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HEART FAILURE WITH PRESERVED EJECTION FRACTION IN PRIMARY CARE

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To Ann, Carl and Daniel

There is nothing impossible for him who will try.

Alexander the Great

ABSTRACT

Background

Heart failure with preserved ejection fraction (HFpEF) is a condition associated with low quality of life, high morbidity and mortality. It constitutes a diagnostic challenge and there is little evidence of effective treatments. In spite of its high prevalence and the fact that many (17-36%) of these patients are managed in Primary Care (PC) most of the studies on the condition were performed in Hospital Care (HC).

Aims

The aim of this thesis was to describe HFpEF in PC, its characteristics, comorbidities and mortality as well as further prognostic and diagnostic difficulties and potential underdiagnosis

Methods

The initial three studies were based on the Swedish quality registry for Heart Failure (HF) patients (SwedeHF). Patients without echocardiographic results (16%) were excluded. A total of 1802 patients from PC and 7852 from HC, all with an Ejection Fraction (EF) ≥ 40% were studied to identify comorbidities, risk factors and outcomes, and to compare PC- with HC-patients in the first study.

The second study analyzed the prognostic value of N-terminal Brain Natriuretic Peptide (NT-proBNP) in HFpEF-patients managed in PC. 924 patients; 360 patients with EF 40-49%, Heart Failure with Midrange Ejection Fraction, (HFmrEF) and 564 patients with EF≥50% (HFpEF).

The third study identified gender differences and was based on the 1802 patients from Study 1, divided into HFmrEF and HFpEF.

The fourth study was performed in Gustavsbergs PC centre. Ninetysix patients that had contacted the General Practitioner (GP) unit for one of the three common HF- symptoms breathlessness, tiredness or ankle swelling were included to find potential underdiagnosis and to evaluate an internet-based self-test for HF.

Results

HFpEF patients managed in PC were older and the majority were women, compared with patients managed in HC. Only 2.8% had no comorbidity and all-cause mortality after 1 year was 7.8%. Smoking, Chronic Obstructive Pulmonary Disease (COPD) Diabetes mellitus

(DM), age and heart rate were shown to be independent risk factors for mortality in PC. Echocardiographc examinations are often missing. In matched controls there were more RAS-antagonists and betablockers prescribed in HC. Study I.

There was a clear association between levels of NT-proBNP and mortality, but only on a group level. Numerous variables were associated with increased NT-proBNP and further independently with mortality. Study II.

Men had higher age-adjusted mortality than women. In women with HFpEF more than half of the cases had another cause of death than cardiovascular diseases. The dominating causes of death were malignant diseases and respiratory diseases but altogether 13 different causes were identified. Study III.

There was an underdiagnosis of HFpEF of 21%, all in women. We also found an acceptable accuracy of an internet-based self-test for HF. Study IV.

Conclusion

Patients with HFpEF in PC constitutes a heterogenous group with high age and many comorbidities that may interfere with the pathophysiology of HF and irrespectively affect both morbidity and mortality. The patients are older (mean 78 y.), the proportion of women is higher (46.7% vs 36.3 %) and they have other independent risk factors than those managed in HC. A single evidence-based treatment of HFpEF-patients is not available. The results of this thesis suggest that HFpEF-patients in PC have an age-related multi-organ damage with great need of careful diagnostic and individualized magement. There is a substantial risk for underdiagnosis.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following original articles, which will be referred to in the text by their Roman numbers.

I. B. Eriksson, P. Wändell, U. Dahlström, P. Näsman, L. H. Lund & M. Edner. Comorbidities, risk factors and outcomes in patients with heart failure and an ejection fraction of more than or equal to 40 % in primary care- and hospital care-based outpatient clinics. A report from the Swedish heart failure registry. Scandinavian Journal of Primary Health Care 2018; 36:2: 207-215.

II. B. Eriksson, P. Wändell, U. Dahlström, P. Näsman, L. H. Lund & M. Edner. Limited value of NT-proBNP as a prognostic marker of all-cause mortality in patients with heart failure with preserved and mid-range ejection fraction in primary care: A report from the Swedish heart failure registry. Scandinavian Journal of Primary Health Care 2019; 37(1):1-10.

III. B. Eriksson, P. Wändell, U. Dahlström, P. Näsman, L. H. Lund & M. Edner. Gender associated differences concerning characteristics and mortality in heart failure patients with ejection fraction equal to or above 40% managed in primary care
A report from the Swedish heart failure registry. Submitted

IV. B.Eriksson, M.Edner, C.Linde, K.Knudsen-Malmqvist & H.Persson. Validation of an internet-based self-test for Heart Failure diagnosis and assessment of underdiagnosis of Heart Failure in Primary Care. Submitted.

CONTENTS

LIST OF ABBREVIATIONS

ACEi	Angiotensin Converting Enzyme inhibitor
AF	Atrial Fibrillation
ARB	Angiotensin Receptor Blocker
BB	Beta Blocker
CABG	Coronary Artery Bypass Graft surgery
CI	Confidence Intervals
CO	Cardiac Output
COPD	Chronic Obstructive Pulmonary Disease
CRT	Cardiac Resynchronization Therapy
DM	Diabetes Mellitus
DT	E-Wave Deceleration Time
E/A	Early/Atrial ratio
EDV	End Diastolic Volume
EF	Ejection Fraction
eGFR	estimated Glomeruly Filtration Rate
ESC	European Society of Cardiology
ESV	End Systolic Volume
GP	General Practitioner
HC	Hospital Care
HFmrEF	Heart Failure with midrange Ejection Fraction
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
HF	Heart Failure
HR	Hazard Ratio
HT	Hypertension
ICD	International Classification of Diseases
ICD	Implantable Cardiac Defibrillator
IHD	Ishemic Heart Disease
IVRT	Isovolumetric Relaxation Time
LA	Left Atrium

LVAD	Left Ventricular Assistant Device
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MRA	Mineral Receptor Antagonists
NP	Natriuretic Peptide
NT-proBNP	N-terminal Brain Natriuretic Peptide
NYHA	New York Heart Association
PC	Primary Care
PCI	Percutaneous Coronary Intervention
RAS system	Renin Angiotensin Aldosteron system
RCT	Randomized Controlled Trial
SD	Standard Deviation
SV	Stroke Volume
Swede-HF	The Swedish Heart Failure Registry

1.1 INTRODUCTION

1.1.1 Background

1.1.1.1 History

Probably, the first case of Heart Failure (HF) is Nebiri, the Egyptian, who lived 3500 years ago and whose remnants were found in the Queens Valley. Histologic examination of the lungs showed findings of suspect pulmonary edema. Various descriptions of cases that could be HFwas then found throughout the antique period, but it was not until the English physician William Harvey in 1628 described the construction of the circulatory system that we began to understand the basis of hemodynamics. Initial therapies included bloodletting, with or without leeches. Another English physician, William Withering, introduced digitalis as therapy in 1785, and in 1918 Henry Starling, physician from Cambridge, contributed to the understanding of heart physiology. Still, in the middle of the 20th century, HF was mainly treated with inactivity, rest and fluid restriction. On the pharmacological side there were no more alternatives than diuretics and digitalis. In 1967 south-african surgeon Christiaan Barnard performed the first heart transplantation, and in the middle of the 1980s there was growing knowledge that HF is to be considered as a disease of the neuroendocrine system. The “Consensus 1” – study was presented in 1987 and could for the first time show the benefits of blockade of the RAS system, followed later on with studies showing the benefits of BB therapy. During the 1990s HF was more and more considered as being a syndrome, instead of merely a disease, and it was also by this time we began to realize the complexity of HFpEF. We now started to understand that this condition is the response of the heart to other strains and diseases, such as diabetes and hypertension, and not like in HFrEF primarily a damage to the heart. In 1995 the European Society of Cardiology (ESC) launched the first guidelines for HF-management and from the period around the millennium shift and further on HF has been one of the most research-intensive areas within cardiology.

Table 1. Important HF studies		
Study	Year	Comments
Consensus	1987	First study to show improved survival with an ACEi
Solvd	1991	Survival benefit from the ACE-inhibitor enalapril
Rales	1999	Survival benefit from spironolactone
Cibis-2	1999	Survival benefit from the betablocker bisoprolol
Merit-HF	1999	Survival benefit from the betablocker metoprolol
Copernicus	2001	Survival benefit from the alfa- and betablocker carvedilol
Val-HeFT	2002	Survival benefit from the angiotensinreceptor blocker valsartan
Charm	2003	Survival benefit from the angiotensinreceptor blocker candesartan
Care-HF	2005	Survival benefit from cardiac resynchronization therapy
Shift	2010	Survival benefit from ivabradine
Paradigm-HF	2014	Survival benefit from sacubitril-valsartan

1.1.1.2 Definition

HF is to be understood as a condition where the heart, due to structural or functional impairment, is unable to deliever oxygenated blood in the required amount that meets the needs of the tissues of the body. It is a clinical syndrome, involving an active neuroendocrine system, and is in the latest ESC guidelines classified as either Heart Failure with reduced Ejection Fraction (HFrEF), Heart Failure with mid range Ejection Fraction (HFmrEF) or Heart Failure with preserved Ejection Fraction (HFpEF). All three categories require typical symptoms and clinical signs for the diagnosis and are thereafter classified due to Ejection Fraction (EF): HFrEF< 40 %, HFmrEF 40-49% and HFpEF ≥50%. Furthermore, HFmrEF and HFpEF, on new onset, must have elevated levels of natriuretic peptides and at least one more of either findings of structural heart disease or diastolic dysfunction. [1] Once the diagnosis is confirmed the patient's functional capacity according to the New York heart Association (NYHA) are also estimated, constituting a base for treatment guidelines.

Table 2. Typical symptoms of HF according to ESC

Breathlessness
Orthopnoea
Paroxysmal nocturnal dyspnea
Reduced exercise tolerance
Fatigue, tiredness, reduced time to recover after exercise
Ankle swelling

Table 3. Definition, at the time of diagnosis, of heart failure with reduced (HFrEF), mid-range (HFmrEF) and preserved ejection fraction (HFpEF) according to ESC guidelines 2016.

Type of HF	HFrEF	HFmrEF	HFpEF
Criteria	Symptoms and signs	Symptoms and signs	Symptoms and signs
	EF<40%	EF 40-49%	EF≥50%
		1. Elevated levels of natriuretic peptides 2. At least one additional criterion: a. Relevant structural heart disease b. Diastolic dysfunction	1 Elevated levels of natriuretic peptides 2 At least one additional criterion: a. Relevant structural heart disease b. Diastolic dysfunction

Table 4. Classification of functional capacity according to the New York Heart Association (NYHA)

NYHA Class	**Symptoms**
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

1.1.1.3 Epidemiology

HF is a common condition and must be considered as a scourge. Various studies estimate the prevalence to be around 2% but rising with age to around 10% at the age of 80 years. Yearly incidence has been estimated to be between 4 and 7 cases per 1000 inhabitants, the higher figure among men. [2-7] Incidence has been declining during the last decades, more so for women, while prevalence in various studies has remained unchanged or decreased, especially among women.[2-5] On the other hand more patients survive myocardial infarctions and may be better treated for Hypertension, (HT) which might lead to increasing incidence in the future. [8, 9] It has further been shown that there is a decrease in mortality among both men and women. [3]

1.1.1.4 Etiology

HF is caused in most of the cases (70%) of either Ischemic Heart Disease (IHD) or HT [2, 6, 10, 11] the former representing an injured myocardium and the latter abnormal loading conditions. However, many patients will have several different etiologies, both cardiovascular and non-cardiovascular, that cooperate to cause HF. Most important other causes are valvular diseases, cardiomyopathies, toxic damage, metabolic derangements, inflammatory damage, infiltration diseases, genetic abnormalitites, anemia, sepsis, renal failure, and arrythmias.

