

Heart failure in the elderly
Clinical phenotype, prognosis and influencing factors

Rúna Björg Sigurjónsdóttir

Department of Molecular and Clinical Medicine
Institute of Medicine
Sahlgrenska Academy at University of Gothenburg



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runa.sigurjonsdottir@vgregion.se

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*“Our greatest weakness lies in giving up.
The most certain way to succeed is always to try one more time”*

Thomas A. Edison

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Sahlgrenska Academy at University of Gothenburg
Gothenburg, Sweden

ABSTRACT

Background: Heart failure has high morbidity and mortality and the incidence increases with age. Most randomized studies in heart failure were conducted in younger heart failure patients, despite the fact that the majority of the heart failure population is elderly. Therefore, the clinical phenotype and prognosis in elderly heart failure patients have been inadequately studied.

Aims: To characterize the clinical phenotype and study the prognosis of the elderly heart failure population, with focus on co-morbidities and biomarkers in three main categories of heart failure: heart failure with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF) and post-infarction HF.

Methods: This thesis comprises four parts: 1) a retrospective study on differences in clinical phenotype between the younger and older heart failure populations and between different heart failure categories in 24236 patients by accessing The Swedish Heart Failure Registry; 2) a prospective study on the correlation between red cell distribution width (RDW) and cardiac function between different heart failure categories in 296 patients referred for echocardiography; 3) a prospective study of 138 elderly acute coronary syndrome (ACS) patients, on prognosis in terms of major adverse cardiovascular events (MACE), including post-ACS heart failure and quality of life during a 3 year follow-up; 4) a retrospective study of 494 patients on all cause mortality and factors influencing mortality in different heart failure categories after 5 years of follow-up.

Results: When compared to the younger heart failure population, the elderly heart failure population had more co-morbidities and more often HFpEF, in addition they received less life-saving therapy. Mortality rates increased with age and were higher for HFrEF than HFpEF. Moreover, prognostic factors varied between different categories of heart failure. In spite of advanced treatment of ACS patients, post-ACS heart failure was still common and was coupled with worse quality of life.

Conclusion: Heart failure in the elderly is a unique clinical entity, not only when it comes to clinical characteristics but also in prognosis and its influencing factors. In the elderly, co-morbidities not only more often accompany heart failure but also affect the clinical phenotype and prognosis and therefore co-morbidities should be regarded as an important part of heart failure.

Keywords: Heart failure, elderly, prognosis, co-morbidities

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SAMMANFATTNING PÅ SVENSKA

Bakgrund: Hjärtsvikt har hög morbiditet och dödlighet och incidensen ökar med ålder. Flesta randomiserade studier som har gjorts har enbart inkluderat yngre hjärtsviktpatienter. Det finns ett begränsat antal studier på hjärtsvikts patienter äldre än 70 år, även om de utgör den största åldersgruppen i hjärtsviktspopulationen. Därför är det viktigt att bättre förstå den kliniska fenotypen i den äldre hjärtsviktspopulationen samt deras prognos.

Frågeställning: Att karakterisera den kliniska fenotypen i den äldre hjärtsviktspopulationen samt studera prognosen i den populationen med fokus på biomarkörer och komorbiditeter i tre kategorier av hjärtsvikt: hjärtsvikt med nedsatt ejektion fraction (HFrEF), hjärtsvikt med bevarad ejektion fraction (HFpEF) och hjärtsvikt efter hjärtinfarkt.

Metodik: Arbetet är indelat i 4 delar: 1) en retrospektiv studie med användning av nationellt register för hjärtsvikt. Där har vi studerat skillnaden i komorbiditeter mellan yngre och äldre hjärtsviktpatienter samt mellan olika kategorier av hjärtsvikt; 2) en prospektiv studie med 296 patienter som genomgått ultraljud av hjärta, för att undersöka kopplingen mellan en biomarkör (RDW) och hjärtfunktion mellan olika hjärtsviktskategorier; 3) en prospektiv studie på 138 äldre patienter med akut kran-skärlssjukdom för att titta på prognosen i form av händelser som bl.a. hjärtsvikt efter hjärtinfarkt och livskvalitet under 3 års uppföljningstid; 4) en retrospektiv studie av 494 patienter för att utvärdera 5 års dödlighet hos patienter med hjärtsvikt och jämföra mellan olika hjärtsviktskategorier samt att identifiera faktorer som påverkar dödligheten.

Resultat: Till skillnad från den yngre hjärtsviktspopulationen har den äldre hjärtsviktspopulationen mer komorbiditeter samt oftare HFpEF, dessutom är de oftare underbehandlade. Dödligheten ökar med ökad ålder och är högre för HFrEF än HFpEF. Det är olika faktorer som påverkar dödlighet i olika hjärtsviktskategorier. Trots nuvarande avancerad behandling av hjärtinfarkt är hjärtsvikt efter hjärtinfarkt fortfarande vanlig händelse med sämre livskvalitet jämfört med de som inte får hjärtsvikt.

Slutsats: Hjärtsvikt hos äldre är en unik klinisk entitet i flera aspekter så som klinisk fenotyp, prognos och faktorer som påverkar prognosen. Komorbiditeter är inte bara vanligare hos den äldre hjärtsviktspopulationen men de påverkar även den kliniska fenotypen och prognosen och bör därför betraktas som en viktig del i hjärtsviktsyndromet.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I Holmström A, Sigurjonsdottir R, Edner M, Jonsson Å, Dahlström U, Fu M. Increased comorbidities in heart failure patients ≥ 85 years but declined from >90 years: Data from the Swedish Heart Failure registry. *Int J Cardiol* 2013; 167: 2747-2752
- II Holmström A, Sigurjonsdottir R, Hammarsten O, Gustafsson D, Petzhold M, Fu M. Red blood cell distribution width and its relation to cardiac function and biomarkers in a prospective hospital cohort referred for echocardiography. *Eur J Int Med* 2012; 23:604-609
- III Sigurjonsdottir R, Barywani S, Albertsson P, Fu M. Long-term major adverse cardiovascular events and quality of life after coronary angiography in elderly patients with acute coronary syndrome. *Int J Cardiol* 2016; 222: 481-485
- IV Sigurjonsdottir R, Kontogeorgos S, Johansson M C, Albertsson P, Fu M. Long-term outcome and influencing factors in different categories of heart failure in the elderly. *Submitted*

