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HEART FAILURE – ASPECTS ON TREATMENT AND PROGNOSIS

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To Erika, Emma and Niklas

ABSTRACT

The aim of this thesis was to describe aspects on treatment and prognosis in heart failure. In paper I, we studied two hundred and seventy-nine hospitalised heart failure patients, and related clinical and demograhic data to the use of diagnostic tests, treatment and follow up. The main part of the thesis, papers II-V, describe results from the OPTIMAL study which included two hundred and eight patients aged ≥ 60 years, hospitalised with systolic heart failure, and followed for (mean) 3.3 years.

In *Paper I* the patients had a poor prognosis, with a 1-year mortality of 30 %. In spite of this, only approximately half of them were followed-up within three months after discharge. The majority of the patients, 57%, were planned for follow up in primary care and 21 % in the hospital outpatient clinic. Young age, male gender and treatment with β-blocking agents were related to follow up at the out patient clinic. There was an underuse of echocardiography and treatment with angiotensin converting enzyme-inhibitors, more pronounced in women than in men.

In *Paper II* a nurse-based management program on heart failure was shown to be more effective than primary care in optimising medication. However, the program did not have a favourable influence on quality of life, readmission rates or mortality.

In *Paper III* traditional markers on prognosis such as age, gender, brain natriuretic peptide levels, left ventricular function and creatinine were shown to influence mortality rates. A poor quality of life predicted increased readmission rates.

In *Paper IV* we report on a subgroup of sixty-seven patients who underwent cardio-pulmonary exercise testing. Peak ventilatory equivalents for carbon dioxide and oxygen, and peak oxygen consumption, were predictors of mortality.

In *Paper V* we describe echocardiographic findings in one hundred and fifty-eight patients and conclude left ventricular mass index to be an important prognostic marker in women.

Conclusions: There is an underuse of investigation and treatment in heart failure and this is more pronounced in women. A nurse based management program is effective in optimising medication but did not influence quality of life, readmission rate or mortality. To the traditional markers on heart failure prognosis in the elderly, cardiopulmonary exercise test results can be added. We suggest further studies on left ventricular mass index and measurements on quality of life as predictors of prognosis.

Key words: heart failure, management program, quality of life, gender, prognosis

LIST OF PUBLICATIONS

I. Mejhert M, Holmgren J, Wändell P, Persson H, Edner M. Diagnostic tests, treatment and follow up in heart failure patients--is there a gender bias in the coherence to guidelines? *Eur J Heart Fail*. 1999;1:407-10.

II. Mejhert M, Kahan T, Persson H, Edner M. Limited long term effects of a management program for heart failure. *Heart*. 2004;90:1010-15.

III. Mejhert M, Kahan T, Persson H, Edner M. Predicting readmissions and cardiovascular events in heart failure patients. *Int J of Card* 2006;109:108-13

IV. Mejhert M, Linder-Klingsell E, Edner M, Kahan T, Persson H. Ventilatory variables are strong prognostic markers in elderly patients with heart failure. *Heart* 2002;88:239-43.

V. Mejhert M, Kahan T, Edner M, Persson H. Gender aspects on systolic heart failure in the elderly. Submitted

LIST OF ABBREVIATIONS

ACE	Angiotensin converting enzyme
AVPD	Atrio-ventricular plane displacement
BNP	Brain natriuretic peptide
LVEF	Left ventricular ejection fraction
NHP	Nottingham Health Profile
NYHA	New York Heart Association
OPTIMAL	Optimising congestive heart failure out patient clinic project
QoL	Quality of life
VE	Ventilatory equivalents
VO_2	Oxygen uptake
VCO_2	Carbon dioxide production

INTRODUCTION

1.1 Definition

According to the guidelines of the European Society of Cardiology the diagnosis of heart failure requires the following features:

- Symptoms of heart failure, typically breathlessness or fatigue, at rest or during exertion.
- Objective evidence (preferably by echocardiography) of cardiac dysfunction (systolic and/or diastolic).
- A clinical response to treatment is supportive but not sufficient for diagnosis.

1.2 Epidemiology

Due to ageing populations and improved survival in cardiovascular diseases, the prevalence of heart failure has been increasing throughout the Western world and affects up to 2 % of the population (1). One year mortality in patients hospitalised with heart failure is high, more than 25 %, and has been shown to exceed that of the most common forms of cancer (2,3).

In Sweden, heart failure is the most frequent discharge diagnosis within internal medicine, comprising about 10 % of all patient stays. Heart failure patients are often old and prone to suffer from both associated and other diseases, and non-cardiac readmissions are as common as cardiac ones (4,5). Approximately 85 % of the heart failure population is being treated in ambulatory care, usually by their general practitioners, and 15 % of patients are hospitalised. Still, hospital costs constitute 75 % of the total expenditure for heart failure in Sweden, while costs for drugs and out patient care are less expensive. The total cost for heart failure care has been estimated to 2 500 million SEK (275 million Euro), a substantial economic burden corresponding to 2 % of the total health care budget (6).

Due to financial restraints and administrative changes, important structural alterations of the Swedish health care system have taken place since 1993 when the "ÄDEL-reformen" was initiated. The aim of this was to reduce hospital costs and to treat the elderly in their homes. Also, many patients in need of full time care were referred to nursing homes. The number of hospital beds decreased from 113 400 in 1985 to 42 400

in 1995, at the same time shifting 31 000 beds to nursing homes. These changes make evaluation of health care consumption a complex issue (7). Paralleling the reduction in hospital beds, the number of patients hospitalised with heart failure has decreased since the 1993 (fig 1) (8). Also, hospital stays have successively become shorter and mean stay was reduced from 10 days in 1987 to 6.9 days in 2003 (8).