1.1.1.5 Comorbidity

Comorbidities are common among HF patients and are associated with increased morbidity and mortality in both HFrEF and HFpEF. [12]Many patients have several comorbidities that together may contribute to a worse prognosis and in many studies it has also been shown that non-cardiac comorbidities substantially play a role for negative outcome. [13-15] Reasons for this may be a direct stress from the comorbidity on the failing heart but potentially also missed diagnosis and delayed treatment of HF. Predictors for worse outcome are also other factors (among others age, anemia and elektrolyte changes) that often may co-variate with several comorbidities. [14]

Several studies have shown that Chronic Obstructive Pulmonary Disease (COPD), Diabetes Mellitus (DM), anemia and obesity is more common among HFpEF patients than HFrEF patients, as well as HT and Atrial Fibrillation (AF) but not IHD.[7, 16-21]

1.1.1.6 Prognosis

Mortality in patients with HF is high but varies with etiology and functional capacity according to NYHA-classification. Only 50% of the patients with the lowest functional capacity (NYHA IV) are alive after one year. [2, 11, 22] Mortality is highest for hospitalized patients [22-24] and is generally comparable with various forms of cancer. [10, 25] One-year mortality in the Swedish Heart Failure Registry for hospitalized patients is approximately 20%, regardless level of EF. [26]

Mortality has remained essentially unchanged or slightly decreased over the past years after a decline in the late 20th century and in spite of new therapies and management [3, 5, 27, 28] but it has been shown that mortality is declining more for men than for women. [28] Most studies have been performed on hospitalized patients, both with HfrEF and HfpEF, [8, 9, 11, 17, 18, 20, 29] where women have been shown to have a lower mortality, [2, 22, 30, 31] and that the mortality is lower both in cardiovascular deaths and non-cardiovascular deaths. Women have also been shown to die to a lesser distinct from cardiovascular deaths than men.[32] The gender difference in mortality is however modified by different conditions (i.e. atrial fibrillation, kidney disease and ischemic heart disease). [33]

Mortality for hospitalized HFpEF patients is high and in many studies comparable to mortality for HFrEF patients. [18, 21, 29, 34] The mortality is modified by various conditions and comorbidities, [12-14, 16, 35] and it has further been shown that patients with HFpEF die to a larger distinct from non-cardiovascular diseases than patients with HFrEF even though the main cause of death is cardiovascular diseases. [13, 21, 34, 36, 37] Similar pattern has been shown for HFmrEF although IHD is more common among HFmrEF than HfpEF. [38, 39] The most common other causes of death are respiratory diseases and malignant tumors. [37, 40-42]

Mortality for HF patients in general, and for HFpEF patients especially, managed in PC, has not been extensively studied but some studies indicate a lower mortality compared with patients managed in HC. [17, 43-45]

1.1.2 Significance of heart failure

1.1.2.1 Significance to patients

Patients with HF have high mortality, well comparable with cancer, [10, 25] and due to high morbidity and many comorbidities [16, 29] a low quality of life, lower than that of most other diseases. [46, 47]

1.1.2.2 Significance to community

HF is one of the most common reasons for need of hospital care, and among persons older than 65 years, in many studies the single most common reason. A vast number of hospital beds and treatment days are required at cardiology-, internal medicine- and geriatric clinics. [5, 17, 48-52]

The cost for HF treatment in Sweden is substantial and there have been several attempts to calculate the total burden. Various studies have ended up with estimations between 3 and 7 billion Swedish kronor yearly for HF treatment, depending on which type of costs and patients that are included in the study.[49-51] The main cost driving factor is hospital care. The frequency of readmissions for HF within 90 days may be as high as 30-40 % [17, 29, 48, 51] . Improved knowledge, information, follow-up and treatment at nurse based outpatient clinics may decrease the readmission rate with up to 50%, leading to substantial reduce of health-care costs.[23, 48, 51, 53-55] There is a large potential for improvements of HF care, not least since many studies furthermore have shown that many patients are not only treated deficiently according to guidelines but also poorly diagnosed. [6, 19, 24, 56-61]

Physiology of heart failure

1.1.2.3 Anatomy

The heart weighs between 200 to 425 grams and is a little larger than the size of a fist. Each day, the average heart beats 100.000 times.

The heart is located between the lungs in the middle of the chest, surrounded by the pericardium. The heart has four chambers; two atria, right and left, and two ventricles, right and left. Between the two atria and ventricles is a wall of muscle, called the septum.Veins

from the blood system deliever deoxygenated blood to the the right atrium from where the right ventricle is filled. The right ventricle pumps the deoxygenated blood to the lungs and oxygenated blood will then return to the left atrium. After filling of the left ventricle, the blood will finally be pumped in to the systemic vessels.

There are four valves regulating blood flow through the heart; the tricuspid valve between the right atrium and right ventricle, the pulmonary between the right ventricle and the pulmonary arteries, the mitral valve between the left atrium and the left ventricle and the aortic valve between the left ventricle and the aorta.

Electrical impulses cause the heart to contract. The electrical impulse starts in the sinoatrial node at the top of the right atrium and travels through the atrioventricular node and then via the atrioventricular bundle and the bundle branches to the ventricles, causing them to contract.

The right and left coronary arteries run along the surface of the heart and provide oxygenated blood to the heart muscle.

1.1.2.4 The healthy heart

The coordinated process of a heart beat, named cardiac circle, consists of two phases; a contraction phase ("systole") and a relaxation phase ("diastole"). The right and left atria and ventricles synchronize during systole and diastole. During the cardiac circle, the pressure in the cardiac chambers increases or falls and this will cause valve opening or closure. This, in turn, will regulate blood flow between the chambers as the blood flows from a high-pressure area to a low pressure-area. Multiple noninvasive evaluations have been utilized in order to stratify heart function. However, the "golden standard" for measuring the heart function is heart catheterization.

At the first part of the cardiac circle, (atrial systole and ventricular filling), when the pressure is low, circulating blood will passively fill the atria on both sides. The atrioventricular valves opens and blood moves into the ventricles. The atria therafter depolarizes, contracts and residual blood is pushed into the ventricles. This is the last part of the diastolic phase and the amount of blood in the ventricles at this phase is named end diastolic volume (EDV). The atria will now relax as the electrical impulse is transmitted to the ventricles that will depolarize. As the ventricles start to contract (ventricular systole),

the pressure in the ventricles increases and at the point where the pressure exceeds the pressure within the arteries, the pulmonary and aortic valves will open, and the blood will be pumped into the vessels. In the next phase (isovolumetric relaxation) the ventricles relax, the pressure in the ventricles drops causing a backflow in the pulmonary and aortic trunks and the pulmonary and aortic valves close. The amount of blood remaining in the ventricles after the contraction is referred to as end systolic volume (ESD). While the ventricles have been contracting, the atria have been relaxing and are now ready to be filled again for the next cardiac circle.

The efficacy of the heart function can be measured as cardiac output (CO), the amount of blood pumped out by the heart in one minute. CO is calculated as the stroke volume (SV) multiplied with the heart rate. SV, in turn, is calculated as the difference beween EDV and ESV. CO varies in respond to metabolic needs, for example with exercise, and where a normal CO at rest is around 5-6 liter /minute it may increase to around 15-25 liter/minute at exercise. In a healthy heart the tonus in the vessels in the body adapts to SV in a well regulated metabolic and neurohormonal balance. Factors as the sympatic and parasympatic nerve system and various metabolic substances influence this reaction and the heart rate.

The SV is dependant on the preload, meaning the filling of the returning blood from the circulation, which in turn determines CO. Increased pressure in the ventricles results in increased contractility. In a healthy heart the preload and contractility of the heart are positively correlated up to a certain point, known as the Frank-Starling law. The contractility of the heart is affected by various hormones and chemicals. If they stimulate contractility, they are said to have a positive inotropic effect, and if they decrease contractility, they are said to have a negative inotropic effect.

1.1.2.5 The viscious circle of heart failure

When the heart, due to various diseases and disturbances in systolic and/or diastolic function, is unable to produce an adequate SV and thus deliever the required amount of oxygen to the body, compensatory mechanisms, mainly from the the RAS- system and the sympathetic nervous system, will be activated. These systems are old compensatory regulators for loss of volume due to bleedings, infections, and thirst and are, as such, effective to maintain CO via increased heart rate, vasoconstriction, sodium and water retention and increased muscle strength. However, in a diseased heart these mechanisms will further strain the situation by increasing the peripheral resistance. The body is unable to differ this situation from that of a

bleeding and further activation of the RAS- and sympathetic nervous system will occur in an attempt to maintain CO but instead gradually activating the vicious circle of HF.