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ABBREVIATIONS

ACEI	Angiotensin converting enzyme inhibitors
ARBs	Angiotensin receptor blockers
ACS	Acute Coronary Syndrome
BB	Beta blockers
CHF	Chronic heart failure
ESC	European Society of Cardiology
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrfEF	Heart failure with reduced ejection fraction
HFmrEF	Heart failure with mid-range ejection fraction
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
NT-proBNP	N-terminal of the pro-hormone Brain Natriuretic Peptide
NYHA	New York Heart Association classification
PCI	Percutaneous coronary intervention
QoL	Quality of life
RDW	Red blood cell distribution width

INTRODUCTION

The aim of this thesis was to characterize the clinical phenotype and study the prognosis, as well as its influencing factors, of the elderly heart failure population, with focus on co-morbidities and biomarkers in three main categories of heart failure: heart failure with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF) and post-infarction HF.

History of heart failure

The earliest descriptions of the symptoms of heart failure such as edema and dyspnoea date back to ancient Greek and Roman texts [1] and the Romans used foxglove as medicine [2]. In Hippocrates time, rales were described by listening with the ear against the chest and pleural effusion was diagnosed by vigorously shaking the patient [3]. However, it was not until much later, in 1628 that it was understood that the heart is a pump that provides blood to the tissues [4]. In the centuries that followed, descriptions of the structure of the failing heart following autopsies became prominent and the investigation of heart failure improved by the discovery of X-rays by Röntgen and the development of electrocardiography in 1890s by Einthoven [2]. However, the pathophysiology behind heart failure was poorly understood until Starling published his law in 1918 [5]. This added to the understanding of the hemodynamics of the healthy heart and much later to the understanding of the failing heart. On the other hand, descriptions on mortality came earlier, when Corvisart described two modes of death of heart failure patients in 1812, with slowly advancing disease and sudden death [6]. However, it is only in the late 20th century that effective means of treating heart failure with beta blockers and ACE inhibitors were discovered that actually decreased mortality and morbidity [7, 8].

HFpEF was first described in 1982 in geriatric patients. However, initially there was a debate as to whether it even existed and had a cardiac basis or was a part of the normal aging process [9]. Later, studies showed not only that HFpEF existed but that it was a common condition and increasing in prevalence [10, 11]. To date, there is still no proven effective treatment that decreases mortality in HFpEF as results have been contradictory in studies on ACE/ARB [12-19], Beta blockers [20-28] and mineral corticoid receptor antagonists [29-34].

The elderly

According to WHO health statistics and information systems, most developed countries have accepted 65 years of age as the definition of elderly but the UN agreed cutoff for the older population is 60+.

The reason for the 65 years of age cut-off has been that this is a common age for retirement. However, with increasing life expectancy, some countries have already raised the retirement age or discuss doing so. Therefore, 65 years may be an inappropriately low cut-off for the elderly. In addition, there is no universal cut-off for elderly heart failure patients and previous studies have had the cut-off at 70 to 80 years [35-38], while >85 year old patients are often classified as the very elderly [39].



Figure 1. Licensed from stock.adobe.com.

Definition of heart failure

Heart failure is described in the European Society of Cardiology (ESC) heart failure guidelines 2016 as a clinical syndrome with typical symptoms, and sometimes signs, caused by structural/functional cardiac abnormality, resulting in reduced cardiac output and/or elevated intra-cardiac pressures at rest or during stress. The symptoms typical of heart failure are breathlessness, ankle swelling and fatigue. The signs are elevated jugular venous pressure, pulmonary crackles and peripheral edema [40]. However, there are many other definitions available and the most quoted one is Braunwald's definition: The pathological state in which an abnormality of cardiac function is responsible for failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues, or to do so only from an elevated filling pressure [41].

Prevalence and incidence of heart failure

Approximately 1–2% of the adult population in developed countries has the diagnosis of heart failure, and the lifetime risk of 40 year olds to develop heart failure is 1 in 5. The prevalence increases with age, rising to $\geq 10\%$ in those over 70 years of age [42–45]. In epidemiological studies, the mean age at first diagnosis of heart failure has increased over the years, to now being at least 80 years old [46]. In Sweden in 2010 the mean age at first diagnosis of heart failure was 77 years, with a prevalence of 2.2% and incidence of 3.8/1000 person-years. In addition, more than 90% of the patients were 60 years and older [47]. The incidence of HFpEF increases with age [48]. Up to 50% of the elderly heart failure population has been reported to belong to the HFpEF group [49]. With increased life expectancy and improved heart failure management, in particular in HFrEF and in the younger heart failure population, it is estimated that the prevalence of heart failure will increase by 46% from 2012 to 2030 [45, 50].

Pathophysiology of the aging heart

With age there is a decrease both in number and in function of myocytes, even in subjects without evidence of cardiovascular disease. This happens because of enhanced necrosis and apoptosis along with reduced regenerative capacity of cardiac progenitor cells. The loss of functioning cardiomyocytes is compensated by hypertrophy of the remaining cells [51, 52]. Also, the myocyte function changes with age. The calcium metabolism and regulation becomes impaired causing an alteration in the process of contraction and relaxation [53]. At the same time, there is an imbalance of extracellular matrix metabolism with a subsequent detrimental increase in myocardial collagen content and development of fibrosis. These changes, along with shortening of telomeres in advancing age, have been associated with worsening cardiac function and development of heart failure [54, 55] irrespective of type of heart failure.

However, there are studies showing differences in molecular aspects of HFpEF compared with HFrEF. In particular, the cytoskeletal protein, titin, which functions as a bidirectional spring and is responsible for early diastolic left ventricular recoil and late diastolic resistance to stretch [56]. Patients with HFrEF have a more compliant isoform of titin than those with HFpEF [57].