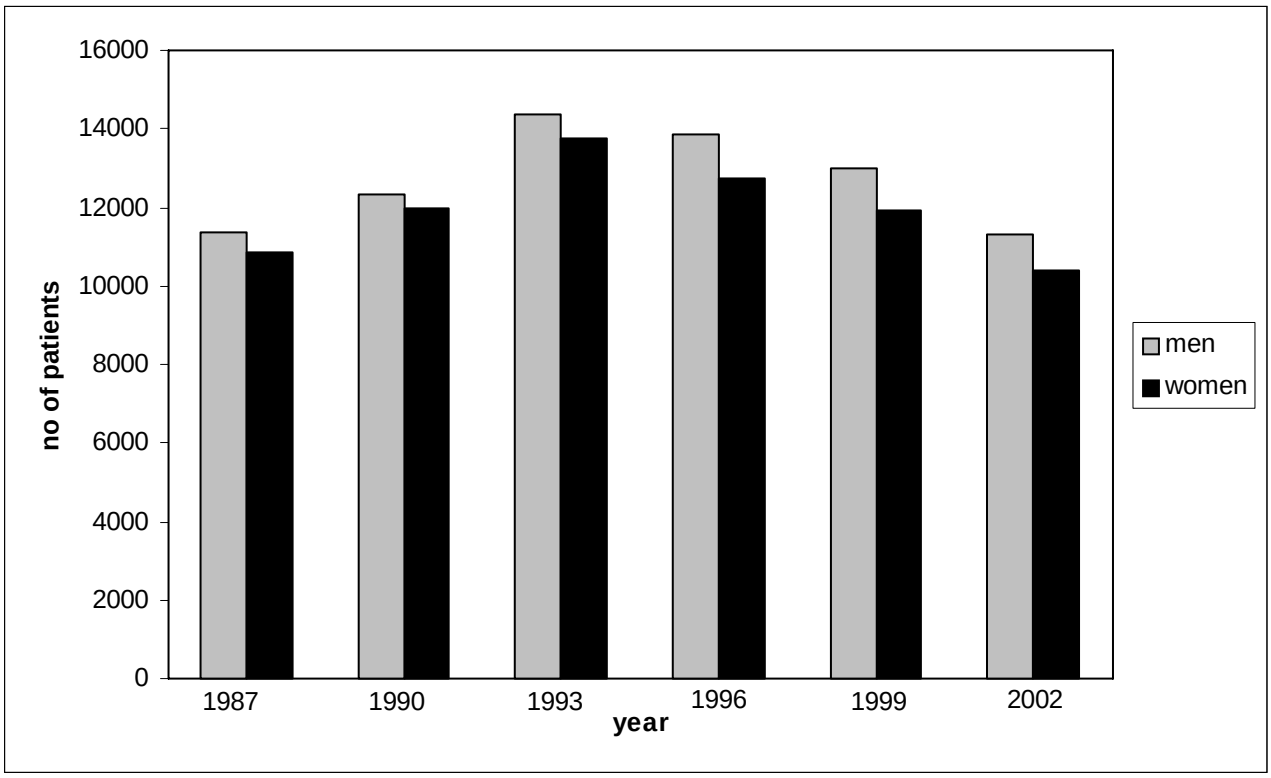

Fig 1 Number of patients hospitalised with heart failure

Interestingly, recent analyses of national Swedish health care registers have shown a decrease in incidence and mortality rate after a first hospitalisation for heart failure (9).

1.3 Diagnostic tests and treatment

To ensure optimal care of heart failure patients continually updated guidelines on examination and treatment are of great importance. The European Society of Cardiology recommends investigation of suspect heart failure to start with an electrocardiogram, x-ray of the heart and lungs and measurements of natriuretic peptides (where available). If abnormal test results, imaging with echocardiography is the next step. After complementing with other diagnostic tests if necessary, aetiology of heart failure in the individual is thereafter determined (10).

Diagnosing heart failure is difficult and echocardiography is a cornerstone in evaluation of cardiac function. Still, low availability and long waiting lists to echocardiography is a problem in many European countries. In the Euroheart Failure survey including patients from 24 countries, only 66 % of patients with heart failure diagnosis had an echocardiography performed (in the Swedish cohort 68 %). Of these, 35 % of the women and 61 % of the men had moderate or severe left ventricular dysfunction, i.e. many had a mild or normal systolic function. Analyses of diastole were seldom carried out (5). One might expect the proportion investigated with echocardiography to be lower in out clinic patients, and indeed in a report from Swedish primary care in 2001 echocardiography was performed in approximately 30 % of all patients only (11).

The importance of diastole has become increasingly clear and diastolic dysfunction of the left ventricle is often coexistent with systolic dysfunction. Diastolic heart failure is diagnosed when "symptoms and signs of heart failure occur in the presence of a preserved left ventricular ejection fraction at rest" (10). Diagnostic criteria of diastolic heart failure are: presence of signs or symptoms of heart failure, presence of normal or only mildly abnormal left ventricular systolic function, and evidence of abnormal left ventricular relaxation, diastolic distensibility or diastolic stiffness (12).

Markers of an activated neurohormonal system, such as the renin-angiotensin system and catecholamines, and several natriuretic peptides, have gained great interest as diagnostic and prognostic markers. Lately, brain natriuretic peptide (BNP) and its precursor pro-BNP, have been discussed for use in clinical practise. Normal BNP levels have been reported to have a strong negative predictive value, i.e. to exclude the heart failure diagnosis (13). The combination of a normal electrocardiogram and BNP-value makes the diagnosis of heart failure unlikely.

Undertreatment of heart failure is a problem in many European countries. The Euroheart Failure study report angiotensin converting enzyme (ACE)-inhibitors to be prescribed to mean 62 % and ß-blockers to 37 % of hospitalised heart failure patients (in the Swedish cohort 40 and 52 % respectively), and the combination to be used in 17 % of patients only (14). In Sweden, general practitioners make the main part of drug prescriptions. Data from the Diagnosis and Therapy survey in Sweden, which are from ambulatory care only, have shown the use of ACE-inhibitors to be low, approximately

25 % (15). In the first report from a Swedish heart failure management program, Charles Cline and co-workers reported in 1992 that 23 % and 12 % of hospitalised heart failure patients were treated with ACE-inhibitors and ß-blockers respectively (16).

1.4 Health related Quality of Life

"Health is not merely the absence of disease but a state of complete mental, physical and social well-being" (WHO) (17).

Measuring quality of life (QoL) is difficult as it is a multidimensional evaluation, comprising the areas of physical symptoms, psychological well being, social ability and perceptions about one's own health (18). Traditional objective biomedical markers on health do not always correlate with the patients' perception of well being. To caregivers it is essential to evaluate QoL results, in research as well as in every day practise as a guide to modify treatment. For instance, if a new drug is shown to prolong life but does not improve, or even deteriorates QoL due to side effects, it might not be appropriate to use it. All QoL instruments must be valid, reproducible and user friendly. Good compliance with the questionnaires is important, as loss of data is a common problem. Use of self reported questionnaires avoids the bias introduced when a caregiver questions the patient (19).

There are two kinds of QoL instruments:

- General QoL instruments have been used to compare chronic diseases. For example, in the Medical Outcomes Study heart failure patients had a QoL more impaired than patients suffering from a variety of other chronic disorders such as arthritis, chronic lung disease, diabetes mellitus and angina pectoris (20). This study used the SF 36 questionnaire (21).

- Disease specific questionnaires, such as the Minnesota Living with Heart Failure instrument, capture aspects of QoL that are most important to the particular patient group, as they cover more distinct aspects of the disease (22).

These two categories of QoL instruments are often recommended to use in combination. In the OPTIMAL study, we used the Nottingham Health Profile (NHP)

that is well validated and has normative values from an age- and gender matched healthy population (23).

1.5 Heart failure management program

To improve clinical outcome and QoL in patients with heart failure, specialised management programs have been initiated. In Sweden, management programs have been an important part of heart failure care since the first one was established in 1990. Today, heart failure clinics exist in more than two thirds of the hospitals in Sweden, and the majority of these are nurse led outpatient clinics (24).

Although there are various health care delivery systems within the programs, most include the following components as described by Jaarsma (25):

- To ensure optimal diagnostics
- To optimise medical therapy with guidelines
- To use a team approach
- Discharge planning
- Vigilant follow up, first follow up within 10 days of discharge
- To increase access to health care
- To educate and counsel
- To attend behavioural strategies
- To address barriers to compliance
- To monitor early signs and symptoms
- To ensure a flexible diuretics regimen
- To provide an exercise program

A number of prospective randomised trials (26-34) have reported upon the effects of management programs, and lately several meta-analyses have been published. In Table 1 all meta-analyses published so far, are listed.

Table 1 Meta-analyses on heart failure management programs

Author (ref)	Studies n	Patients n	Year	Mortality (RR)	HF readm (RR)	All readm (RR)
McAlister et al (35)	11	2067	2001	*0.94 ns*		0.87
multidisciplinary						0.77
telephone contact						*1.15*
McAlister et al (36)	29	5039	2004			
multidisciplinary				0.75	0.74	0.91
enhanced patient self care				*0.66 ns*	0.66	0.73
telephone contact				*0.82 ns*	0.75	*0.98 ns*
Gonseth et al (37)	54	3160	2004		0.70	0.88
Phillips et al (38)	6	949	2004	0.80	0.65 - 0.70	0.91
Gwadry-Sridhar et al (39)	8	1139		*0.98 ns*		0.79
Holland et al (40)	30	8158	2004	0.79	0.70	0.87
home visit interventions				*0.87 ns*	0.62	0.80
telephone interventions				0.70	0.70	*0.86 ns*
hospital based interventions				*1.0 ns*	*0.94 ns*	*0.99 ns*
Roccaforte R et al (41)	33	7621	2005	0.84	0.69	0.86

hf=heart failure; ns = non significant; RR = relative risk

In conclusion, most meta-analyses evaluating management programs report a reduction of the costly heart failure- and all cause readmissions to hospital. Data on mortality are inconclusive. Various results on QoL and life style changes have been reported in several Swedish and other prospective randomised trials (16,42). However, data pooling on QoL results is difficult because of the diversity of QoL scales used, small sample sizes and short follow up times and only a few of the meta-analyses have reported on this endpoint.