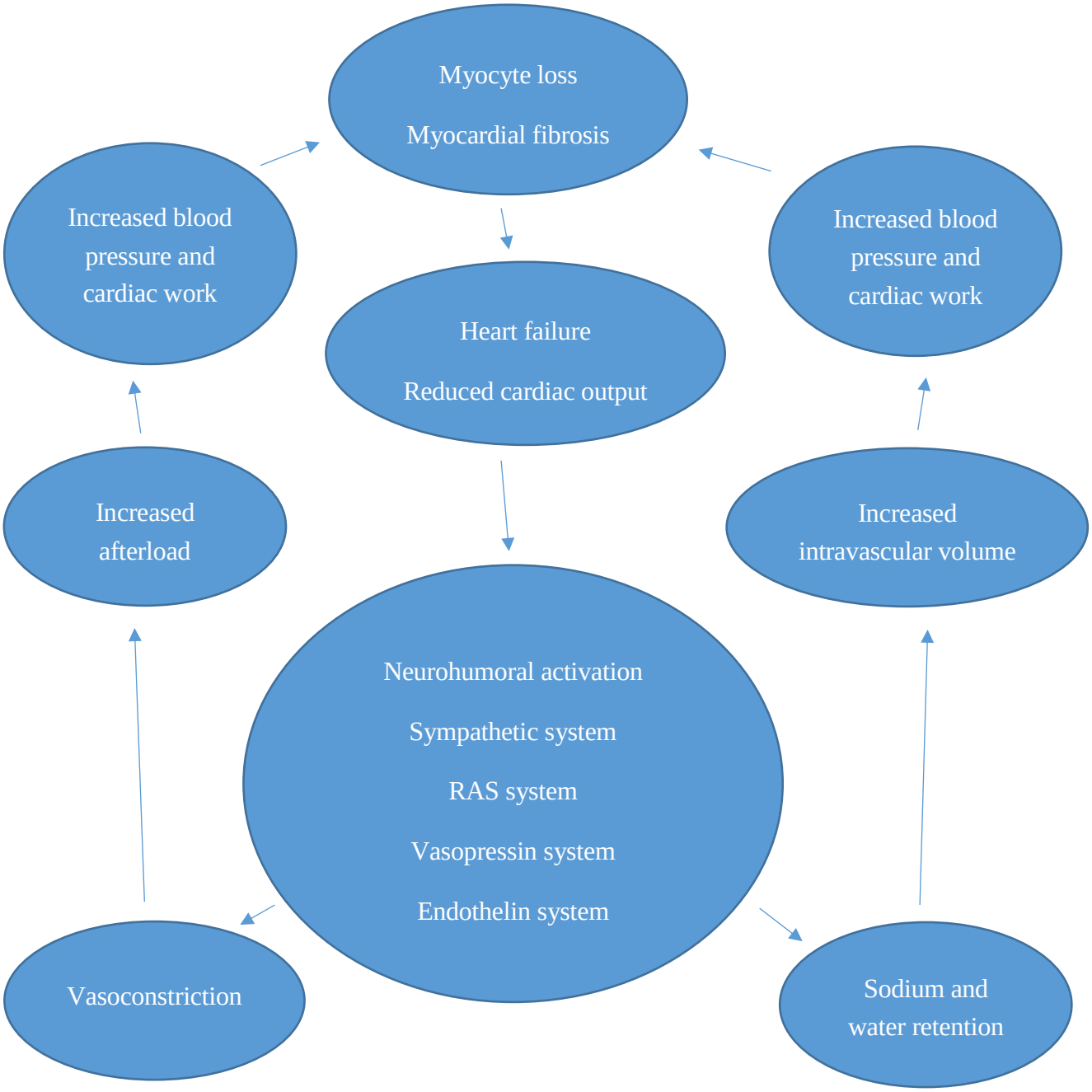


Figure 1. The vicious circle of HF

1.1.2.6 Systolic dysfunction

Systolic dysfunction is in a way the easiest to understand, and also the easiest to measure. Consquently many studies have been performed on the condition leading to multiple effective treatments. When the heart muscle, due to for example a myocardial infarction, is damaged the ventricular contraction will be impaired and as a result SV will be decreased. The most

common method to measure systolic function in clinical praxis is by defining Left Ventricular Ejection Fraction (LVEF or often EF), either with echocardiography (most common) or magnetic resonance imaging. EF is calculated as the difference between EDV and ESV (=SV), divided with EDV and expressed in percent where EF over 55% is considered normal. In the latest ESC guidelines, however, HF with EF <40% is classified as HFrEF, HF with EF 40-50% as HFmrEF and HF with EF ≥50% as HFpEF. [1]

1.1.2.7 Diastolic dysfunction

Diastolic dysfunction is somewhat more difficult to understand and to measure, compared with systolic dysfunction, and to do this properly it is important to be familiar with the different phases of diastole. There are four phases: the isovolumetric relaxation time (IVRT), the early rapid filling, the diastasis and the late filling as a result of atrial contraction. IVRT is the period between the closure of the aortic valve and the opening of the mitral valve during which time the pressure in the heart is falling. When the pressure in the ventricle is below that in the atrium the mitral valve will open, and the early rapid filling occurs. This can be measured with doppler-echocardiography as the E-wave or early diastolic phase and is normally caused both by the suction from the ventricle and the pressure in the atrium. The speed of the E-wave is normally higher in younger individuals due to better relaxation and suction in the ventricle. The phase after the E-wave is the diastasis in which the difference in pressure between the atrium and the ventricle is around zero and almost no flow occurs. The last phase of diastole is the atrial component in which the contraction of the atrium causes the A-wave, measured with doppler-echocardiography. Normally the E/A-ratio is 1.5-2.0 in younger individuals and between 0.7-1-0 in persons over 70 years of age.

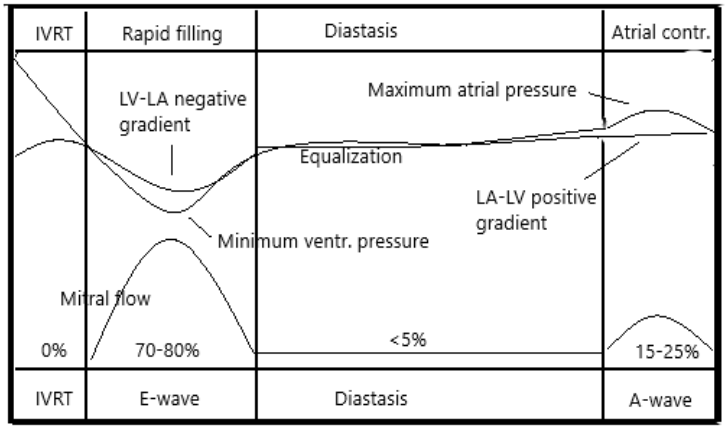


Figure 2. The normal diastolic phase

There are different methods to measure diastolic function in clinical praxis. All are based on and compared with cardiac catheterization which is “golden standard”.

Evaluation of the mitral inflow with doppler-echocardiography. Measures the E/A-ratio, the DT (E-wave deceleration time = DT = time for declining of the flow velocity in early diastole) and the IVRT (length of the isovolumetric relaxation time = IVRT = time to start of ventricles filling after relaxation).

Tissue Doppler measuring of the motion of the mitral annulus. Similar to conventional doppler-echocardiography the method will show an E- and A-wave, here named e´ and a´, representing early and late diastolic filling. Tissue Doppler is also useful for measuring time intervals. In a situation of diastolic dysfunction / impaired relaxation, e´ will be lower, and at the same time the E-wave increases with elevated filling pressures. The E/e´ ratio will increase and an E/e´ratio >14 is highly suggestive of elevated filling pressures.

Pulmonary vein flow. This technique enables measuring the blood flow in the pulmonary vein which, in a situation of diastolic dysfunction, will be shifted from systole to diastole.

Color Doppler M-mode. Studies early diastolic inflow into the left ventricle.

Indirect signs of diastolic dysfunction. Atrial enlargement. Left ventricular hypertrophy. Dilated pulmonary veins. Raised pulmonary artery pressures. Tricuspid regurgitation. Pulmonary hypertension.

Diastolic dysfunction can be divided into four different grades:

Grade I (impaired relaxation): The normal filling of the ventricle is disturbed due to ventricle stiffness and the E-wave will decrease. More blood is left in the atrium and the A-wave will be larger. As the E wave velocity is reduced the E/A is reversal (ratio < 1.0). The left atrial pressures are normal. The E/e’ ratio measured by tissue Doppler is normal. This can also be a normal finding and occurs in many individuals by the age of 60 years.

Grade II (pseudonormal): As the diastolic dysfunction progresses the pressure in the atrium will rise and the E-wave increase. The E/A ratio will return to the range of 0.8 to 1.5, looking very much like normal diastolic function and therefore named pseudonormal dysfunction.This is however pathological. Pseudonormal diastolic dysfunction may be

distinguished from normal function by the pulmonary vein flow, the presence of structural heart disease such as left atrial enlargement, left ventricular hypertrophy or systolic dysfunction and further by an elevated E/e' ratio (>14). Valsalva will also distinguish pseudonormal from normal as the E/A ratio will be < 1 during the maneuvre.

Grade III (reversible restrictive): In this phase with further increased pressure in the atrium the gradient between the atrium and the ventricle will increase.The flow into the ventricle starts earlier and terminates quickly. Thus, the E/A ratio is > 2.0, the deceleration time is < 160 ms, and the E/e' ratio is elevated.Valsalva maneuvre may change the pattern to that of pseudonormal dysfunction.

Grade IV (fixed restrictive): This is the most severe form of distolic dysfunction, indicating a poor prognosis and very elevated left atrial pressures. The E/A ratio is > 2.0, the deceleration time is short and the E/e' ratio is elevated. The major difference distinguishing grade III from grade IV diastolic dysfunction by echocardiography is the lack of E/A reversal with the Valsalva maneuver.

The diagnosis of HfpEF by echocardiography is a difficult task and it has been pointed out in the ESC guidelines that the diagnosis requires either evidence of diastolic dysfunction or findings of structural heart disease.

Understanding the mechanisms of diastolic dysfunction will help us to understand HFpEF since this condition is associated with aging and remodeling due to hypertension. Further, we begin to realize why HFpEF is more common among women. It has been shown that women have more remodeling and less dilatation than men [9] . The age-related stiffness of the heart is more pronounced among women which may be one explanation to the greater predisposition for HFpEF in women compared with men. [9, 62]

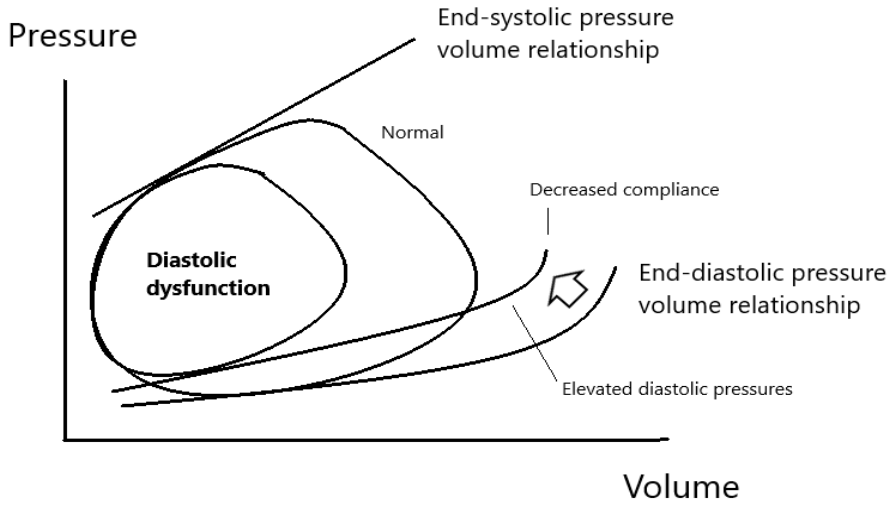


Figure 3. Diastolic dysfunction. Pressure-Volume curve

1.1.3 Diagnostics of heart failure

1.1.3.1 Symptoms and signs

There are numerous symptoms and clinical signs associated with HF, often classified with the Framingham criteria. [2] However, symptoms and clinical signs have generally low sensitivity (varying between 10 and 90% with the highest sensitivity for breathlessness on exertion) and specificity (varying between 70 and 99% with the highest specificity for breathlessness at rest) for diagnosing HF and are unsufficient alone for the purpose. [7, 63-66] At best, symptoms and clinical signs may help the clinician to catch attention for the diagnosis and lead to futher proper examination.[64]

1.1.3.2 Differential diagnosis

Mentionable conditions that may resemble HF include IHD, lung diseases (preferably COPD), arythmias, anemia, venous insufficiency, kidney disease, obesity and thyroid diseases. Given the low sensitivity and specificity of signs and symptoms mentioned above, further diagnostic procedures are essential. Many studies have shown that patients may be underdiagnosed or misdiagnosed. [6, 7, 19, 24, 57-61] There is also evidence of overdiagnosis in up to 30% of the cases [67] , potentially leading to wrong treatment and damage to the patients, and a poor use of recommended diagnostic procedures. [24, 57, 59-

61, 68] Not least in PC may this be a problem, considering the extensive disease panorama that meets the PC clinician every day.