Main categories of heart failure

Roadmap for diagnosis of heart failure

According to the 2012 ESC heart failure guidelines [58] the diagnosis of HFrEF requires three conditions to be satisfied:

1. Symptoms typical of HF
2. Signs typical of HF
3. Reduced LVEF

And the diagnosis for HFpEF requires four conditions to be satisfied:

1. Symptoms typical of HF
2. Signs typical of HF
3. Normal or only mildly reduced LVEF and left ventricle not dilated
4. Relevant structural heart disease (Left ventricular hypertrophy/Left atrial enlargement) and/or diastolic dysfunction

Typical symptoms of heart failure are: breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, reduced exercise tolerance, fatigue/tiredness/increased time to recover after exercise and ankle swelling [40].

Typical signs of heart failure are elevated jugular venous pressure, hepatojugular reflex, third heart sound (gallop rhythm) and laterally displaced apical impulse [40].

However, the 2016 ESC heart failure guidelines [40] have made some updates compared to the 2012 guidelines. Regarding diagnosis, one change is a new heart failure category, i.e. Heart failure with mid-range ejection fraction (HFmrEF). Another change is a modification of the diagnostic criteria for HFpEF.

Type of HF	HFrEF	HFmrEF	HFpEF
1	Symptoms ± Signs	Symptoms ± signs	Symptoms ± Signs
2	LVEF <40%	LVEF 40-49%	LVEF ≥ 50%
3		1. Elevated levels of natriuretic peptides 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE) b. diastolic dysfunction	1. Elevated levels of natriuretic peptides 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE) b. diastolic dysfunction

LVH = left ventricular hypertrophy, LAE = left atrial enlargement

The *post infarction heart failure* diagnosis in this thesis was made according to the following criteria [59]:

1. Early post infarction heart failure

- a. Reduced ejection fraction <50% and symptoms or signs of heart failure within 7 days of admission with acute myocardial infarction (AMI) or ACS, or
- b. Preserved ejection fraction but signs and symptoms of heart failure within 7 days of admission as well as diastolic dysfunction or other structural cardiac abnormality (left ventricular hypertrophy, left atrial enlargement)
- c. Absence of heart failure before index AMI or ACS

2. Late post infarction heart failure – same criteria as above but with occurrence later than 7 days after admission with AMI/ACS and after excluding other possible reasons for new onset heart failure, such as new onset of atrial fibrillation.

HFpEF vs. HFrEF

Although morbidity patterns and functional decline are similar in patients with HFpEF and those with HFrEF, HFpEF represents a greater challenge because there is no proven treatment to improve mortality and morbidity, despite efforts in the past two decades. Therapies effective for HFrEF, including angiotensin-converting enzyme inhibitors (PEP-CHF), angiotensin receptor blockers (CHARM-PRESERVE, I-PRESERVE), mineral corticoid receptor antagonist (TOPCAT) and beta-blockers (J-DHF), have not been shown to improve outcome in HFpEF in randomized studies [12, 14, 18, 28, 32]. However, some registry studies and meta-analysis have shown improved survival in HFpEF patients with the use of ACEI/ARB, beta blockers and mineral corticoid receptor antagonists [15-17, 20-24]. Therefore, the results are ambiguous and further studies are needed on the subject.

Because HFrEF and HFpEF have distinctly different structural remodeling patterns and responses to therapy, these two subtypes of chronic heart failure (CHF) are now

thought to have a fundamentally different pathophysiology. A recently proposed mechanism for the development of HFpEF identified a systemic pro-inflammatory state, induced by co-morbidities, as the primary cause of HFpEF [60, 61]. According to this hypothesis, a high prevalence of co-morbidities such as overweight/obesity, diabetes mellitus, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea and hypertension, induces a systemic pro-inflammatory state causing coronary microvascular endothelial inflammation. Coronary microvascular endothelial inflammation results in stiff cardiomyocytes and interstitial fibrosis that contribute to increased diastolic left ventricular stiffness and the development of HF [60, 61]. In recent years, growing recognition of the importance of co-morbidities in HFpEF has led to the realization that HFpEF may actually represent a spectrum of co-morbidities in elderly patients with HFpEF.

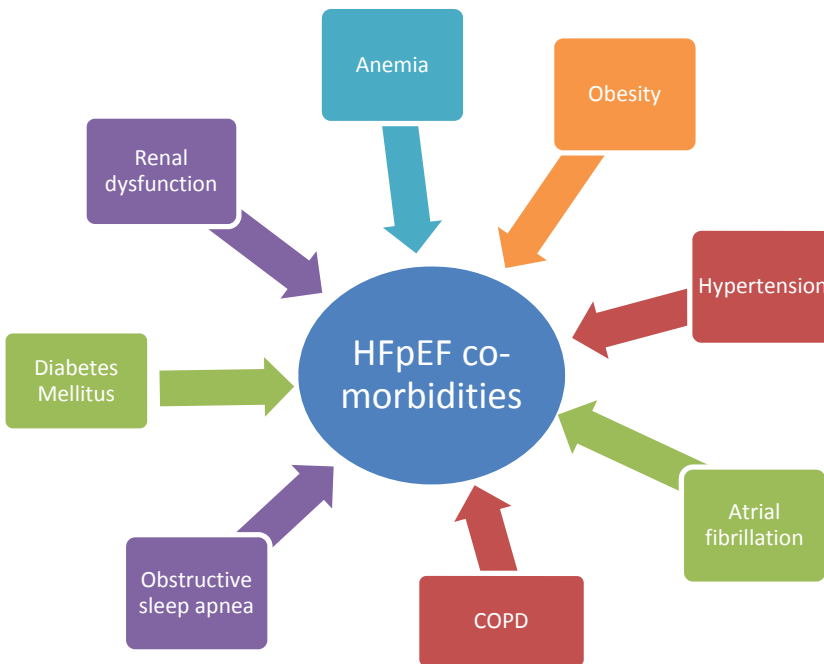


Figure 2. Different co-morbidities in HFpEF.

