finns brister avseende diagnostisering av hjärtsvikt eftersom endast 31 % genomgått ekokardiografi och att det i detta avseende finns könsskillnader. Intervention med hjärtsviktsmottagning i primärvården har visat att det är möjligt att minska behovet av sjukvårdskontakter samt minska sjukvårdskostnaderna.
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