Furthermore, it has been shown that women may be diagnosed in a more deficient way than men. [24]

1.1.3.3 Electrocardiogram

Electrocardiogram is a valuable, cheap and harmless tool in the diagnostic procedures of HF. It is efficient to rule out HF, [69] and furthermore adds information upon the cause of the disease. In the latest ESC guidelines for all types of HF it is recommended as an important diagnostic step, [1] together with analysis of natriuretic peptides.

1.1.3.4 Natriuretic peptides

Natriuretic peptides (NPs) (Atrial natriuretic peptide (ANP), Brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) are synthesized by cardiovascular, brain and renal tissues.[70] NPs provide vasodilation and natriuresis and acts as a compensatory mechanism against cardiac overload in a HF situation. In that way, they counteract the activated RAS-system and other neurohormonal systems.[71] They are regulators of blood pressure, water and salt homeostasis and also markers of cardiac dysfunction.[72, 73] Elevated levels of NPs correlate with the severity of HF and high levels of NPs also indicate a worse prognosis for both readmission and mortality.[74, 75] This has been shown both for HFrEF and HFpEF. [76, 77] Most studies have been performed on hospitalized patients but there are some data from PC. [59, 78, 79]

Low values of NPs (particularly BNP and N-Terminal proBNP (NT-proBNP)) are efficient to rule-out suspected HF [80, 81], due to a high negative predicitive value, and are now recommended in international guidelines as an important diagnostic step together with an ECG. The combined use of ECG and NPs has a negative predicitive value of 0.94-0.98 to exclude HF.[1, 69, 81-86] Important to remember for the clinician, however, is that there are numerous other conditions (renal failure, pulmonary embolus, pulmonary hypertension) causing elevated NPs, hence the varying specificity for HF diagnosis between 75 and 94% and the importance of further diagnostic procedures. [87, 88]

Although measuring NPs is a simple and not too costly tool to help the clinician to diagnose suspected HF, it has been shown that the method is poorly used [61] but recently, however, there are reports of increased use in PC.[89]

NPs has been well established in the diagnostic procedure as well as prognostic markers. Consequently, there has also been hopes that they may support management and treatment of HF. However, several randomized clinical trials (RCTs) have shown that NP-guided treatment has given conflicting results and it is uncertain whether this would lead to a better outcome than simply optimizing treatment according to guidelines.[90, 91]

1.1.3.5 Chest X-ray

Although chest x-ray is often performed in the diagnostic procedures to find HF, its contribution to the HF diagnosis itself is poor and the importance of x-ray is merely to establish other differential diagnosis such as lung diseases.

1.1.3.6 Echocardiography

The most important diagnostic procedure for HF in clinical praxis is echocardiography which not only is essential for the diagnosis but also provides information about type of HF, severity and sometimes underlying mechanisms. [92, 93] In spite of its importance many studies have pointed at a low use of the method. Hobbs et al showed that echocardiography was only used in 32% of HF-patients in PC.[57] In HC, Cleland could show somewhat better, but still not satisfactory, results (66%) [94] as well as Valk (73%) [67] In PC, other studies results are even worse with a use of echocardiography ranging from around 30% [59, 60] down to as low as 8.5%. [44] The combined use of NPs and echocardiography has further been shown to have a low degree of utilization. (9%) [68, 95]

Heart-catheterization is considered "golden standard", however not possible to perform in clinical praxis.

1.1.4 Treatment of heart failure

Treatment of heart failure with reduced ejection fraction

There are multiple evidence-based and established therapies for HFrEF, many of which are introduced in the late 20th century. Common factor for these therapies is the perception that

what is essential in HFrEF is a neuro-hormonal dysfunction. The most important pharmacological categories are:

-Angiotensin Converting Enzyme inhibitors (ACEi)

-Angiotensin Receptor Blockers (ARB)

-Betablockers (BB)

-Mineral Receptor Antagonists (MRA)

All these pharmacological treatments have been able to show positive effects on morbidity, mortality and quality of life in large RCTs [96-105] If there are no contra-indications they should always be considered for managing HFrEF and are well established in international guidelines. [1]

Beyond these established base-treatments, patients with HFrEF may also benefit from treatment with diuretics, Angiotensin Receptor–Neprilysin Inhibitors (ARNI), iron-infusion and digitalis and further, on certain indications, Cardiac Resynchronization Therapy (CRT), Implantable Cardiac Defibrillator (ICD), Left Ventricular Assistant Device (LVAD) and heart transplantation.

There is also substantial evidence that nurse-led HF receptions with patient education can improve functional capacity, adherence to guidelines therapy and reduce readmission rates. [53, 55] as well as that physical exercise reduces mortality and hospitalization [106]

Some patients may also benefit from procedures directed to the ethiological cause of their HF, i.e. Coronary Artery Bypass Graft surgery (CABG), Percutaneous Coronary Intervention (PCI), valvular surgery or heart transplantation.

The above mentioned therapies are all established and recommended in international guidelines but, in spite of that, there are many studies indicating lacking or poor use in a real-world setting.[57, 60, 89, 107]

Further, it has also been shown that women receive less treatment according to guidelines, concerning particularly HFrEF. [24, 107, 108]

1.1.4.1 Treatment of heart failure with preserved ejection fraction

There have been many attempts to find an evidence-based reliable pharmacological therapy for HFpEF but no RCT has yet managed to show significant effects similar to those for HFrEF. Some effects have been shown on hospitalization and diastolic function but still not on mortality. [109, 110] Some observational studies indicate positive effects of RAS- and beta-blockade [111, 112] and it has been shown that physical activity may have positive effects on physical capacity and quality of life and further that weight reduction may be beneficial among obese patients. [113, 114] Saltreduction has been associated with reduced 30 days mortality [115] and a structured nurse-led programme with improved lipid profile, functional capacity, quality of life and weight loss.[45]

Most important, given the large proportions of comorbidities among HFpEF patients, and the contribution of these comorbidities to mortality, not least non-cardiac mortality, is to adequately treat these comorbidities and other conditions that may affect the HFpEF patient.[116, 117]

1.1.5 Heart failure with preserved ejection fraction

A large group of HF patients is the one with preserved ejection fraction, HFpEF. This condition is as common as HFrEF but in contrast there is no evidence-based treatment. Morbidity and mortality is comparable with that of HFrEF when hospitalized and there is still lack of knowledge about the development and progress of the disease.[118-120] Many studies have shown that the mortality for HFpEF patients is equal to, or slightly lower than, the mortality for HFrEF patients with a one-year mortality of 20-25% for those requiring hospital care. [8, 17, 18, 21, 29, 34] Even the rehospitalization frequency is comparable [23] Diagnostics of HFpEF is more challenging than in HFrEF and there is probably substantial underdiagnostics, especially since many variables may be normal at rest but pathological at exercise. [121] The patients normally do not have a dilated left ventricle but instead more often left ventricular hypertrophy and/or a dilated left atrium as a sign of increased filling pressure. The insights that HFpEF is a complex syndrome where systolic, chronotrop, vascular, endothelial and peripheral factores contribute and where a disturbed active relaxation and a passive stiffness is present are becoming increasingly obvious [121] Most patients have signs of disturbed diastolic function which also is considered the main mechanism of the condition.[9, 62] The patients are older, more often women and with more hypertension and atrial fibrillation than HFrEF patients but more seldom ischemic heart disease.[7, 9, 11, 17-21, 122] It is a heterogenous group with different ethiologies and pathopfysiological abnormalities and it has further been suggested that, compared with

HFrEF patients, hospitalization and mortality is more often caused by non-cardiac conditions. [34, 54, 109]

There are differences between women and men where women are older and more overweight, have a higher NYHA-class, more often treated with diuretics, have less ischemic heart disease but more hospitalizations than men. [30] In contrast, men have more IHD, AF and DM, are more often current or previous smokers compared with women and have higher age-adjusted all-cause mortality than women.[22, 30-32]

No treatment has yet been shown to convincingly have effect on morbidity and mortality in this group. Since the patients often are elderly, with many symptoms and a low quality of life, much of the care must be concentrated on managing the due diseases and relieve symptoms.[116, 117] Physical activity has been shown to improve the physical condition and quality of life and, among obese patients, weight loss may improve the prognosis.[113, 114] If the patients have fluid excess they may benefit from salt- and fluid restriction. Comorbidities have a greater impact on functional class and physical capacity among HFpEF patients and hospitalization is more often caused by non-cardiac conditions than for HFrEF patients.[12-14, 21, 34, 54, 123, 124]

The diagnose of HFpEF is difficult and the condition may be undetected, not least in primary care that manages patients with many diagnoses and often diffused symptoms.[7, 18, 44, 57, 58, 95, 125]

1.1.6 Heart failure in primary care

Many HF- patients are managed in PC, often in cooperation with HC but also mainly in PC, in various studies between 17 and 36%.[3, 15]

Patients managed in PC are older with a higher proportion of women and a lower mortality than those managed in HC.[29] There are relatively fewer patients having HFrEF and, although the mortality is lower than in HC, it has been shown that the quality of life is poor among both HFrEF and HFpEF patients.[29, 126, 127] Comorbidities are common and for example COPD coexists in up to 25% and may often be underdiagnosed.[15, 67] There are some studies on diagnostics and treatment of HF in PC, generally showing a need for improvement.[57, 60, 67, 86, 94, 107] Early intervention and team-based management are

important [128, 129] but it has been shown that follow-up and adherence to guidelines is poorer in PC than in HC.[57, 60, 89, 94, 107]

Most importantly, there are a limited amount of studies on HFpEF in PC. Some studies have shown that patients in PC are older with a higher proportion of women and a better functional capacity according to NYHA-classification, compared with HC.[17, 44, 68, 122, 126] Overweight, diabetes, low hemoglobin are strongly associated with HFpEF whereas male gender is strongly associated with HFrEF.[122] It has been shown that HFpEF is more common than HFrEF in PC [126] and that risk factors for developing HFpEF is obesity, hypertension, diabetes and kidney disease.[122] Many studies have described a high frequency of comorbidities but have not consequently distinguished PC from HC.[12-14, 16, 17, 54, 123] It has though been shown the importance of these comorbidities, not least for COPD and diabetes.[15, 125] Further, it has been described that the use of diagnostic tools, such as ECG, NPs and echocardiography, is poor which markedly diminishes the possibility to adequately determine type of HF and design the right treatment.[44, 95] Consequently, many studies point at underdiagnostics of the condition.[57, 60, 61, 66, 68, 94] Correct identification of the type of HF is important not only for the patient, with potentially wrong, harmful and expensive treatment, but also for future research and development.[44, 95] Concerning treatment of HFpEF pharmacologically there are few studies in PC but it has been shown that a structured nurse-led management can improve quality of life, body weight, emotional status, functional capacity and lipid profile.[45]

There are also a limited number of studies on mortality for HFpEF patients in PC but it has been shown that men have a higher risk of mortality and hospitalization together, compared to women.[44]

1.1.7 Quality registries

National quality registries have been used in Sweden for more than forty years and are a system of quality tools designed to develop and improve care management.[4] All registries contain information about the patients' diagnosis, treatment and results. There are today around one hundred different registries, sponsored by the government and producing continuous information to the health care system.