Risk factors and co-morbidities in heart failure

Most of heart failure patients have antecedent hypertension [62], which together with ischemic heart disease are considered the most common risk factors for heart failure. Other risk factors are smoking, diabetes and obesity [63]. In the Swedish Heart Failure Registry annual report from 2015, 52% of the patients had atrial fibrillation. The most common co-morbidities in HFpEF were hypertension (61%) and atrial fibrillation (59%) while in HFrEF it was ischemic heart disease (52%) [64]. However, there are studies showing that ischemic heart disease is also an important co-morbidity in HFpEF and its presence is coupled with increased mortality [65].

Non-cardiac co-morbidity is a striking feature in heart failure. 74% of heart failure patients have one or more co-morbidities and 55% of heart failure patients have 5 or more co-morbidities and the most common are renal disease, anemia and diabetes mellitus [66, 67].

However, identification and grading of the severity of co-morbidities is challenging in HFpEF, partly because the symptoms are often overlapping between different co-morbidities and between co-morbidity and heart failure, and partly because some co-morbidities are not symptomatic in the early stage despite the fact that they may have a negative impact on cardiac function/structure in the long run. Therefore, it is difficult to obtain a complete picture of the co-morbidities and their severity without a systematic screening with a thorough objective examination. The data available for the evaluation of co-morbidities so far is insufficient in order to determine their severity. Thus, the impact of co-morbidities in HFpEF is poorly understood because data were often obtained from patient reports or registries in which the data were not sufficiently validated. Moreover, information about the severity of co-morbidity is rarely available.

Heart failure treatment

Guideline directed medical therapy (GDMT)

HFrEF treatment consists of evidence-based pharmacological treatment, cardiac device treatment, coronary reperfusion therapies, mechanical circulatory support, heart transplantation and holistic management including exercise training and multidisciplinary management programs, patient monitoring, and palliative care in end stage heart failure. However, HFpEF treatment consists mostly of treating co-morbidities and decreasing congestion with diuretics and relieving symptoms.

Pharmacological treatment

In HFrEF neurohormonal blockers such as ACEI/ARBs, beta-blockers and mineral-corticoid receptor antagonists have been proven to decrease morbidity and mortality and are recommended in all HFrEF patients as they are fundamentally important in modifying the course of HFrEF. They are often used together with a diuretic to relieve symptoms and signs of congestion. In addition, angiotensin receptor neprilysin inhibitor is now recommended as a replacement for ACEI to further reduce the risk of HF hospitalization and death in patients who remain symptomatic despite optimal treatment with ACEI/ARB, beta-blockers and mineralcorticoid receptor antagonists [40]. Also, in patients who poorly tolerate high doses of beta blockers or have a resting heart rate above 70 beats per minute despite highest tolerated beta blocker dose, Ivabradine should be considered [40].

In HFpEF there is still no proven medical treatment that improves morbidity and mortality. Therefore the guideline recommended treatment thus far is to treat both cardiovascular and non-cardiovascular co-morbidities. Also, diuretics will usually reduce congestion and improve the symptoms and signs of HF. In addition, endurance/resistance training may help these patients improve exercise capacity and physical functioning score [40].

Devices

In HFrEF implantable cardiac defibrillators (ICDs) are recommended as a secondary prevention in patients who have had ventricular tachycardia but also as a primary prevention in symptomatic HFrEF patients with LVEF $\leq 35\%$ despite optimal medical treatment, as it has been proven to reduce the risk of sudden death and all-cause mortality. Moreover, cardiac resynchronization therapy (CRT) is recommended for symptomatic HFrEF patients with a QRS duration ≥ 130 ms and LBBB morphology and LVEF $\leq 35\%$ despite optimal medical therapy in order to reduce morbidity and mortality, and CRT should also be considered for patients with QRS ≥ 150 ms and non-LBBB morphology as well, provided they fulfill the other abovementioned criteria. In HFpEF there is no evidence showing that devices help reduce mortality or morbidity [40].

Current implementation of treatment in HF

A recently published study by M. Komajda et al. showed that adherence to guideline recommended treatment in HFrEF is quite high when prescribing ACEI/ARB (86.7% treated), beta blockers (86.7% treated) and mineral-corticoid receptor antagonists (69.3% treated). However, there were few patients that received ivabradine (33.4%). Moreover, the dosage of the recommended medications was low in most instances with only 27.9% of patients on ACEI reaching target dose and only 14.8% of patients on beta blockers reached target dose. In addition, the proportion of patients with devices (ICD, CRT-D) was low, with only 9% of patients having an implanted device [68]. This calls for an improvement in the up-titration of recommended treatment as well as implementation of devices.

Prognosis in heart failure

Mortality in HF

The one year mortality rate for heart failure patients in Sweden in 2015 was 18.6 % according to the Swedish Heart Failure Registry annual report. The mortality rate increases steeply with increased age and in the registry the patients that were <65 years of age had an annual mortality rate of 5.4% while patients aged >85 years had an annual mortality of 39% [64]. Previous studies have shown improved survival in heart failure patients over the years with contemporary therapies, even in the elderly cohort [45, 46]. Despite this achievement, the mortality rate remains high and approximately 50% of people diagnosed with heart failure will die within 5 years [62, 69].

Prognosis in post infarction HF

In patients with ACS, around 25-30% develop heart failure and a staggering 40% develop left ventricular systolic dysfunction [70-72]. However, studies on post ACS heart failure in the elderly are limited despite the fact that most of ACS patients are elderly.

In previous studies on post infarction heart failure the one year mortality rates have ranged from 12-39% [72-74] but some of those studies were conducted before the current recommended treatment with early percutaneous coronary intervention (PCI) and

medication with statins, dual anti-platelet therapy, ACE inhibitors and beta blockers. Patients with left ventricular systolic dysfunction (LVSD) after a myocardial infarction have a 3 to 4 fold increased risk for death compared with patients who do not have LVSD [75]. Compared with patients with asymptomatic LVSD, patients who develop post infarction HF are at a higher risk for adverse outcomes, including cardiac rupture, cardiac arrest, stroke, longer hospitalizations, ventricular arrhythmias, recurrent myocardial infarction and death [76].