1.6 Prognosis

Many measurements have been proposed to predict admission rates and mortality. Age and gender have consistently shown to be predictive of mortality. Framingham data demonstrate five-year mortality in men to be 75 %, in women 62 %, and a median survival time of 1.7 and 3.2 years respectively (43). Several comorbidities such as diabetes mellitus, anaemia and untreated hypertension affect prognosis (4,44). Also, patients with heart failure symptoms or depressed left ventricular systolic function, in association with ischemic heart disease have a worse outcome (45).

Functional markers on heart failure such as the New York Heart Association (NYHA) class and measurements from cardiopulmonary exercise testing, such as maximal oxygen uptake (VO_2) and the quotient between ventilatory equivalents (VE) and peak carbon dioxide concentrations (VCO_2), are robust markers on outcome (46,47).

Echocardiographic data on left ventricular volumes and function are interrelated and complex to analyse. Lately, analyses of the large CHARM population showed the strongest predictors of mortality and morbidity to be a low left ventricular ejection fraction (LVEF), old age and diabetes mellitus (48). However, LVEF often fails as a prognostic marker (49,50). From population- and other studies on hypertension we have learnt left ventricular hypertrophy to affect prognosis (51,52). Also, diastolic dysfunction has been shown to increase mortality in heart failure (53,54).

Interestingly, in a recent study, a worse QoL was shown to predict increased readmission rate and mortality (55).

Increased levels of natriuretic peptides have predicted mortality and increased readmission rates in some studies (56,57).

1.7 Gender differences

From epidemiological data we know women with heart failure to be older at diagnosis, and to have a better prognosis than men (43). Equal prevalence rates in both genders might be explained by the lower incidence but longer survival time after diagnosis in women. Data from the Swedish hospital discharge registers, administered by the National Board of Health and Welfare, reported more men to be hospitalised with heart failure than women in all age groups during 1987-2002 (fig 1). Hospital stays have

become shorter. Thus, from 1996 to 2003, mean stay in men has decreased from 7.5 to 6.8 days and in women from 8.3 to 7.5 days (8).

Similar to our findings in a Swedish population (55 vs 68%), in the Euroheart Failure study women were less often examined with echocardiography than men (41 vs 57%), (12). Few clinical studies have reported on gender-associated differences in echocardiographic measurements. Still, dissimilarities in remodelling have been described in for example patients with aortic stenosis, and in left ventricular dysfunction (58,59,60).

In trials on ACE-inhibitors, women have been underrepresented, comprising 11 to 33 % of the study populations (61,62). In part, this could be explained by the commonly used exclusion criteria of old age, better preserved LVEF and presence of comorbidity, all more prevalent in women. Still, the small number of women in these trials makes it difficult to evaluate gender differences. However underpowered, results from substudies have suggested that women might benefit less from ACE-inhibitor treatment than men (63).

Reports on prescription patterns of drugs to hospitalised heart failure patients have shown women to receive less inotropic agents, spironolactone, amiodarone, nitrates, statins and anti- platelet drugs than men. In contrast, one study described digoxin to be prescribed to more women than men (64,65). Paradoxically, in a post hoc analysis by the Digitalis investigation group, mortality was increased in women treated with digitalis, possibly due to over dosage of the drug (66).

In a Swedish study QoL was reported to be worse in women with heart failure compared to men (67). This study used the NHP questionnaire and in this, women reported a worse QoL in the reference population also. In a substudy of the OPTIMAL population, females seemed to profit more than males from a nurse based management program (68).

2 AIMS

- To describe the use of diagnostic tests, treatment and follow up in a group of patients hospitalised with heart failure

- To investigate the effect of a nurse based management program on quality of life, hospitalisation and mortality in patients with systolic heart failure

- To analyse the predictive value in heart failure of clinical, neurohormonal, echocardiographic and functional variables on readmission and mortality, and to evaluate methodological aspects on cardiopulmonary testing in elderly heart failure patients

- To describe gender aspects in patients with heart failure

3 MATERIAL AND METHODS

3.1 Paper I

This study is a retrospective examination of all hospital records from patients discharged with a primary diagnosis of heart failure (the Ninth Division of the International Classification of Diseases Code 428 A, B, X) at Danderyd university hospital and Nacka county hospital in Stockholm during the second half of year 1995. The study was performed in cooperation with the National Board on Health in Sweden. The catchment areas of the hospitals corresponded to a population of approximately 425 000 inhabitants. Charts from within 3 months after discharge were obtained from 379 patients and data concerning demographics, aetiology, Killip classification, diagnostic tests, and treatment and follow up analysed. Data on mortality was collected from Statistics Sweden.

3.2 The OPTIMAL study, papers II-V

3.2.1 Study design and patients

The optimising congestive heart failure outpatient clinic project (OPTIMAL) included patients hospitalised with systolic heart failure in Danderyd Hospital from January 1996 to December 1999, with the last follow up visit in June in 2001. The catchement area of the hospital in north-eastern Stockholm is characterised by a high socio-economic standard, and the population is somewhat older but healthier than the average Swede. A health care plan for primary care of heart failure had been initiated some years earlier in cooperation with the general practitioners, and a nurse based out patient clinic for heart failure patients had been established in Danderyd Hospital in 1992.

Participants of the OPTIMAL study were ≥60 years old with heart failure NYHA class II-IV and left ventricular systolic dysfunction by echocardiography, defined as LVEF < 0.45 or atrio-ventricular plane displacement < 10 mm. Exclusion criteria were valve stenosis, a myocardial infarction or unstable angina pectoris within the last three months, dementia and severe concomitant disease. All patients were followed for at least 18 months, mean follow up was 1122 days. In all, 285 patients were screened for inclusion but 77 patients were not included as they did not wish to participate (n=32), did not have systolic dysfunction (n=23), had a valve stenosis (n=5) or a recent ischemic event (n=4), or suffered from dementia or other severe concomitant disease

(n=13). Some of the excluded patients (n=77) were lost to follow up, but in the remaining sixty-four patients, 53 % were women and mean age was 79.3 years at baseline. This suggests the excluded cohort to be older, and to have a higher female proportion than the OPTIMAL population.

All included OPTIMAL patients were randomly assigned to follow up in a nurse based outpatient clinic at the hospital or to conventional follow up, usually in primary care. The primary endpoint of the study was to assess whether the nurse based clinic lead to improved QoL. Evaluation of cardiac function, morbidity and mortality were secondary endpoints.