The HF quality registry (SwedeHF) was founded in 2003 by Ulf Dahlström, Magnus Edner and Åsa Jonsson and it serves particiant units with:

-Continous information about carachteristics, diagnostics, treatment, quality of life and functional capacity for their HF patients.

-Continous information on-line to concerning their own data compared with the national data.

-Information on adherence to guidelines for every unit.

-Yearly reports on mortality, morbidity, diagnostics, medical treatment, functional capacity and quality of life to every unit and compared with the national data.

-Research on the HF data.

When creating the registry a national group of experts developed a protocol with indicators of quality of life, background, diagnostics, treatment and follow-up of the HF-patients in the registry and the registry has been the base for many scientific articles.[26]

1.2 AIMS

1.2.1 Gaps of knowledge

Despite the fact that HFpEF is a common disease, often managed in PC, there are substantial gaps of knowledge. We lack information of;

-The characteristics of the HFpEF population in PC

-The mortality of the HFpEF population in PC

-Comorbidities in HFpEF patients in PC

-Gender differences among HFpEF patients in PC

-Prognostic factors

-Potential underdiagnosis

1.2.2 Main aim

The main aim of this thesis is to describe characteristics, comorbidities, challenging diagnostic, prognosis and potential underdiagnosis of the HFpEF population in PC.

-The characteristics of the HFpEF population in PC vs HC. Study I.

-Prognostic factors. Study I.

-The utility of NT- proBNP. Study II.

-Gender differences among HFpEF patients in PC. Study III.

-The mortality of the HFpEF population in PC and causes of death. Study III.

-Potential underdiagnosis. Study IV.

1.2.3 Secondary aim

The secondary aim of this thesis is to describe and evaluate an internet-based diagnostic tool to improve diagnosis.

1.3 MATERIALS AND METHODS

1.3.1 Material (I)

In the first study we used data from SwedeHF. SwedeHF is one of the world's largest HF registries and was created in 2003. It is an Internet-based registry designed to help the participating units to improve the management of their patients, having unrestricted access to their own data, but also to form a base for research on HF. Both hospitals and PC centres in Sweden participate in the registry but it is not mandatory even though there has been recommendations from the Swedish Board of Health and Wellfare. Approximately 80 variables including demography, concomitant diseases, diagnostics, medication and laboratory data are prospectively entered into the registry. Registration is performed either at discharge from hospital or at an out-patient visit at hospital or in PC. Patients are informed that their hospital or PC centre is participating in the registry and that it is approved by a multisite ethic committee. Patients are allowed to opt out.The database is built to handle sensitive information and each participating unit can only have access to their own data, but after application to the Steering Committee, data from the entire registry can be obtained for research purposes.

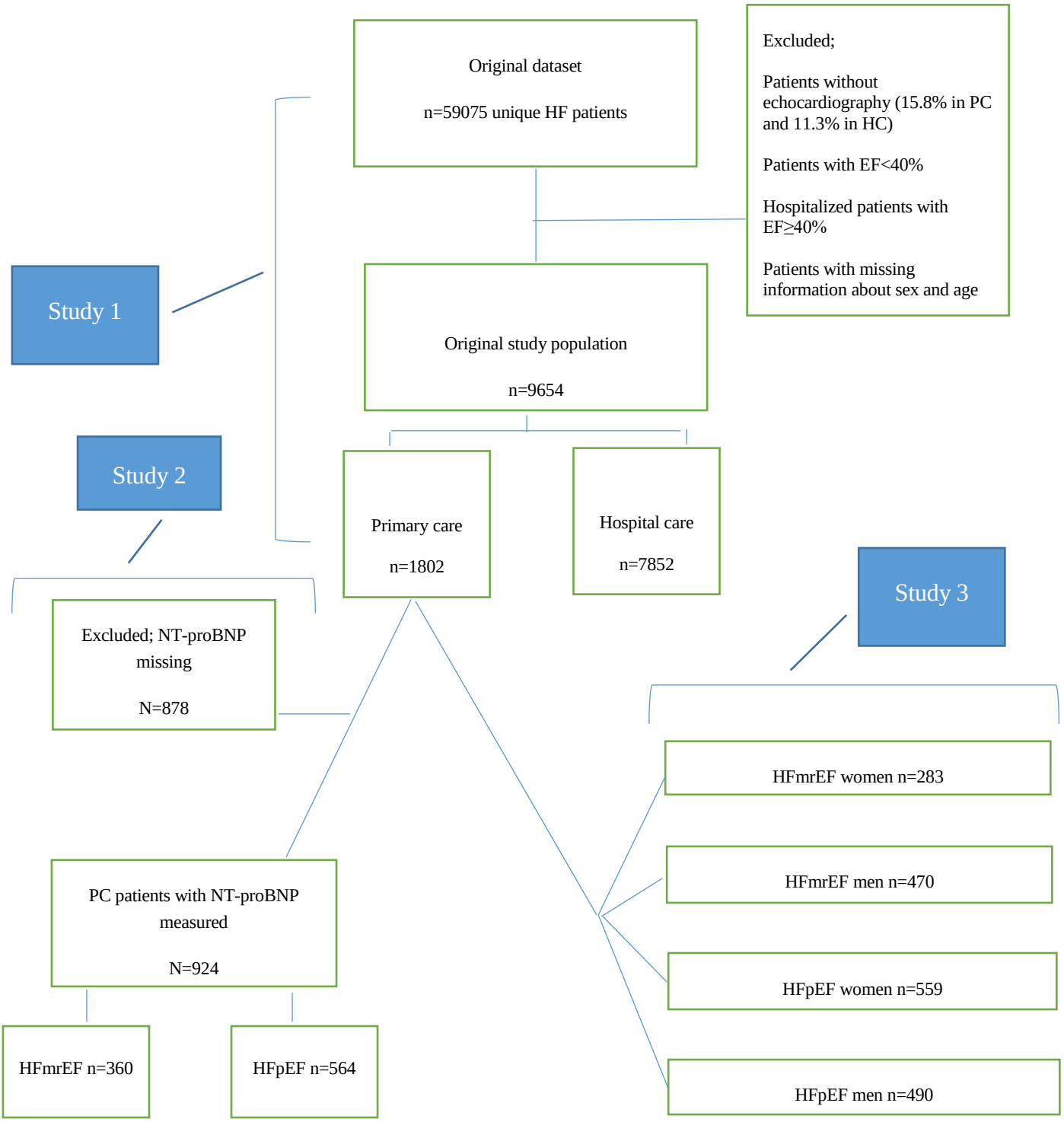
Data from a prospectively collected material in a registry form a solid base for observational studies but is not ideal for studying the effect of treatment where a RCT is the optimal choice. However, in a RCT many patients are excluded due to high age, certain comorbidities and

other factors, whereas in a registry all patients remain, regardless of these factors. The registry therefore constitute a research base that is more representative to real.

Furthermore, the size of the registry, the participation of both hospitals and PC centres and the possibility to merge the registry with other national registries expands the utility of the registry.

We used data in SwedeHF recorded between First of September 2001 and 15th of May 2014 for this study and the database was merged with the Swedish population registry and the Swedish patient registry of hospitalization. By 2014 Sweden had 1156 PC units and 67 hospitals out of which 116 PC units and 67 hospitals participated in the registry. The registry contained 59075 patients in 2014, 6579 from PC and 52496 from HC. Since we wanted comparable data from both PC and HC we only included patients recorded at an out-patient visit. We also wanted to be sure that the patients had HF (inclusion criteria in the registry is clinician-judged HF), and further whether their EF was equal to or above 40%, and therefore we excluded patients without information about echocardiography (1041 = 15.8% in PC and 5938 = 11.3% in HC). Finally, we excluded patients with an EF<40 % and patients with EF≥ 40% but hospitalized. The total number of patients remaining in the study was then 1802 from PC and 7852 from HC. (fig 4)

Figure 4. Schematic patient selection, study 1,2 and 3.



1.3.2 Method (I)

We used both descriptive and analytical methods to analyze the cohort in the first study. We constructed baseline tables for PC and HC patients respectively and for all patients in the database but also for the subgroups with EF 40-49% and with EF ≥50%.

We calculated and chartered mortality for the whole group, and for EF 40-49% and EF≥ 50%, using the Kaplan-Meier method and we constructed tables for 1, 3 and 5 years mortality rates for the same three groups. Tables for the above mentioned mortality ranges were also contructed for patients with no comorbidity in PC or HC and for those with any comorbidity.

Multivariate regression analyses were performed for time dependent different variables, calculating hazard ratios (HR) with 95-% CI for mortality.

We wanted comparable groups when analyzing medication, and since patients with higher age, renal function impairment and low blood pressure might be referred to hospital before RAS-antagonists or betablockers are prescribed. We matched patients in the overall cohort for age (±1 year), gender (same), systolic blood pressure (>110 mm Hg) and eGFR-class (same). After matching, 1499 patients remained in each group. Baseline tables were constructed, and mortality rates were calculated, as for the whole cohort.

1.3.3 Material (II)

For the second study we used the same data-base from Swede-HF as in study one. After exclusion of patients not suitable for our work, that population consisted of 1802 PC patients and 7852 HC patients, all with an EF of more than or equal to 40%.(fig.3)

In the second study we aimed to assess the prognostic significance of plasma NT-proBNP in patients with HFmrEF and HFpEF in PC. We therefore excluded patients in HC and those in PC without a measurement of NT-proBNP registered. The data-base for this study consisted after that of 924 patients. All patients were divided into two groups: 360 patients with EF 40-49% (HFmrEF) and 564 patients with EF≥50% (HFpEF).

1.3.4 Method (II)

We constructed baseline tables for the two EF-groups separately using descriptive statistics.

All-cause mortality was calculated and chartered for the two EF-groups using the Kaplan-Meier method (KM). KM curves for quartiles of NT-proBNP and mortality were constructed for the whole cohort as well as for HFmrEF and HFpEF separately and we also calculated 1-, 3- and 5-years mortality rates for the two EF-groups.