Readmissions

Repeated hospitalizations are common in heart failure patients. Dunlay et al studied hospitalizations after a heart failure diagnosis and found that 83% of the patients followed had one or more hospitalizations during the follow-up period. Also, for each year after a HF diagnosis patients were hospitalized nearly once per year [77]. Moreover, only 16.5% of readmissions were because of heart failure, other reasons were other cardiovascular events (21.6%) and more than half were non-cardiovascular reasons (61.9%). Independent predictors of hospitalization were male sex, diabetes mellitus, anemia, chronic obstructive pulmonary disease (COPD) and impaired kidney function [77]. Another study showed that in one year 65% of the heart failure cohort had at least one hospitalization, of which 50% were potentially preventable. The group with most co-morbidities accounted for most of the hospitalizations and the co-morbidities associated with higher hospitalization rate and higher mortality were COPD, renal failure, diabetes, depression and other lower respiratory diseases [78]. Co-morbidities lead to 21-34% of readmissions and the most common reasons for readmissions were hypertension, diabetes, metabolic syndrome, atherosclerotic disease, anemia and depression [79].

Quality of life

Heart failure patients have a reduced quality of life (QoL) compared with the normal population, and the poor QoL seems to be similar between HFpEF and HFrEF [80, 81]. In addition, studies have shown a correlation between functional status and self assessed quality of life with questionnaires [82]. Many questionnaires are available for assessment of quality of life. The one used in this thesis is the Swedish version of the medical outcomes study short form 36 (SF-36). It is a norm-referenced measure of QoL and contains 36 items to measure 8 QoL domains from the patient's point of view: physical functioning, physical role, bodily pain, general health perceptions, vitality, social functioning, emotional role and mental health. The Swedish version of SF-36 has shown good reliability and validity [83, 84]

Prognosis in HFrEF vs. HFpEF

Previous studies have shown contradicting results when it comes to mortality rates in different heart failure categories. Some studies have shown a higher mortality rate in HFrEF compared with HFpEF while in other studies there was no significant difference in mortality rates between the two heart failure categories [13, 85-90]. One possible reason for this divergence in prognosis between HFrEF and HFpEF in previous studies could be due to different inclusion criteria applied. For example, cut-off

values for left ventricular ejection fraction (LVEF) in HFpEF have varied from 40 to 55% [16, 34, 86, 91, 92]. Moreover, the mode of death seems to be different in those two categories, with HFrEF patients having higher cardiovascular mortality and the HFpEF patients having mortality due to a non-cardiovascular cause in almost half of cases [13, 85-90, 93].

Co-morbidities and mortality

Co-morbidities affect mortality in heart failure patients, especially in the elderly. One study found that age, ACS, renal dysfunction, cancer, dementia and infection were independent predictors of in-hospital mortality in the elderly [49]. Other studies have shown that COPD and chronic kidney disease increase mortality in HF patients [94, 95]. Moreover, The Charlson Co-morbidity Index (CCI) was shown to be an independent predictor of mortality. CCI assigns points to several medical conditions to evaluate the severity of co-morbidity. A higher number of co-morbidities increased the hazard ratio for mortality greatly [96].

COPD is a predictor of mortality in both HFpEF and HFrEF and seems to increase non-cardiovascular mortality during HF hospitalizations but also long term mortality. Studies have shown that COPD contributes to a higher hazard for mortality in HFpEF compared with HFrEF [78, 97, 98]. Anemia is more frequent in HFpEF than in HFrEF patients but has the same effect on mortality in both HFpEF and HFrEF, with around 25% increase in mortality risk [97, 99]. The impact of diabetes in HFpEF versus HFrEF is not well defined but formal statistical testing has not demonstrated an interaction between diabetes and the different heart failure groups [97]. Moreover, renal dysfunction is as common in HFpEF as it is in HFrEF and causes an approximately 25-30% increase in mortality in both groups [97, 99].

Obesity is common in the heart failure population and has a higher prevalence in HFpEF patients [97, 99]. However, the relationship between mortality and weight is unclear as studies have shown varying results. Some studies show that a higher BMI is coupled with increased survival [100, 101]. One study showed a U-shaped relationship between BMI and adverse clinical events in HFpEF patients [102]. Another study found that increased BMI in HFpEF patients was associated with a worse NYHA class and that NYHA class III-IV was a strong independent predictor of adverse outcome (combined endpoint of hospitalizations and mortality) [103]. Dietary weight loss significantly reduced symptoms and improved NYHA class in HFpEF patients [104]. Thus, obesity can be a key co-morbidity that contributes to the HFpEF pathophysiology as adipose-induced inflammation has wide-ranging adverse effects. Therefore, weight loss could possibly improve survival in this heart failure category, but further studies are needed on the subject.

Biomarkers and prognosis

The risk of death for patients with HF can only be partly explained by established mortality risk factors, including NYHA, NT-proBNP and LVEF. This is particularly true for older individuals, where HF often coexists with other life-threatening diseases.

Some biomarkers are useful predictors of mortality and studies have shown that higher levels of NT-proBNP are coupled to higher mortality [105, 106]. NT-proBNP and BNP are important prognostic biomarkers in younger patients with HF. They appear to be better predictors of survival than many traditional prognostic indicators, including the NYHA class, serum creatinine and possibly LVEF [107]. The relative risk of death among younger patients with HF was shown to increase by about 35% for each 100 pg/ml increase in BNP [107, 108]. Therefore, BNP or NT-proBNP assessments have been recommended in the ESC guidelines [40]. However, most prognostic studies that included BNP or NT-proBNP assessments were performed in patients whose mean age was under 68 years [107]; thus, the predictive power of BNP and NT-proBNP lack sufficient validation in older patients with HF. This can be explained by the fact that NT-proBNP levels are linked to several other factors that affect prognosis in HF, including pulmonary disease and renal disease which are common among older patients. Therefore, as shown in a study by Bjurman et al from our group, NT-proBNP levels only predict mortality well at very high levels in the elderly and therefore a multi-marker modality, or a combination of other factors, for an accurate predictive model for prognosis is preferred [109]. However, further studies are needed on this subject.