At Danderyd University Hospital a nurse monitored management program for heart failure patients was set up in 1992. A senior cardiologist supervises the program. After referral to the program, the patient pays regular visits to the outpatient clinic and is encouraged to keep in contact with her nurse. At each visit the nurse checks symptoms and signs of heart failure, blood pressure, heart rate, and weight. Laboratory tests include creatinine, sodium and potassium. Before initiation of β- blocking agents, an electrocardiogram is checked. Nurses working in the program are allowed to institute and change the doses of ACE-inhibitors, β-blocking agents, diuretics, potassium substitution, and potassium sparing diuretics according to a standard protocol. The dosing goal of captopril is 100 mg/day, enalapril 20 mg/day, and ramipril 10 mg/day. A routine for titration of β-blocking agents was not set up until some years after study start. The patients are instructed to check their weight on a regular basis, and to monitor early signs of deterioration. Patients with good compliance are instructed to change dosing of diuretics on their own. Dietary advice includes recommendations of restricted sodium, fluid and alcohol intake. Information is repeated in computerised educational programs, by video, and in booklets.

According to our routine, written information is given in a structured format to the general practitioner at discharge of a patient from our institution. Patients randomised to usual care typically were followed by their general practitioners, to be treated according to the local health care plan for heart failure. There are 28 community health centres in the catchment area of the hospital. In co-operation with primary care, a health care plan for heart failure patients has been developed. This states, for example, that an echocardiogram should be carried out in all patients

with a history of an acute myocardial infarction, or with clinical signs of heart failure. If left ventricular systolic function is reduced, with an ejection fraction < 0.40, ACE inhibitor therapy should be initiated. Several meetings with hospital specialists and general practitioners have addressed the importance of optimised medication and education of heart failure patients.

In addition to the visits outlined above, all patients were scheduled for clinical examinations and detailed control of medication at 6, 12 and 18 months at the cardiovascular research laboratory at our institution. One and the same cardiologist met all patients at all visits. The patients were informed at start of the study that these visits were purely observational and with no intention to initiate examinations or to change medication.

Data on out patient visits and readmissions were collected from the National Board of Health and Welfare. Outcome and all cause mortality were determined from death certificates.

3.2.2 Health related Quality of Life

The Nottingham Health Profile is a non-disease specific questionnaire, which has been tested for reliability and validity in England and in Sweden. Reference values, originally derived from an English population, have been validated for use in Sweden. (69,70). NHP comprises 38 yes/no questions on emotional reaction, sleep, energy, pain, physical mobility and social isolation. The answers are weighted and scores of the six dimensions and the total sum are calculated. All OPTIMAL patients were asked to complete the questionnaire at baseline and at all three follow up visits. If the patient was unable to attend a follow up visit, the NHP questionnaire was sent by mail.

3.2.3 Echocardiography

Echocardiography was performed with an Acuson 128XP/10 (Mountain View, California, USA). The left ventricular measurements of volumes and function were calculated according to the recommendations of the American Society of Echocardiography (71). The atrioventricular plane displacement method (AVPD) was used as well, and measured by M-mode from an apical window (72). Diastolic function was evaluated according to a modified Mayo clinic protocol (73). Patients were enrolled if a screening echocardiography showed an EF $\leq$ 0.45 or AVPD$\leq$ 10 mm. After inclusion in the OPTIMAL study an extensive echocardiographic examination

was performed, sometimes a few days later. The mitral end point septal separation (EPSS) was measured from the E-point of the anterior mitral leaflet to the interventriuclar septum (74).

3.2.4 Neurohormonal measurements

Blood samples were obtained on ice after 30 minutes of supine rest, immediately centrifuged at + 4 C and thereafter frozen at – 70 C until analyses. BNP was measured by an immunoradiometric assay (75) and catecholamines by high performance cation exchange liquid chromatography (76).

3.2.5 Cardio-pulmonary exercise testing

The exercise test was performed on an electrically braked bicycle. The equipment used was Medical Graphics Cardiopulmonary Exercise Systems (St Paul, MN, USA) for determination of breath-by-breath measurements of ventilation (VE), oxygen uptake (VO_2) and carbon dioxide production (VCO_2). Derived entities such as ventilatory equivalents for O_2 and CO_2 (VE/VO_2, VE/VCO_2), the respiratory quotient VCO_2/VO_2 and respiratory rate per minute were presented on-line. The equipment was calibrated before every test. A twelve lead electrocardiogram was monitored for possible arrhythmia and ST-segment changes. The test began with two minutes of sampling at rest, and was followed by two minutes of freewheeling exercise. A ramp test with a continuous increase of workload by 10 Watt/min was chosen. The exercise test was symptom-limited, using a Borg scale 0-10 for dyspnoea, fatigue and chest pain (77). The patients were encouraged to exercise until they were exhausted. Interference by the physician was due at standard criteria. Blood pressure and heart rate were measured every other minute. All respiratory measurements were made from plots over time, presenting moving average values. Peak VO_2, VE/VO_2 and VE/VCO_2 were calculated as the last value of three, during the last 30 seconds of exercise. If this last value was not the highest, a mean value of the last three values was calculated. Anaerobic threshold was calculated by the V-slope method (78). Two observers independently categorised all results of the tests.

3.3 Statistics

In the OPTIMAL study, to detect a clinically significant difference in QoL at 18 months of follow up with ß = 0.80 and 2 α = 0.05, it was calculated that 180 evaluable patients would be required. To account for some 10-15 % estimated loss we intended to enrol

210 patients, and 208 were eventually included. Analyses were conducted according to the intention to treat principle.

Routine summary statistics are presented as mean ± SD, median, range, and percent. For comparisons between two groups, Students t-test was used for continuous variables of normal distribution, and Mann-Whitney's U-test for discrete or skewed variables. Chi-square test was used for comparison of proportions. Pearson correlation coefficients were calculated to check for colinearity between the univariate prognostic indicators. If a high colinearity was found, only the factor with the highest correlation to mortality was chosen in the final multivariate analysis. Prognostic information was analysed by Cox regression multivariate analyses. Kaplan-Meier survival curves were generated and a log-rank test performed to assess differences in outcome between two groups. A p-value < 0.05 was considered statistically significant. When appropriate Hazard Ratios (HR) and 95 % confidence intervals (CI) were calculated.

In paper two, if the rate of missing answers in the analyses of QoL were < 30 % in one dimension, it was substituted by the mean value of the entire group. The last follow up value during the 18-month period was carried over for patients alive but with missing data.

In paper three, the data was reduced by a factor analysis in which each domain was analysed separately to choose the strongest factor from each domain. Thereafter, a subsequent Cox regression analysis was performed for mortality and readmission rates. The results were finally adjusted for randomisation group, age and gender.

The analyses were performed with STATISTICA (StatSoft, Inc, Tulsa, Oklahoma, USA). In paper four statistical analyses were performed using the SAS statistical package (SAS Institute Inc, Cary;North Carolina, USA).

4 RESULTS

4.1 Paper I

The aim of this study was to relate clinical data in heart failure patients to demographic data and to the use diagnostic tests, medical treatment, care process and mortality.

Median age was 78 years in men, 81 years in women. Ischemic heart disease was the most frequent aetiology in both genders. Heart failure was previously known in a majority (77 %) of the 379 patients. Still, echocardiography was made during the last two years in 68 % of men and 55% of women only ($p<0.01$). Medication differed between genders as women more often were prescribed digoxin (44 vs 33 %, $p<0.05$) and more seldom ACE-inhibitors (46 vs 60 %, $p<0.05$) than men. If echocardiography had been performed, the proportion treated with ACE-inhibitors increased in men from 38 to 72 %, in women from 38 to 55 % (all $p<0.01$). Length of hospital stay was mean 6.4 days. Fifty-seven % of the patients were discharged to follow up by a general practitioner and 21 % to the out patient clinic of the hospital. Some patients were referred to a private specialist (11 %) or a geriatric clinic (10 %). One year mortality was 30 %. Within three months after discharge, 62 % of the patients had returned for a check up at their general practitioner, 49 % at the hospital out patient clinic. In a multivariate analysis young age, male gender and treatment with ß-blocking agents were related to follow up at the hospital out patient clinic (all $p<0.05$).