We performed univariate and multivariate regression analysis for mortality to calculate Hazard Ratios (HR) for the different variables in the data-base in order to analyze whether NT-proBNP was an independent risk factor for mortality.

Variables that were associated with increased NT-proBNP were analyzed with same method as for those that were associated with mortality. Both EF-groups were analyzed with this method.

Finally, we identified comorbidities in the two EF-groups separately and which comorbidities that were associated with all-cause mortality after a primary univariate and secondary multivariate Cox proportion hazard regression analysis.

1.3.5 Material (III)

In the third study we aimed to study gender differences in patients with either HFmrEF or HFpEF, managed in PC. We therefore used the entire PC data-base of 1802 patients, described in Study 1(fig nr 3). Patients were divided into four groups, women with EF 40-49% (HFmrEF, n=283), men with EF 40-49% (HFmrEF, n=470), women with EF≥50% (HFpEF, n=559) and men with EF≥50% (HFpEF, n=490)

1.3.6 Method (III)

We constructed baseline tables for the whole cohort of 1802 patients and for the four EF-groups separately.

Mortality among women and men was analyzed with the KM method. We primarily constructed curves for crude mortality and secondarly, since age highly affects mortality, age-adjusted KM-curves.

Mortality difference between women and men was further analyzed with multivariate Cox proportion hazard regression analysis taking into account age, COPD, IHD, AD, valvular disease, DM, HT, NYHA-class, Hb-level and kidney dysfunction.

Further, using logistic regression analysis, we calculated the one-year mortality rate for the different age-groups <60, 60-69, 70-79. 80-89 and >90 years for both women and men.

Univariate regression analysis for various comorbidities and their association with mortality were performed for women and men in the four EF-groups and the result presented as a Forest Plot.

Causes of death were analyzed for women and men in the whole cohort and in the four EF-groups separately. Groups were presented as in the International Classification of Diseases (ICD) registry. Differences were analyzed with the Chi-square test. The result was presented with pie charts.

1.3.7 Material (IV)

In the fourth study we aimed to validate an internet-based questionary to detect HF (described below) and further to investigate potential underdiagnosis of HF at a PC unit. We actively scanned medical records at the PC centre of Gustavsberg, (Stockholm, Sweden) for patients that had searched for one or more of the three HF symptoms breathlessness, tiredness or ankle swelling during the period January to March 2019. Those that already had an established HF diagnosis were excluded as well as those that at the following doctor's visit were properly examined for HF. Patients that remained were contacted and asked if they were willing to enter the study. The study was improved by ethnic committee and all patients received written information and signed Informed Consent.

1.3.7.1 Internetbased questionary

A questionary for potential HF was constructed in care of a HF quality project (4D HF project 2012-2018) in Stockholm, Sweden and presented at an internet platform. The questionary contained nine questions regarding age and gender, hereditary factors, etiology, symptoms and signs. Specifically, these issues were further divided into; breathlessness at exertion, breathlessness at rest, weight gain, ankle swelling, previous diseases, cytostatic treatment and hereditary factors. Various points were given to the answers and an automatic reply with one of the three following alternatives; HF unlikely (<3 points), HF possible (3 to 8.5 points but not answer yes on breathlessness at rest) , HF likely (9 to 12.5 points or 3 to 9.5 points and answer yes on breathlessness at rest) was linked to the result.

1.3.8 Method (IV)

Patients that agreed to participate in the study, and had signed informed consent, were summoned to an appointment with a doctor. Medical history and status was uptaken whereafter patients were asked to fulfill the internet-based questionary for HF and to estimate their quality of life according to the EQ5D scale. ECG and blood test for NT-proBNP was performed and all patients were referred to spirometry and echocardiography.

The complete results were then analyzed first separately by an experienced general practioner (BE) respectively a cardiologist (HP) and secondary as a common consensus and following the diagnostic criteria from ESC. Points of judgement were symptoms, clinical signs according to the Framingham criteria, ECG, NT-proBNP values, echocardiographic findings of either systolic or diastolic dysfunction and finally a consensus on whether the patients had HF or not and, if so, which type of HF defined as either HFrEF, HFmrEF or HFpEF. ECG was classified as normal or pathological and a cut off value of >125 ng/l for NTproBNP was used.

The result of the consensus assessment was then used as a "golden standard" when evaluating the internet-based questionary's reliability to detect HF or not. Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio for positive and negative results were calculated for the test.

All patients were contacted when the study was finished and informed of their results. Those that received a new diagnose of HF were given a personal appointment and follow-up at the GP unit.

1.3.9 Statistics

Descriptive statistics were used and results presented as numbers and percentages or means with standard deviations (SD). Categorical variables were analyzed using the chi-square test and continuous variables using the student t-test. Levels considered statistically significant were a p-value<0.05. All p-values and 95% confidence intervals (CI) were 2-sided. (Study I, II and III) Univariate regression analyses were used to calculate hazard ratios for mortality for different variables. Variables with a p-value of 0.1 or below in that analysis were then entered into a multivariate logistic regression analysis to determine Hazard Ratio (HR) with 95% CI for mortality. (Study I, II and II) The result was presented as a Forest plot. (Study I and II) HR for medication was finally also analyzed for the matched cohort. (Study I)

All statistical analyses were performed using SAS statistical software, version 9.4.

1.3.10 Ethics

All studies were approved by a multisite or local ethic committee.

1.4 RESULTS

1.4.1 Study 1, paper I

1.4.1.1 Characteristics

Patients managed in PC were significantly older than those managed in HC, 77.5 vs 70.3 years ($p<0.0001$) and there were more patients with an EF≥50% (26.1% vs 13.4%, $p<0.0001$). In the PC cohort the proportion of women was greater than in HC. (46.7% vs 36.3%, $p<0.0001$). When dividing the overall cohort into EF 40-49% and EF≥50% there were considerably more women in the PC cohort with EF≥50% (53.3% vs 44.0%, $p<0.0001$). Functional capacity according to NYHA classification was often missing (45.4% missing in PC and 46.1% in HC) but, when reported, patients managed in PC had a better functional class (72.2% in NYHA I or II vs 69.1% in HC, $p<0.01$). This difference was most pronounced in the group with EF≥50%.

Patients in PC had higher heart rate, systolic blood pressure (mean 134 mm Hg vs 129, $p<0.0001$), diastolic blood pressure (mean 75.1 mm Hg vs 73.7, $p<0.0001$) and more renal dysfunction (48.1% eGFR< 60 ml/kg/min vs 41.5%, $p<0.0001$).

1.4.1.2 Comorbidities

There was a high frequency of comorbidities in both the PC and the HC cohort. In PC only 2.8% had no comorbidity vs 7.7% in HC. Figures for comorbidity in the two different EF-cohorts were similar in both PC and HC. Patients in PC had significantly more AF (53.0% vs 47.2%, $p<0.0001$), HT (67.0% vs 48.9%, $p<0.0001$), IHD (57.8% vs 32.7%, $p<0.0001$) and COPD (24.5% vs 15.2%, $p<0.0001$).

1.4.1.3 Mortality

Mortality after 1 year was 7.8% in the PC cohort and 7.0% in the HC cohort, corresponding figures after 3 years was 22.8% in the PC cohort and 17.0% in the HC cohort and after 5 years 28.9% vs 23.0%. Mean follow-up time was 1151 days in PC and 1286 days in HC after which mortality was 31.5% in PC vs 27.8% in HC. When comparing the subgroups with EF 40-49% vs EF≥50% the results were consistent.

After multivariate logistic regression analysis smoking, COPD, DM, age and heart rate were shown to be independent risk factors for mortality in PC and in HC valvular disease, kidney dysfunction, IHD, COPD, AF, low diastolic blood pressure, high heart rate and age.

1.4.1.4 Medication

Medication was only compared in the matched cohorts. There were more prescribed RAS-antagonists in the HC cohort (83.7% in PC vs 87.6% in HC, $p<0.05$) and betablockers in HC (74.2% in PC vs 85.7% in HC, $p<0.0001$). In HC the combination of RAS-antagonists and betablockers was more used (63.8% in PC vs 75.2% in HC, $p<0.0001$). There was no difference concerning MRAs.

1.4.2 Study 2, paper II

1.4.2.1 Characteristics

There were more women (54% vs 39%, $p<0.0001$) and higher age (mean age 78.2 vs 76.3, $p<0.01$) in the HFpEF group compared to the HFmrEF group. More interventional procedures (Coronary artery bypass grafting or Percutaneous coronary intervention) were performed among HFmrEF patients whereas HFpEF patients more frequently had sinus-rhythm on the ECG and normal chest x-ray. ACE-inhibitors, betablockers and statins were all prescribed more within the HFmrEF group. There was also a tendency, however not statistically significant, to more patients with IHD in the HFmrEF-group.

There was no significant difference between the two EF-groups concerning mortality ($p=0.26$) and the 1-year mortality was 8.1% for HFmrEF-patients and 7.3% for HFpEF-patients. Corresponding figures for 3- and 5 years mortality were 23.9% vs 23.6% and 44.7% vs 37.2%.

1.4.2.2 The prognostic value of NT-proBNP

There was a clear association between levels of NT-proBNP and mortality where the patients that died after 1 year had the highest levels of NT-proBNP. However, the SD- values were huge.

After Kaplan-Meier analysis, there was a significant association between NT-proBNP quartiles and mortality the highest quartile having the highest mortality ($p<0.0001$). (mean follow-up time of 1100 ± 687 days).

1.4.2.3 HFmrEF

As for the whole cohort patients that belonged to the group with the highest NT-proBNP quartile had the highest mortality. (HR 1.96 (95% CI 1.60-2.39, p<0.0001 in a univariate analysis and HR 1.83 (95% CI 1.38-2.44, p<0.0001) after multivariate Cox proportion hazard regression analysis).

1.4.2.4 HFpEF

The same pattern as for HFmrEF patients were observed in the HFpEF group. Patients with the highest NT-proBNP quartile had the highest mortality (HR 1.72 (95 % CI 1.49-1.98) p-value < 0.0001, in a univariate analysis and HR 1.48 (CI 1.16-1.90) p-value <0.0001 after multivariate Cox proportion hazard regression analysis).

1.4.2.5 Variables associated with increased NT-proBNP

In the HFmrEF group numerous variables were associated with increased NT-proBNP in a univariate analysis (age, NYHA-classification, hemoglobin level, systolic blood pressure, diastolic blood pressure and body weight) but following multivariate Cox proportion hazard regression analysis only age and low hemoglobin level remained statistically significantly associated with increased NT-proBNP.

For HFpEF patients there was also an association between numerous variables and increased NT-proBNP in a univariate analysis (age, NYHA-classification, hemoglobin level, diastolic blood pressure, body weight, valvular disease, AF, DM and kidney dysfunction) but after multivariate Cox proportion hazard regression analysis only valvular disease and low body weight remained statistically significantly associated with increased NT-proBNP.