RDW, a marker of anisocytosis in red blood cells, has previously been studied as a marker of increased mortality in numerous diseases, such as coronary artery disease, stroke and peripheral artery disease [110-118]. Previous studies have also found that high RDW values predict mortality in heart failure [119-122]. In addition, one study showed a relationship between RDW and cardiac function [119]. However, the relationship between RDW and other biomarkers known to predict mortality, such as NT-proBNP, has not been studied in different categories of heart failure.

Prognostic models

Many prognostic models exist for predicting outcome in heart failure patients. One of the most developed model is MAGGIC which is based on data from 30 cohort studies and the score is based on 13 highly significant independent predictors of mortality [123, 124]. MAGGIC has also been validated in patients with the mean age of 75 years and found to accurately predict outcome in that age group [124]. Furthermore, other well known predictive models such as Seattle Heart Failure Model, the Heart Failure Survival score, the PACE score and the SHOCKED predictors have been validated in independent cohorts. However, in a systematic review by Alba et al they were found to have poor to modest discrimination [125]. In addition, these predictive models have not been validated in the elderly heart failure population. Some models were developed previous to the widespread use of GDMT.

Bjurman et al from our group proposed a composite risk score based on age, Troponin T and Cystatin C levels in elderly heart failure patients [109]. This composite risk score was able to differentiate older patients with HF into high-risk and low-risk groups. The score was particularly useful among older patients with HF who had moderately elevated NT-proBNP, a group that is often difficult to evaluate. This composite risk score needs to be further validated in an independent and larger cohort before it can safely be implemented in clinical practice.

AIM

The overall aim of this thesis is to characterize clinical phenotype and study prognosis as well as its influencing factors of the elderly heart failure population with focus on co-morbidities and biomarkers in three main categories of heart failure: heart failure with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF) and post-infarction HF. We chose these aims in light of the fact that these subjects have not been adequately studied in the elderly hitherto.

Study I

The aim of this study was to find possible differences in phenotype with focus on both cardiovascular and non-cardiovascular co-morbidities as well as treatment pattern of heart failure in different age groups as well as different heart failure categories.

Study II

The aim of this study was to study the association between RDW and cardiac function and other biomarkers and to study if there was a difference in RDW levels between different heart failure categories.

Study III

The aim of this study was to evaluate major adverse cardiovascular events (MACE) in elderly patients with acute coronary syndrome, with special emphasis on heart failure and to see if patients with post-ACS heart failure had worse outcome and worse quality of life during follow-up.

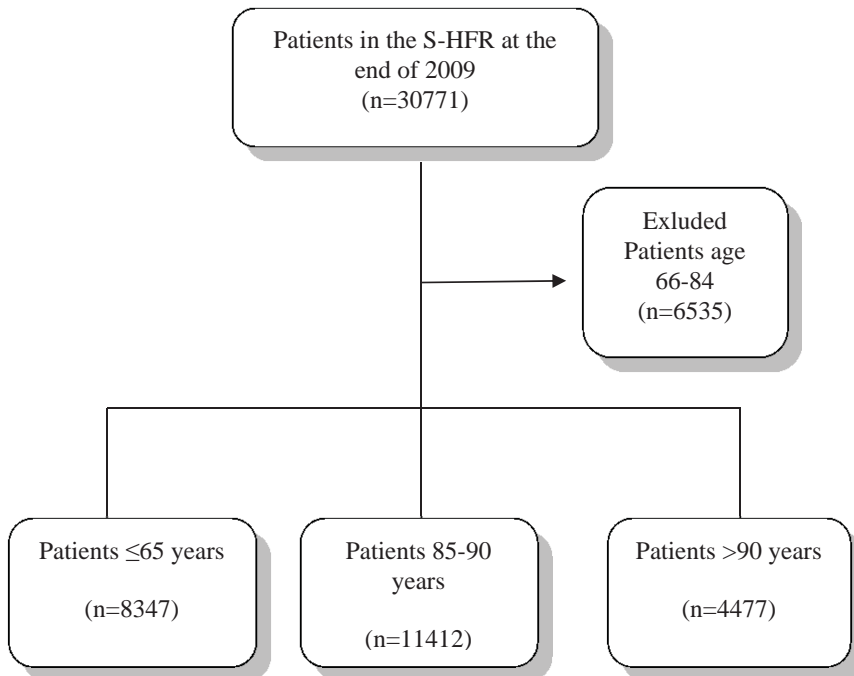
Study IV

The aim of this study was to compare 5 year mortality rates and their influencing factors in different heart failure categories using the current ESC guidelines for diagnosis.

PATIENTS AND METHODS

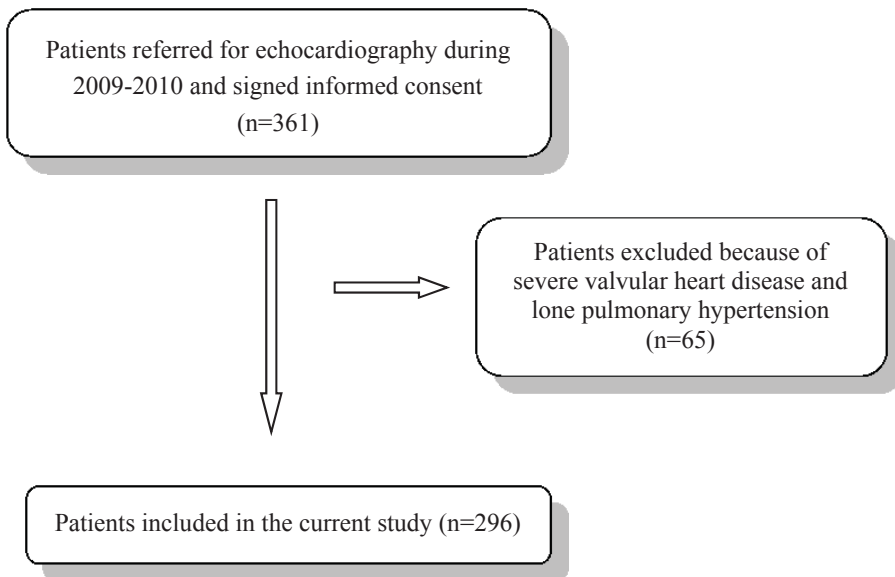
Study I

This was a retrospective study using the Swedish Heart Failure Registry (S-HFR/Rikssvikt). The registry was created in 2003 and is an internet based registry with more than 70 variables on demographics, concomitant diseases, diagnostic procedures, hemodynamics, laboratory data and medications [126]. This study included patients entered into the registry from 2003 to 2009. The patients were included in the registry either after being admitted for heart failure or during follow-up in an out-patient clinic. In last year's report 54.3% of the Swedish heart failure population was registered in the registry [64]. The elderly population included in study I was from age 85 years and upwards (15889 patients) and was divided into two age groups, 85-90 and >90 years. As a control, a younger population <65 years (8347 patients) was included for comparison. The cut-off for LVEF in HFrEF was <50% and for HFpEF it was $\geq 50\%$.