4.2 The OPTIMAL study (papers II-V)

Presented in Table 2 are the baseline demographics of the 208 patients included into the OPTIMAL study. There were no significant differences between study groups. The patients were randomised to follow up at the nurse led out patient heart failure clinic (intervention group, IG) or to usual care (control group, CG). At baseline approximately 95 % of the patients were prescribed furosemide, 74 % ACE-inhibitors, and 52 % ß-blocking agents. The women were older than the men (78 vs 74 years, $p<0.05$). Each patient was followed for at least 18 months, mean follow up time was 1122 days. During follow up 74 patients (36%) died.

Table 2 Baseline characteristics in the OPTIMAL study

	Total	Intervention Group	Control Group
	n=208	n=103	n=105
Age, years	75.8 ± 7.1	75.9 ± 7.7	75.7 ± 6.6
Male sex, n	120 (58%)	58 (56%)	62 (59%)
Marital status, single	93 (52%)	46 (52%)	47 (52%)
NYHA class I/II/III/IV	0/129/77/2	0/60/43/0	0/69/34/2
Ejection fraction %	0.34 ± 0.11	0.34 ± 0.12	0.35 ± 0.11
Systolic blood pressure (mm Hg)	134 ± 25	135 ± 24	133 ± 26
Diastolic blood pressure (mm Hg)	79 ± 14	79 ± 14	79 ± 13
Plasma BNP, pg/ml	331 ± 369	342 ± 323	320 ± 412
Serum creatinine, μmol/l	115 ± 37	114 ± 36	117 ± 39
Medical history			
previously known heart failure	119 (57%)	59 (57%)	60 (57%)
ischemic heart disease	139 (67%)	65 (63%)	74 (70%)
arrhythmia	111 (53%)	54 (52%)	57 (54%)
hypertension	65 (31%)	38 (37%)	27 (26%)
diabetes mellitus	46 (22%)	26 (25%)	20 (19%)
cardiomyopathy	20 (10%)	10 (10%)	10 (10%)
valve disease	17 (8%)	9 (8%)	8 (8%)

Data are ± SD; ns = non significant; NYHA = New York Heart Association; BNP = brain natriuretic peptide;

4.2.1 Paper II

The aim of this study was to evaluate the effects of a nurse based outpatient management program for elderly patients discharged from hospital with heart failure. Already at study start, 55 % of patients had target doses of ACE-inhibitors. Compared to the control group (CG), the intervention group (IG) received higher doses and 90 % achieved target doses during follow up. Demonstrated in Fig 2 is the proportion of patients on target doses of ACE-inhibitors during 18 months of follow up.

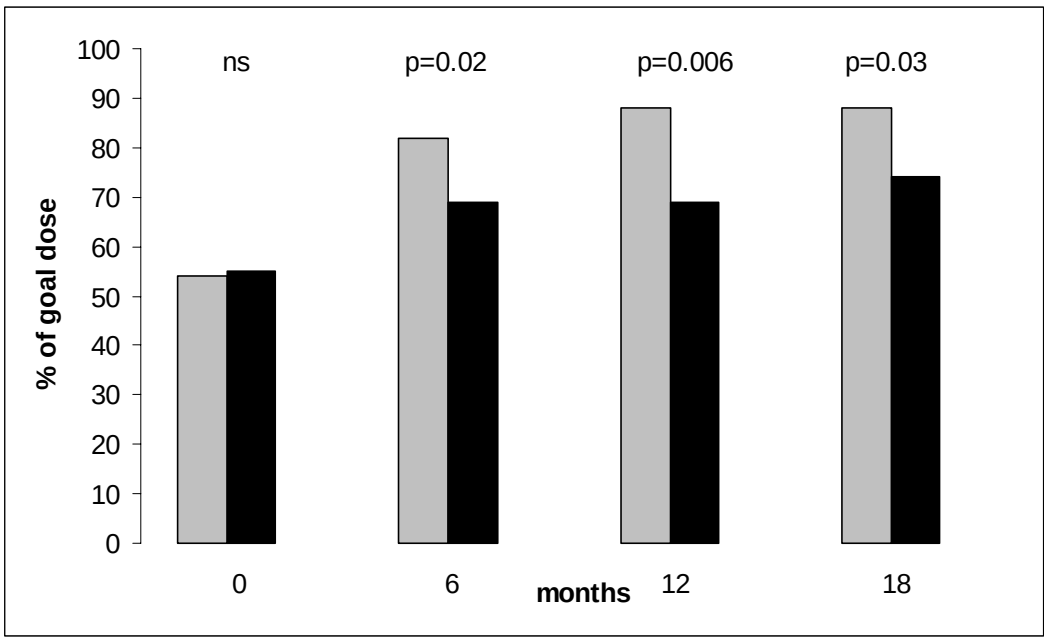

Fig 2 Proportion of patients who received target doses

Grey bars = intervention group; black bars = control group

During eighteen months after inclusion, 69 % of the patients in both study groups were readmitted. During the entire follow up, 85 vs 86 % of intervention vs control group was hospitalised (all cause). Time to first readmission was 246 vs 294 days respectively (p = ns). In all, 74 patients (IG 54% vs CG 46%, p = ns) died during the entire study period. Interestingly, patients with initial low QoL had a poor prognosis.

In summary, paper II shows that a nurse based outpatient clinic is more effective than usual care in optimising doses of ACE-inhibitors. However, these changes did not improve outcome on QoL, morbidity or mortality.

4.2.2 Paper III

The aim of this paper was to evaluate measurements of clinical function, functional capacity, left ventricular function and size, and neurohormonal activation for the ability to predict mortality and morbidity in the OPTIMAL study.

In Table 3, baseline characteristics are described.

Table 3 Baseline characteristics of survivors and non-survivors

	Survivors n=134	**Non-survivors** n=74	**p value**
Age, years, mean	75.8	77.8	<0.05
Gender, male, n (%)	68 (51)	52 (70)	<0.05
Hospital stay, days	6.3	7.6	<0.05
Time to readmission, days	365	104	<0.05
Readmissions, all cause	3.6	4.3	ns
Clinical function			
Medication n (%)			
Angiotensin converting enzyme inhibitors	100 (75)	54 (73)	ns
ß blocking agents	71 (33)	38 (51)	ns
Furosemide	123 (92)	71 (96)	ns
Ischemic heart disease	82 (61)	57 (77)	<0.05
Hypertension	46 (34)	19 (26)	ns
Hemoglobine, g/l	135	128	<0.05
Creatinine, µmol/l	104	136	<0.05
Functional capacity			
NYHA class II	92 (69)	37 (50)	<005
NYHA class III and IV	42 (31)	37 (50)	<005
QoL total score	142	182	<0.05
Neurohormonal activation			
Noradrenaline, nmol/l	3.0	4.4	ns
Adrenaline, nmol/l	0.2	1.9	ns
Brain natriuretic peptide, pg/ml	272	439	<0.05
Sodium, mmol/l	140	141	ns
High sensitive C-reactive Proteine, mg/l	11.1	16.3	ns
Furosemide, mg/day	151	98	ns
Blood pressure, systolic, mm Hg	136	129	ns
Blood pressure, diastolic, mm Hg	80	80	ns
Heart rate, beats/min	87	83	ns
Echocardiography			
Ejection fraction, %	35.8	31.4	<0.05
Atrioventricular plane displacement, mm	6.9	6.0	<0.05
Mitral end point septal separation, mm	1.4	1.8	<0.05
End systolic volume, ml	78	99	<0.05
End diastolic volume, ml	116	139	<0.05

All values are mean; QoL=quality of life; ns=non significant

Predictors of mortality

By multivariate analyses high age (HR 1.004/year), male gender (HR 2.0), high BNP values (HR 1.4/log unit), high values of end pointal separation (HR 1.6/cm) and high creatinine (HR 1.008/mmol/l) (all $p<0.05$) were independent predictors of mortality.