1.4.2.6 Comorbidities affecting all-cause mortality

Frequency of comorbidities were high in both EF-groups (97% in HFmrEF and 98% in HFpEF), the most common comorbidity being HT (64% among HFmrEF patients and 70% among HFpEF patients) followed by AF (more than 50% in both groups). Combinations of comorbidities were common and among HFpEF patients the combination of COPD and HT was twice as common as among HFmrEF patients.

Numerous comorbidities were associated with all-cause mortality in a univariate analysis among HFmrEF patients age, low body weight, low diastolic blood pressure, low hemoglobin level, low creatinine clearance class and high NYHA class and among HFpEF patients age, low body weight, low diastolic blood pressure, low hemoglobin level, creatinine clearance class, COPD, valvular disease and NYHA class) but after multivariate Cox proportional hazard regression analysis only NYHA class remained highly significant with all-cause mortality in the HFmrEF group (HR 2.09 (CI 1.37-3.18),) and age (HR 1.07 (CI 1.02-1.12)), low body weight (HR 0.98 (CI 0.96-1.00)), COPD (HR 2.13 (CI 1.21-3.74) and NYHA class (HR 1.67 (CI 1.08-2.59) in the HFpEF group.

1.4.3 Study 3, paper III

1.4.3.1 Baseline characteristics and gender differences in the whole cohort

Women were older (mean age 78.7 vs 76.4, p<0-0001), had more valvular disease (26.5% vs 21.4%, p<0.05), higher systolic blood pressure (mean 136.1 vs 133.1, p<0.01), lower hemoglobin level (mean 130.6 vs 136.8, p<0.0001) and more kidney dysfunction (mean eGFR 58.4 vs 65.7, p<0.0001) whereas men were more smokers (38.3% vs 60.8%, p<0.0001), had more IHD (34.9% vs 48.7%, p<0.0001), AF (49.6% vs 56.1%, p<0.01) and DM (17.2% vs 24.5%, p<0.01). Men also more frequently had gone through cardiovascular revascularization procedures (11.7% vs 29.0%, p<0.0001).

1.4.3.2 HFmrEF vs HFpEF

Age increased with EF-group among both women and men but women were still older than men in both groups. The proportion of women increased from 37.6% in the HFmrEF-group to 53.3% in the HFpEF-group and the prevalence of IHD decreased in both women and men. Men still were more smokers and had more IHD in both groups but the difference concerning AF and DM was only seen in the HFpEF-group. In both groups women had more kidney dysfunction and lower hemoglobin levels.

1.4.3.3 Medical drugs in HF-patients with EF equal to or above 40%

Women in the HFpEF-group were more often treated with digitalis (17% vs 13%, p<0.05) while men in the whole cohort more often were prescribed statins (37.3% vs 52.1%, p< 0.0001), aspirin (40.8% vs 47.9%, p<0.01) and ACE-inhibitors (51.5% vs 60.2%, p<0.0001).

There was a low prescription rate of anticoagulantia in the whole cohort among both women and men (37.9% vs 41.2%), in spite of AF frequency of 49.6% vs 56.1%.

1.4.3.4 Mortality and gender differences in HFpEF-patients

When assessed with the Kaplan-Meier method there was no difference in crude mortality between women and men. However, when the analysis was age-adjusted, men had highly statistically significantly higher mortality (p<0001). After adjusting for COPD, IHD, AF, valvular disease, DM, HT, age, NYHA-class, Hb-level and kidney dysfunction this difference remained highly statistically significant.

1.4.3.5 Mortality and gender associated co-morbidities

Comorbidities that were associated with higher mortality were in the HFmrEF-group among women valvular disease (p <0.05), AF (p <0.05) and kidney dysfunction (p <0.001) and among men kidney dysfunction (p<0.0001) and Hb level (p<0.0001). In the HFpEF-group the corresponding associations were among women COPD (p<0.01) and among men valvular disease (p <0.01), COPD (p <0.05) and kidney dysfunction (p<0.001).

1.4.3.6 Causes of death and differences by gender and ejection fraction

In the whole cohort there was a significant difference between women and men concerning malignant tumors as cause of death, where the figures were 8.6% among women and 15.4% among men (p<0.05). The major cause of death was however in both groups cardiovascular diseases (includes myocardial infarction, HF and stroke), (55.6% among women and 59.8% among men (n.s)), followed by respiratory diseases (15.2% among women and 11.3% among men (n.s)). These three causes of death were dominating in the cohort but there were 11 more groups of death-causes, and more than 90% of the patients had one or more comorbidities that potentially could influence the cause of death.

In the HFmrEF-group there was no significant difference between women and men and the three dominating causes of death were the same. In the HFpEF group cardiovascular diseases were still dominating as cause of death but decreasing among women (65.0% in the HFmrEF group vs 45.1% in the HFpEF-group (p <0.01), however not statistically significantly different compared with men (45.1 % vs 55.4% (p=0.06). Malignant tumors were more frequent cause of death among men (9.3% vs 16.5% (p<0.05).

1.4.4 Study 4, paper IV

We found 96 patients that had contacted the GP unit for one of the three symptoms breathlessness, tiredness or ankle swelling during the examined period of time. After excluding those that already had a diagnosis of HF (n=18) and those that were properly investigated for HF (n=45) 33 patients remained and were contacted. 24 responded positively, signed informed consent and entered the study. Mean age was 70.5 years, and the range was 52 to 85 years, 11 were women and 13 men. The underlying diagnosis was IHD in 3 of the cases, HT in 16 and COPD in 9 of the cases. 5 of the patients had none of these diagnoses. Symptoms were breathlessness in 18 of the cases, tiredness in 18 and ankle swelling in 6 of the cases (some patients had more than one of the symptoms) The EQ5D score ranged from 30 to 99 and the NT-proBNP value from 28 to 1090.Pathological ECG was found in 7 of the cases, spirometry with findings of COPD in 6 cases and asthma in 3 cases.

1.4.4.1 Validation of the internet-based questionary

As stated below, 5 of the patients proved to have HFpEF and in these cases the test showed possible or likely HF in 4 of the cases and HF unlikely in 1 of the cases. Within the 19 patients that were considered not having HF the test indicated HF unlikely in 14 of the cases but HF possible or likely in 5 of the cases.

Based on these results for the test we calculated a sensitivity of 80% and a specificity of 74%. The negative predictive value for the test was 93% and the positive predictive value 44%. Likelihood ratio for positive results was 3.08 and likelihood ratio for negative reuslts 0.27.

1.4.4.2 Underdiagnosis of HF

The result of the echocardiographic examination was normal in 19 of the cases. We found no patient with disturbed systolic function but 5 with disturbed diastolic dysfunction. All these patients were also considered having HFpEF after GP and cardiologist concensus taking into account symptoms, signs, ECG, NT-proBNP and echocardiography and following the diagnostic criteria of ESC. 4 of the patients were women and 1 a man. Age ranged from 67 to 84 years and mean-age was 75.8. NT-proBNP ranged from 87 to 743. Symptoms were tiredness within all 5 and breathlessness within 3 of the patients. 18 of the 96 original patients had known HF and we found another 5 with unknown HF, all with HF and preserved ejection fraction (HFpEF), among the 24 that joined the study. Based on this, we estimated under-

diagnosis of HF (HFpEF) in a population with HF symptoms that was not properly examined to 21%.

1.5 DISCUSSION

General comments

HFpEF patients are to a large extent (17-36%) managed in PC. They have low quality of life, high morbidity and the costs for care are substantial. In spite of this there is limited knowledge on HFpEF in PC and a need for further research.

In the field of medical research, quality registries provide a unique possibility to obtain and analyze large data bases. Sweden's personal number system further gives opportunities to link data from a registry to other national registries, thus creating even more information upon the different cohorts of patients. The SwedeHF is one of the largest heart failure registries in the world, both in the number of patients and the amount of variables, and has been the base for many scientific publications. Collecting corresponding data on HFpEF in PC without a quality registry would be very difficult and time-consuming.

Of obvious importance when analyzing data is that the diagnosis of the disease is correct. When discussing HFpEF this is of extra interest since the diagnosis is depending on well-performed echocardiographic examinations with specific diagnostic criteria. We compensated for the lack of echocardiographic examinations by excluding patients without information upon the examination (16 % in the PC registry). Thus, we only had patients with knowledge of EF left. Still the registry does not contain information about the other requiered information concerning diastolic function and structural changes, wherefore the diagnosis is based on clinical judgement and EF. Patients in SwedeHF, and in our studies, are also prospectively registered from 2001, and criteria of diastolic HF have endeed changed since we started our study. SwedeHF also lack information concerng some important coconmittent diseases as MT and psychologic disorders.

Finally, studying HFpEF patients without any other disease would perhaps be optimal to really identify the unique character of the disease. However, such a scenario is only existing in the imagination. The real-world panorama is, as this thesis shows, quite opposite.

Characteristics

Patients with HFpEF managed in PC are characterized by higher age and a larger proportion of women than those managed in HC. Further there are more patients with an EF≥50% and this is most pronounced among women. Furthermore, patients in PC have higher blood

pressure and more kidney dysfunction than those managed in HC, perhaps reflecting that patients in PC suffer from multi-organ damage and that HFpEF in this cohort is merly a part of a more complex and pathological aging. In contrast to HFrEF patients, where IHD is dominating as an obvious, and easy to identify, cause of HF, patients with HFpEF in PC stands out as a noticeably heterogenous group. Many of their various diseases affect each other, for example HF and kidney disease, HF and COPD, HF and DM, HF and malignant tumors, and in the individual case it may be difficult to identify which disease or diseases are most responsible or the most important for the pathological process and should be treated most intensively. In the light of this kaleidoscope of diagnosis it is easier to understand why RCTs so far have been unable to find a single evidence-based therapy for HFpEF. Perhaps a more thourough matching for different comorbidities in this population would help to identify target groups for specific treatments.

Comorbidity and risk factors

A common finding in the first three studies is the large frequency and possible importance of comorbidities. These comorbidities are important diseases that all may interfere with the pathophysiology of HFpEF and we have found that they all in different ways have their own association with morbidity and mortality. Various mechanisms are likely for this interference, the comorbidity itself may lead to extended stress on a failing heart, as in the case of DM and COPD, but may also contribute to missing diagnosis as the symptoms of, for example COPD, may resemble those of HF and prevent further investigations. Advanced malignant tumors have also potential to stress the failing heart but are reasonably not likely to lead to underdiagnosis. It is a well established insight that managing HF patients requires careful monitoring of all other factors, and maybe the burden of comorbidities must be correlated to the fragility of HF patients where one more disease is actually one to many. Especially in the group with EF≥50% among women we have seen that more than half of the deaths are caused by other factors than cardiovascular diseases. Given the complexity of the HFpEF group with elderly patients in PC it is also understandable that the risk factors for worse prognosis were different from patients with HFpEF managed in HC. Besides this, it must be kept in mind that SwedeHF only contains information about six other comorbidities whereas a GP every year handles hundreds of other diagnoses, many of which probably also may affect HFpEF patients. Treating HFpEF constitutes a major problem, numerous randomized trials have not been able to convincingly produce evidence for effective treatments. In light of this, and the insights that comorbidities play a central roll for the prognosis in PC, diagnosing and treating

these comorbidities stands out as a major task when managing HFpEF patients. This is an even more challenging mission since these comorbidities often interact and affects their various treatments. In our study we also found a different pattern in HC patients, where there was more use of RAS- and betablockade, perhaps reflecting a more severe form of disease in HC or the fact that PC physicians, with all other diagnosis to attend to, sometimes may miss to fully initiate this medication. Interestingly though, many of these patients should not be treated with these substances for their HFpEF according to guidelines but it may be that they suffer from other diseases that requires the therapy. It is important to be aware of that we, to some extent, are a bit spoiled by the fact that patients with HFrEF have an evidence-based treatment including RAS-antagonists and BBs, which work very well in most patients. However, patients with HFpEF in PC have a very different etiology of their HF, and therefore they require another diagnostic and treatment approch.