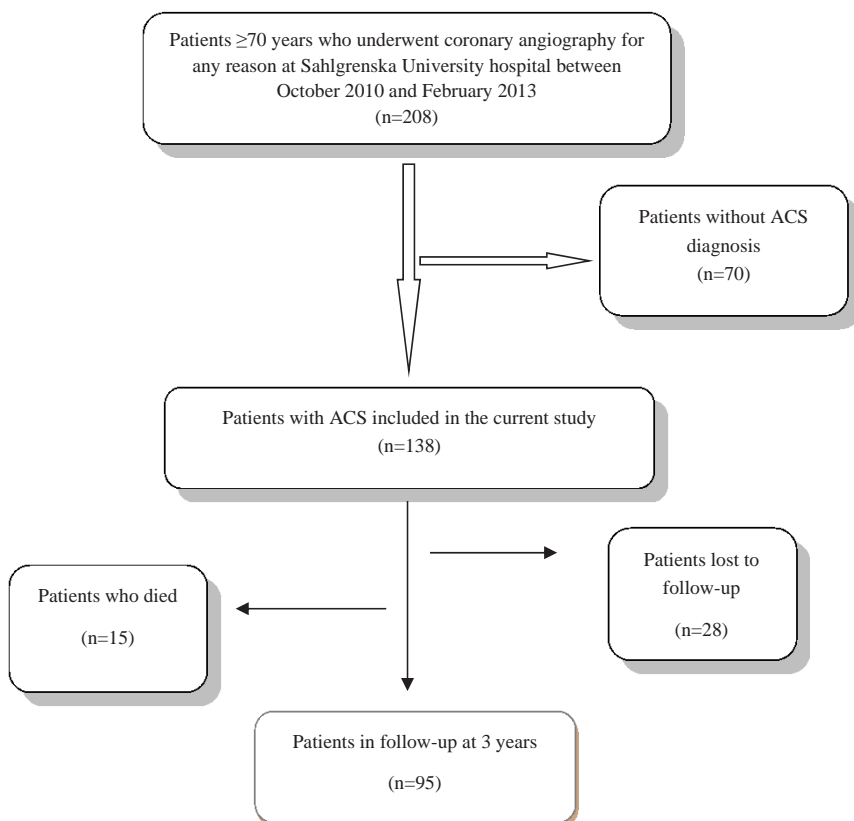
Study II

This was a prospective study of 296 patients referred for echocardiography, enrolled during 2009-2010. All patients gave informed consent and ECG, blood samples and a clinical examination were performed within 24 hours of the echocardiography. The echocardiography was analyzed by a specialist in the field and diastolic dysfunction was judged on a routine basis including E/A ratio and S/D ratio along with deceleration times. Tissue Doppler was performed in selected cases. Depending on the results of echocardiography, symptoms and NT-proBNP levels the patients were then divided into HFrEF, HFpEF, gray zone and normal. NT-proBNP and RDW were analyzed by the laboratory at Sahlgrenska University Hospital as per routine.



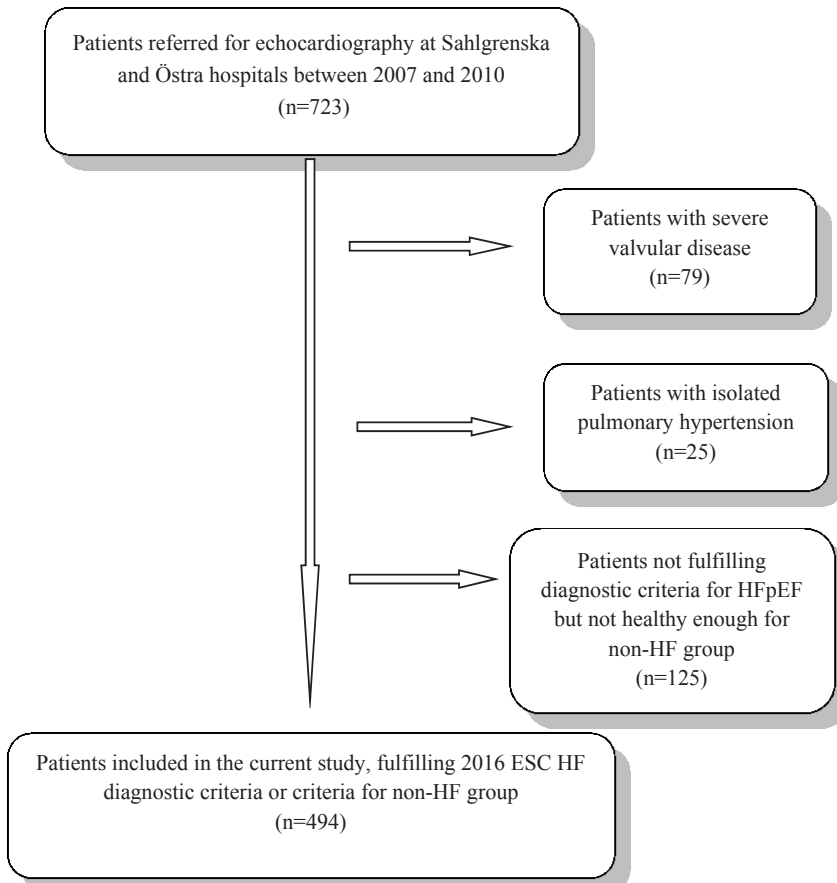
Study III

This was a prospective study of 208 patients ≥ 70 years referred for coronary angiography for any reason between October 2010 and February 2013 during office hours only. One inclusion criterion was that blood tests needed to be taken within 24 hours of coronary angiography. Included in the analysis are only patients with acute coronary syndrome (138 patients), although initially even patients doing angiography because of valvular heart disease were included in the cohort of 208. The patients were then followed for 3 years and mortality and MACE data were collected. All 208 patients signed informed consent and all patients that were not lost to follow-up or died (77%) had a clinical examination, quality of life questionnaires (SF-36), ECG and vital parameters along with an interview at 3 years follow-up.