Predictors of readmission

A worse QoL, high age, high creatinine and low hemoglobine values predicted readmissionn in a univariate analysis. Entered into a Cox regression analysis, total score of QoL was the only predictor of readmission. Patients with the highest QoL scores (>302) had a very high early readmission rate and all patients of this group were readmitted within two years whereas only half of the group with the lowest QoL scores (<11) were readmitted during the entire follow up.

4.2.3 Paper IV

The aim of this study was to evaluate the safety and prognostic capacity of cardiopulmonary exercise test in elderly patients hospitalised with systolic heart failure. After medical stabilisation, all patients of the OPTIMAL study were asked to perform a cardio-pulmonary exercise test. In all, sixty-seven patients, mean age 74 years and 66 % men with an LVEF of 0.36 were included. Missing cases (n=141) were due to unwillingness to perform the test (n=46), other conditions such as asthma, blindness (n=42), other cardiovascular diseases (n=21), joint disease (n=11) and non-availability of the exercise equipment (n=21). Aetiology of heart failure was similar to the original OPTIMAL population. In this group of 67 patients 82 % and 60 % of the patients were prescribed ACE-inhibitors and ß-blocking agents respectively. The cohort was well comparable to the original OPTIMAL population but somewhat younger (mean 74 years) and with a higher proportion of men (66 %). No adverse events occurred during the exercise test. Table 4 show the results of the cardiopulmonary exercise test.

Table 4 Results of the cardio-pulmonary exercise test

	Anaerobic threshold mean ± SD	**Peak exercise** mean ± SD
Work load (W)	21 ± 20	72 ± 29
VO_2 (ml/kg/min)	7.7 ± 2.6	11.7 ± 3.6
VE/VO_2	38 ± 9	46 ± 11
VE/VCO_2	43 ± 9	43 ± 9

VO_2 = oxygen uptake; VE = ventilatory equivalent; VCO_2 = carbon dioxide production

When all patients had been followed for at least one year after inclusion (range 12-59 months), 14 (21 %) of the patients had died. Peak VO_2, VE/VO_2 and VE/VCO_2 were all strongly related to mortality in a univariate analyses ($p<0.01$). In a multivariate analysis, after adjusting for age, sex and NYHA class, peak VE/VCO_2 was the strongest predictor of death (Wald $\chi^2 = 11.3$, $p <0.001$), followed by left ventricular end systolic volume (Wald $\chi^2 = 10.6$, $p = 0.001$). A cut off value of peak $VE/VCO_2 \geq 45$ gave a hazard ration of 6.7 for death during follow up.

4.2.4 Paper V

In this paper, results from 158 patients of the OPTIMAL population with complete echocardiographic evaluations were analysed with regards to gender differences. Baseline characteristics of the 66 women and 92 men were very similar to the 208 patients in the original OPTIMAL study (Table 2). The women were older than the men (77±7 vs 74±7 years, $p<0.01$) but aetiology and medication did not differ between the groups. Serum creatinine was higher in men but estimated glomerular filtration rate was lower in women. Mortality was markedly lower in the females (24 vs 43 %, $p<0.05$). Increased left ventricular mass index, diameters and volumes were all associated with increased mortality in women. In a multivariate analysis left ventricular mass index was the strongest independent predictor in women but this measurement was not significantly related to death in men (Fig 3 a, b). In men BNP, estimated glomerular filtration rate and QoL were associated with a fatal outcome. Diastolic dysfunction was equally common (89%) in both genders and related to mortality in univariate but not multivariate analyses.

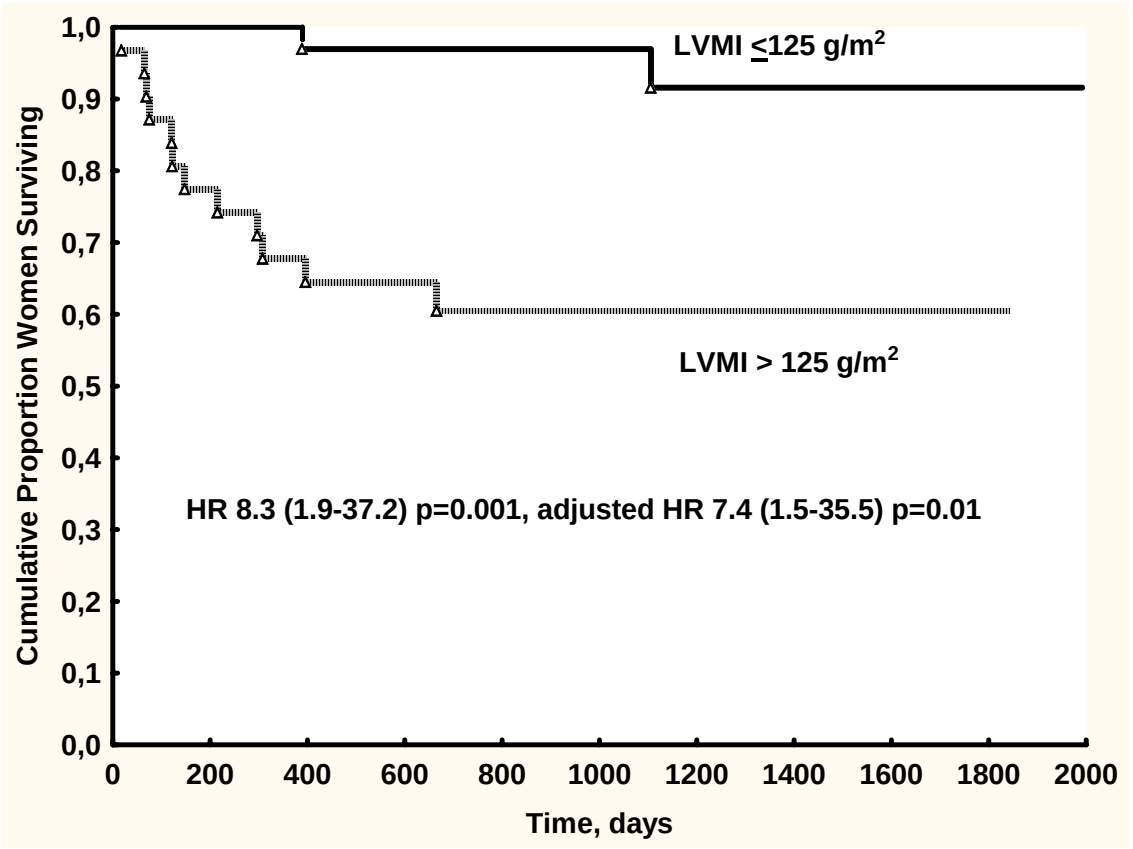

Fig 3 a Survival in woman in relation to left ventricular mass index (LVMI)