The prognostic value of NT-proBNP

The use of NT-pro BNP is well established as a rule-out tool when diagnosing HF but its prognostic significance for HFpEF patients in PC has not been described until now previously. We found that there is a statistically significant association between high NT-proBNP levels and all-cause mortality on a group level. However, due to high standard deviations, the clinical usefulness seems limited. The single patient in a GPs office with a certain NT-proBNP value may have either a bad or a good prognosis, measuring this will not help us. Instead, carefully diagnosing and managing risk factors and comorbidities is possible to perform and will actively influence the patients prognosis.

Gender perspectives

We found in our study significant differences between men and women with HFpEF, both when it comes to age, prognosis and morbidity. This is in line with previous studies, but these studies have mainly been performed on patients managed in HC. The differences between the sexes were most pronounced in the group with EF≥50% where women have a more varied pattern of causes of death, perhaps reflecting partly different types of disease. We showed that men have a higher age-adjusted mortality. Men are also more often smokers and have more IHD, factors that may, at lest partly, explain the higher mortality. Women further have

lower functional capacity, in turn possibly coherent with higher age and multiple comorbidities.

Diagnostics

Numerous studies before have shown diagnostic difficulties for HFpEF in PC, and that adherence to guidelines is limited. Following these guidelines would otherwise help the clinician to properly diagnose not only HF itself but also the type of HF. This, in turn, is essential as wrong diagnosis may lead to potentially harmful wrong treatment and further a lack of knowledge and research upon HFpEF. As mentioned above, in our study we have not been able to thoroughly identify whether the patients in SwedeHF classified as HFpEF have all the diagnosric criteria that are required and the diagnose is based on clinical judgement and a preserved EF. This is partly understandable since the patients were prospectively registered from 2001, when the criterias were different, but may also signify, to some extent wrong diagnosis. We have found in our studies a one-year mortality of approximately 7% but since only around 55% die from cardiovascular diseases there is a possibility that the other 45% have another disease, more important than the heart function. If so, one-year mortality for those with a more reliable diagnose of HFpEF would be only around 4%. Compared to normal one-year mortality for people of this age this is not a high figure which may lead to the perception that this is not a fatal disease but it must be kept in mind that the effects on quality of life and morbidity of HFpEF is substantial.

Our fourth study, performed under nowadays conditions, indicate though that there is still room for improvement of the diagnostics. An alternative way to help the clinician to pay attention to the condition could be to encourage the patients to address the question of HFpEF, being alerted via a self-test on the internet.

Limitations

The SwedeHF is one of the largest HF registries in the world. However, participating in the registry is not mandatory in Sweden. Therefore, there is a risk that PC units reporting to the registry are more interested in HF and more dedicated to managing HF patients and following the current guidelines, potentially leading to a selection of PC units not being representative of Swedish PC in general. Possibly the PC cohort in the present study might show better results than a study of PC units, in general, would do.

Another circumstance of importance, mentioned above, is that the registry does not provide information on all possible comorbidities that may influence outcome and prognosis. Further, as commented under Diagnostics, is that we have no information on whether the diagnosis of HFpEF has been thoroughly established according to the ESC classification. This is a clear limitation, as well as the fact that we do not know exactly when in the clinical course the NT-proBNP values was examined. However, we know that samples most often, according to local routines, are taken in conjunction with the visit.

1.6 CONCLUSIONS

HFpEF- patients managed in PC, are characterized by higher age, higher proportion of women and more patients with EF≥50% than patients managed in HC. **Study I**

Mortality for HFpEF patients in PC is not higher than for out-patients in HC. In total, 97% of the patients have more than one disease. Various comorbidities and other factors contribute to mortality and must be treated carefully. **Study I**

An increased NT-proBNP level is associated with increased all-cause mortality in HFpEF-patients. However, its clinical usefulness to diagnose or rule out a poor prognosis on individual base is limited due to high SDs and the fact that NT-proBNP is not independent in this population which is characterized by large heterogeneity, many comorbidities and high age. **Study II**

Men with HFpEF managed in PC have more IHD, AF and diabetes whereas women have more HT and kidney dysfunction. Men have higher age-adjusted mortality, but women have worse functional capacity. **Study III**

Cardiovascular diseases are the dominating causes of death among both women and men but more than a third of the deaths are caused by other diseases where respiratory diseases and malignant tumors dominate. In the group with women with EF≥50% this was even more pronounced with more than half of the deaths caused by non-cardiovascular diseases. Altogether 13 different causes of death were noted. This illustrates the complexity of this group of HF patients and the need to carefully diagnose and treat all associated comorbidities. **Study III**

We found a potential underdiagnosis of HF in 21% of the studied patients. All these patients had HFpEF and 80 % were women. **Study IV**

An on-line self-test for HF may help patients to pay attention to the disease and thus help the clinician. Evaluation of such a test to diagnose HF showed an acceptable sensitivity (80 %) to find HF and a high negative predictive value of 93 % to rule out the diagnose. The sensitivity and negative predictive values were equal to those of the combined use of ECG and NT-proBNP to diagnose new onset of HF. **Study IV**

1.6.1 Future perspectives

A common group of patients, from a GPs point of view, is the elderly women with many comorbidities, seeking for tiredness and lack of strength. Many of these women may well have HFPEF. In the light of the knowledge, from this thesis, upon the complexity of this group, with its broad spectrum of comorbidities and different causes of death, future research on diagnostics and treatment is important. The results of this thesis indicate that treatment of HFpEF-patients should focus more on concomitant diseases and medical history, for example CV-diseases and HFpEF, COPD and HFpEF, malignant tumors and HFpEF and so on. Such an approach would probably lead to a more individualized management.

Forthcoming research should further focus on the combination of COPD and HFpEF among both men and women as well as the effects of anemia and kidney dysfunction on HFpEF patients. This area was only partly studied in this thesis but is of vital importance in this elderly population.

Of great interest would also be to more in detail study the group of patients that die from another cause of death than cardiovascular diseases and to cooperate with resarchers in other fields, such as oncology, to deeper analyze the potential of missing HFpEF and treatment possibilities.

1.7 SVENSK SAMMANFATTNING/SWEDISH SUMMARY

Bakgrund

Hjärtsvikt med bevarad ejektionsfraktion (HFpEF) är ett sjukdomstillstånd associerat med låg livskvalitet, hög sjuklighet och dödlighet. Tillståndet utgör en diagnostisk utmaning och det finns ingen vetenskapligt bevisad effektiv behandling. Trots hög prevalens och det faktum att många (17-36%) av dessa patienter sköts i primärvården (PV) har de flesta studier utförts i sjukhusmiljö (SV).

Syfte

Syftet med denna avhandling är att beskriva HFpEF i PV, karakteristika, betydelsen av andra samtidigt pågående sjukdomar och dödlighet. Vidare att belysa prognostiska och diagnostiska svårigheter samt potentiell underdiagnostik.

Metod

De första tre studierna baseras på det svenska hjärtsvikts-kvalitetsregistret Rikssvikt. Patienter som saknade ekokardiografisk undersökning (16%) exkluderades. Totalt studerades 1802 patienter från PV och 7852 från SV, alla med en ejektionsfraktion ≥ 40% med avseende på samsjuklighet, riskfaktorer och förlopp. PV jämfördes med SV i den första studien.

I den andra studien analyserades den prognostiska betydelsen samt värdet av att mäta N-terminal Brain Natriuretic Peptide (NT-proBNP) hos HFpEF patienter i PV. 924 patienter; 360 med EF 40-49%, Heart Failure with Midrange Ejection Fraction, (HFmrEF) och 564 patienter med EF≥50% (HFpEF).

Den tredje studien analyserade könsskillnader och baserades på de 1802 patienterna i studie I, uppdelade på HFmrEF och HFpEF.

Den fjärde studien utfördes på Gustavsbergs VC. 96 patienter som sökt vårdcentralen under en tremånads-period för ett vanligt hjärtsviktssymptom som andfåddhet, bensvullnad eller trötthet inkluderades för att identifiera eventuell underdiagnostik samt för att evaluera ett internet-baserat självtest för hjärtsviktsdiagnostik.

Resultat

HFpEF-patienter I PV var äldre med en större andel kvinnor jämfört med SV. Endast 2.8% hade ingen samsjuklighet alls och 1-årsmortaliteten var 7.8%. Rökning, KOL, diabetes mellitus, ålder och hjärtfrekvens befanns vara oberoende riskfaktorer för ökad mortalitet i PV. Ekokardiografiska undersökningar saknas ofta. I en matchad kontrollgrupp förskrevs mer RAS- och betablockad I SV jämfört med PV. Studie I.

Det fanns en klar association mellan NT-proBNP-nivåer och mortalitet men bara på gruppnivå. Ett flertal variabler var associerade med ökade nivåer av NT-proBNP och även oberoende med ökad mortalitet. Studie II.

Män hade högre ålders-justerad mortalitet än kvinnor. Hos kvinnor med HFpEF hade över hälften en annan dödsorsak än kardiovaskulära sjukdomar. De dominerande andra dödsorsakerna var maligniteter och lungsjukdomar men totalt identifierades 13 andra dödsorsaker. Studie III.

Vi fann en underdiagnostik av hjärtsvikt ise kommentar ovan, 21% .samtliga kvinnor. Vi fann även en acceptabel tillförlitlighet för det internet-baserade hjärtsviktssjälvtestet. Studie IV.

Slutsats

Patienter med HFpEF i PV utgör en heterogen grupp med hög ålder och många andra sjukdomar som kan påverka hjärtsviktsförloppet men också, oberoende och var för sig, är associerade med sjuklighet och dödlighet. Patienterna är äldre (medelålder 78 år) och andelen kvinnor är högre (46.7% vs 36.3 %) jämfört med de som sköts inom SV. Det finns ingen vetenskapligt dokumenterad behandling som fungerar för hela gruppen.
Resultaten i denna avhandling talar för att HFpEF-patienter inom PV har en åldersrelaterad multi-organ skada vilket ställer krav på noggrann diagnostik och ett individualiserat omhändertagande. Det finns också en betydande risk för underdiagnostik.

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