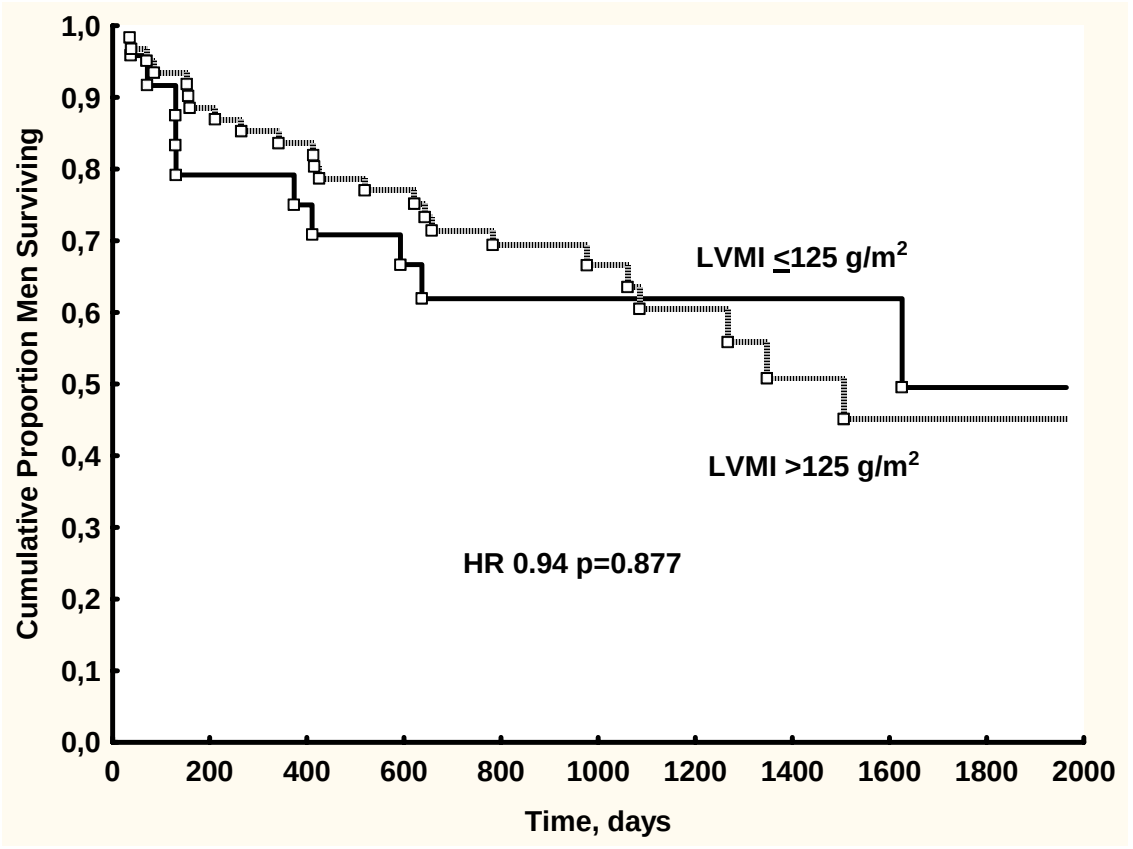

Fig 3 b Survival in men in relation to left ventricular mass index (LVMI)

5 DISCUSSION

5.1 Aspects on treatment

5.1.1 Medication

In Table 5, the use of ACE-inhibitors and ß-blocking agents is exemplified by baseline prescription patterns in a few studies, from the first report on management programs by Cline and coworkers from 1992 to similar reports ten years ahead. As expected, during the last decade results from the large trials on ACE-inhibitors and ß- blocking agents have translated into every day practice and the proportions of patients with such treatment have increased. Of note, most reports are from patients hospitalised with heart failure as few studies have reported on prescription rates in primary care (11). Importantly, one can expect prescription patterns to differ between hospitals and primary care, as well as between genders and age groups.

Table 5 Proportion of patients receiving ACE-inhibitors and ß-blockers

STUDY	Inclusion year	ACE-inhibitors %	ß -blockers %
Cline C (16)	1992	23	12
Rich M (26)	1990-1994	54 to 64	11 to 13
Strömberg A (42)	1997-1999	42 to 45	28 to 33
Kasper E (28)	1996-1998	82 to 90	38 to 40
Doughty R (27)	2002	88 to 89	nr
Euroheart Failure study (14)	2000-2001	62	37

ACE=angiotensin converting enzyme; nr=not reported

In the OPTIMAL study that included patients in year 1996-1999, high proportions of the patients were treated with ACE-inhibitors and/or ß-blockers already at baseline, 72 and 52 % respectively. We suggest this, in part was due to the health care plan for heart

failure established in our area, indicating the importance of establishing effective health care programs in cooperation with primary care.

In paper I, we found underprescription of ACE-inhibitors, and follow up at general practitioners, to be more common in women than in men. This finding is similar to that of the Euroheart Failure survey program where the odds of receiving ACE-inhibitor treatment were increased for male patients (OR 1.34, 95% CI 1.22 to 1.48) compared to females (14). Also, a Swedish study report the use of ACE-inhibitors for heart failure to be higher in patients followed by hospital specialists compared to general practitioners (70 vs 55 %) (79). Thus, age and gender seem to influence the choice of follow up and treatment. These findings illustrate the importance of adherence to practice guidelines, and to equal access to heart failure care in all heart failure patients.

5.1.2 Heart failure management program

In summary, the OPTIMAL study showed a nurse based hospital out patient clinic management program is more effective than primary care in optimising doses of ACE-inhibitors in elderly patients with systolic heart failure. However, this did not affect QoL, hospitalisation rates or mortality. The results can depend on several factors:

-QoL was measured with a non-disease specific questionnaire, the Nottingham Health Profile, which might not be sensitive enough to capture all symptoms typical of heart failure.
-Although patients with severe comorbidity were excluded, readmissions were equally frequent for non-cardiac as for cardiac causes. This makes it difficult to attribute causation as an impaired QoL could be due to other illness than heart failure. Still, the OPTIMAL population is well representative of elderly patients hospitalised with systolic heart failure and high comorbidity is well known in this group (36).
-A health care program for patients with heart failure was instituted in cooperation with primary care in year 1994. Thus, differences between primary and hospital care might not be as pronounced as in other settings.
-The potential improvement might have been limited by the already at baseline high proportions of patients treated with ACE-inhibitors and ß-blockers. Thus we lost statistical power in our trial to detect a difference in the primary and secondary clinical outcomes.

-The intervention might have been too weak to influence outcome, as the majority of patients in the intervention arm made (mean) two visits to the management program only. Still, we did not change the predefined setting of the nurse led out patient clinic, as we wished to study the program as it existed in real life since many years.

Still, the OPTIMAL study was well powered to analyse changes in QoL and follow up time was long, more than three years Another strength of the study was that measurements of health care consumption was thoroughly analysed, as we did not use hospital charts only. Instead, by using coded personal identity numbers of the patients we were able to pool data from the national insurance database, which provides detailed information on all hospitalisations and readmissions.

The aim of most management programs on heart failure is to decrease the frequent and costly readmissions to hospital, and to enhance survival and QoL. To accomplish this, the programs optimise medical treatment and educate and counsel their patients. Non-pharmacological management is now recommended as Class 1 (level of evidence C) in the guidelines of the European Society of Cardiology on chronic heart failure (80). From meta-analyses the positive effect on readmission rates is evident (Table 1). Data on mortality are inconclusive. Many trials evaluating the effect of management programs on QoL, have reported improved QoL in the intervention arms (16,42,26-31), others have failed in this aspect (32-34).

Compliance to medication and non-pharmacological treatment is of great importance in heart failure. In a recent report, van der Wal and coworkers describe compliance to medication and appointments in five hundred heart failure patients to be high (>90%) but compliance with diet (83%), fluid restriction (73%), exercise (39%) and weighing (35%) to be lower (81).

As the management programs have used a large variety of working strategies, it is difficult to evaluate which mechanisms are most beneficial to the individual, and a critical appraisal is needed. The settings, the patient characteristics, the structure and interventional part of the programs and the measurements of outcome can all be quite different in the various programs. Still, it is reasonable to believe that the most important factor in management programs on heart failure is the optimisation of, and compliance to medication. Supportive of this, in a recent study Zaphiriou and co-

workers presented data from 165 hospitalised heart failure patients where medical treatment was optimised already before discharge from hospital as 94.5 % were being treated with ACE-inhibitors and 42.7 % with ß-blocking agents. One half of the patients were referred to the management program at discharge, the rest to usual care. After follow up, no differences were found in morbidity or mortality between groups (82).

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5.2 Aspects on prognosis

However complex, it is of great importance to assess prognosis in heart failure. In order to choose intensity of treatment in the individual and to prevent readmissions by identification of high-risk patients, risk stratification is essential. As the heart failure syndrome is complex, with several aetiologies and frequent comorbidity, it is not realistic to expect a single measurement to evaluate the global risk of outcome. Instead markers from different domains could be used. In the OPTIMAL study, traditional markers such as high age, male gender, increased levels of BNP and creatinine were independent predictors of mortality. Also, we found results from cardiopulmonary testing to predict outcome. Interestingly, an increased QoL-score at baseline was a predictor of mortality.

5.2.1 Quality of life

In paper II, baseline QoL was reduced in patients who subsequently died compared with survivors. This finding was further addressed in paper III where QoL univariately was associated with mortality and in multivariate analysis a strong multivariate predictor of readmissions. These findings are supported by others (83,84). Thus, we have shown QoL to be a useful instrument to predict outcome. This need to be confirmed in a larger, prospective study as an exploration of a valid QoL instrument, easily available in every day practise, could be of great use in the future.

5.2.2 Neurohormonal activation

In paper III, a high BNP level was an independent predictor of mortality in the OPTIMAL patients. These results are similar to those of Bettencourt et al who reported on the usefulness of natriuretic peptide levels to predict outcome after hospital discharge (85). Also, in paper five, high BNP levels were associated with a fatal outcome in men. In clinical use, BNP and its precursor proBNP, are the most studied of the natriuretic peptides. As it has a high negative predictive value, BNP is now

recommended to use in the diagnosing of suspect heart failure in Sweden (86). The next step would be to use natriuretic peptides in treatment monitoring and to identify patients at high risk, in need of intensified treatment and rapid follow up. However, we need consensus on how to measure it, and reference values according to age and gender need to be established.

5.2.3 Echocardiography

In paper III neither LVEF nor left ventricular volumes gave independent prognostic information. This may be due to the small size of our study, since all measured echocardiographic parameters of left ventricular size and function were univariate predictors of mortality. In paper IV, peak VE/VCO_2 was the strongest predictor of mortality followed by left ventricular end systolic volume. Left ventricular mass index was calculated in paper five only. In this paper, we found left ventricular volumes and mass index to be independent predictors of mortality in women, and left ventricular mass to be the strongest one in a multivariate analysis. Concomitant diastolic dysfunction was frequently found in the OPTIMAL population (89%) regardless of gender, and was related to mortality in univariate but not in multivariate analyses.

5.2.4 Gender

The better survival rate in females with heart failure is often explained by a more frequent hypertensive aetiology in this group, causing heart failure with a more preserved systolic function than ischemic heart disease (5,87). Still, in our study restricted to systolic heart failure and with no difference in aetiology between genders, the women had a better prognosis than men pointing to other factors as well to determine different outcome between genders.

Diastolic dysfunction is difficult to measure, and is commonly diagnosed by echocardiographic indirect measurements that can be acquired without using invasive methods. In routine echocardiography diastolic function is not always evaluated. Understanding heart failure with a preserved systolic function is essential, in particular as the heart failure population can be expected to get older and predominately female in the future, and evaluation and interpretation of diastole of is a great challenge of the future.

Interestingly, an increased left ventricular mass index was a more ominous sign in women than in men. One might speculate this is due to biological differences, established during puberty, and illustrated by the relative left ventricular hypertrophy in males compared to females. Thus, at the same amount of cardiac stress a larger contractile reserve would make women transit from left ventricular dysfunction into overt heart failure, at a later stage than men. Our results argue for patophysiological differences between genders, and this necessitates further research. Thus, gender specific studies on neurohormonal and hemodynamic response to pressure and/or volume overload are needed.

5.2.5 Cardio-pulmonary testing

In paper four, we evaluated the safety and predictive potential of cardiopulmonary exercise test in elderly heart failure patients, containing a third of the OPTIMAL population. Peak VE/VCO_2 was the strongest predictor of death in both univariate and multivariate analyses, followed by left ventricular end systolic volume. To our knowledge, no previous studies on exercise testing have been made in an elderly, hospitalised heart failure population. However, Davies et al report results similar to ours in an elderly out patient population (88). We found it safe to perform the test, and the results found in younger patients could be extended to the elderly as peak VO_2, VE/VO_2 and VE/VCO_2 were powerful predictors of prognosis in this age group as well. This method ought to become more wide spread as it can add important information e.g. on prognosis and in evaluation of new treatment strategies.

5.3 Clinical implications and future aspects

Heart failure care has improved greatly during the last decade. Still, there is an underuse of investigation and treatment and this might be mort pronounced in elderly and in women. To further develop the management programs a critical appraisal is needed. For example, we need to identify which patients are most likely to profit from various interventions. Patients with newly diagnosed heart failure, at high risk of readmission or death, living in areas where no health care plan for heart failure is established could be such subgroups. Also, we need to attribute causation, evaluating which parts of the programs are most effective, in order to enhance working strategies and individualise treatment. As the general practitioners care for the majority of heart failure patients, high priority must be given to the implementation of guidelines in primary care. As

heart failure patients are likely to be hospitalised at one or several occasions, the need of communication between hospitals and primary care is obvious.

To individualise the intensity of treatment and to optimise the use of health care resources, assessment of prognosis is of great importance. Ideally, an algorithm of markers from clinical, functional, echocardiographic and neurohormonal dimensions of the heart failure syndrome could be used to identify patients at high risk of readmission or death. Our results suggest that such an algorithm could consist of for example age, gender, NYHA class, QoL, BNP and in women LVMI – all relatively easily available in every day practise. However, this needs further study. Results from cardiopulmonary testing are robust prognostic markers in the elderly and could be taken into account when evaluating for example new costly treatment strategies, such as biventricular pacemaker treatment.

As treatment of women today often is based on trial results from male dominated populations it is absolutely essential to increase the proportion of female participants in clinical and other research,. Studying gender differences today, it is difficult to evaluate what has the greatest impact in heart failure - biological dissimilarities and/or effects from bias in the use of investigations and treatment. Thus, addressing gender aspects of heart failure, in both basic science on cardiovascular pathophysiology, and in clinical studies of studies on prescription patterns and evaluation of dosage and side effects are needed.

5.4 Limitations

In paper one, hospital charts of patients with the primary diagnosis of heart failure were studied. A limitation of this study was that the heart failure diagnose was not always established in accordance with guidelines, i.e. not all patients were examined with an objective functional test. Also, the retrospective approach calls for careful interpretation of results.

In the OPTIMAL study of hospitalised patients one inclusion criterion was echocardiographic findings of systolic left ventricular dysfunction. Still, many elderly have a preserved systolic left ventricular function and suffer mainly from diastolic dysfunction. Thus, the results may not be representative of the heart failure population in general. Another inclusion criterion in the OPTIMAL study was NYHA class II-IV.

This functional classification is a subjective evaluation made by the doctor on basis of patient's symptoms. NYHA class, in particular class II with few symptoms, can be difficult to clearly define in a hospital setting.

The study population of OPTIMAL was relatively small. However, predictors of prognosis shown in other studies were confirmed in our results, indicating that the patients were representative for a population hospitalised with heart failure.

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