Study IV

This retrospective study included 494 patients from a database in both Östra and Sahlgrenska hospitals from April 2007 to October 2010. The echocardiography was analyzed by a specialist in the field and diastolic dysfunction was judged on a routine basis including E/A ratio and S/D ratio along with deceleration times. Tissue Doppler was performed in selected cases. Exclusion criteria were severe primary valvular disorder, isolated pulmonary hypertension, and disease complicating correct diagnosis of HFpEF such as severe COPD (requiring chronic oxygen supplementation) and severe anemia (hemoglobin <90). Then the study population was divided into 3 heart failure categories according to the 2016 ESC heart failure guidelines [40]: HFpEF, HFrEF and HFmrEF. Also, a healthy group was included for comparison. The mortality data was acquired from medical journals 5 years after inclusion.



Ethics

All of the studies included in this thesis conformed to the ethical guidelines of the declaration of Helsinki and all of the study protocols were approved by the Ethical Committee at the University of Gothenburg. Moreover, in both prospective studies all patients gave informed consent.

Statistics

Statistical Package for Social Sciences (PASW statistics) and SAS version 9.4 were used for data analysis. Categorical variables are expressed as percentages and continuous variables as mean \pm SD except for non-normally distributed continuous variables that are expressed as median (inter quartile range (IQR)). The student's unpaired t-test was used for normally distributed continuous variables and for skewed data the Mann-Whitney test was used or the data was log-transformed prior to analysis. For categorical variables the chi-square test was used. Cox-proportional hazard survival models were used for survival and MACE analysis both in univariate and multivariate analyses. Hazard Ratios (HRs) with 95% Confidence Intervals (CIs) and associated p-values were described from the Cox analyses. A two-tailed p-value <0.05 was considered statistically significant.

In *study II*, NT-proBNP and creatinine levels were not distributed normally, so log-transformed values were calculated prior to analysis. For normally distributed variables the Pearson correlation was used to study correlations between RDW and other variables. The Spearman correlation was used to study correlations between NT-proBNP and RDW. To analyze independent associations between RDW and other factors a stepwise multiple linear regression was used.

In *study III*, TNT was not normally distributed so log-transformed values were calculated prior to analysis.

In *study IV*, interaction analysis was done between predictors and the heart failure category variables in order to identify significant differences in predictors between heart failure categories. In those analyses, a two sided p-value <0.10 was considered significant.

RESULTS

Study I

In this retrospective registry study we found that both the 85–90 year old group and the >90 year old group had characteristics that were different from the younger population ≤ 65 years. As compared with the ≤ 65 year old group, the ≥ 85 year old group was characterized by more women, lower BMI, higher systolic blood pressure (SBP), lower diastolic blood pressure (DBP), more left bundle brunch block (LBBB), more than twice as many patients with HFpEF (Figure 3), more cardiovascular co-morbidities (ischaemic heart disease, hypertension and atrial fibrillation) and more non-cardiovascular co-morbidities (anaemia, pulmonary disease, stroke and renal insufficiency), except diabetes which decreased with ageing. Compared to the 85–90 year old group, the >90 year old group had a decline in cardiovascular and non-cardiovascular co-morbidities, except for renal insufficiency and anaemia which continued to increase with ageing. Moderate renal insufficiency in terms of GFR < 60 mL/min kept increasing from 10.9% in patients ≤ 65 years old to 89.8% in patients 85–90 years old and continued increasing to 97.2% in patients >90 years old. An even more dramatic increase was observed in severe renal insufficiency in terms of GFR < 30 mL/min from 1.8% in patients ≤ 65 years old to 28.0% in patients 85–90 years old and continued increasing to 53.1% in those >90 years old. Likewise, the incidence of anaemia increased from 22.4% in patients ≤ 65 years old to 44.3% in patients 85–90 years old and furthermore to 47.2% in those >90 years old.

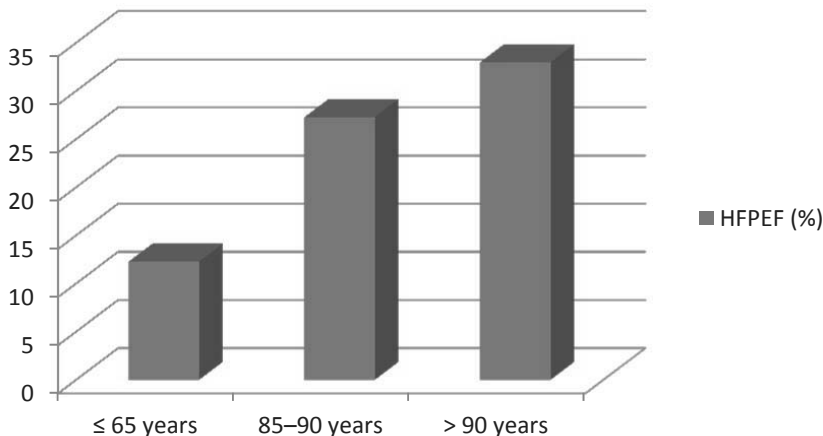


Figure 3. Percentage of the heart failure population with HFpEF.

Moreover, the older heart failure patients received less treatment than the younger patients when it comes to life prolonging treatment: ACEI/ARBs, beta blockers and mineral corticoid receptor antagonists, but the use of diuretics increased with higher age (Figure 4). The prevalence of HFpEF more than doubled with increasing age. The HFpEF group had more women, more prevalent hypertension, atrial fibrillation, lower NT-proBNP levels and less ischemic heart disease compared with the HFReEF group.

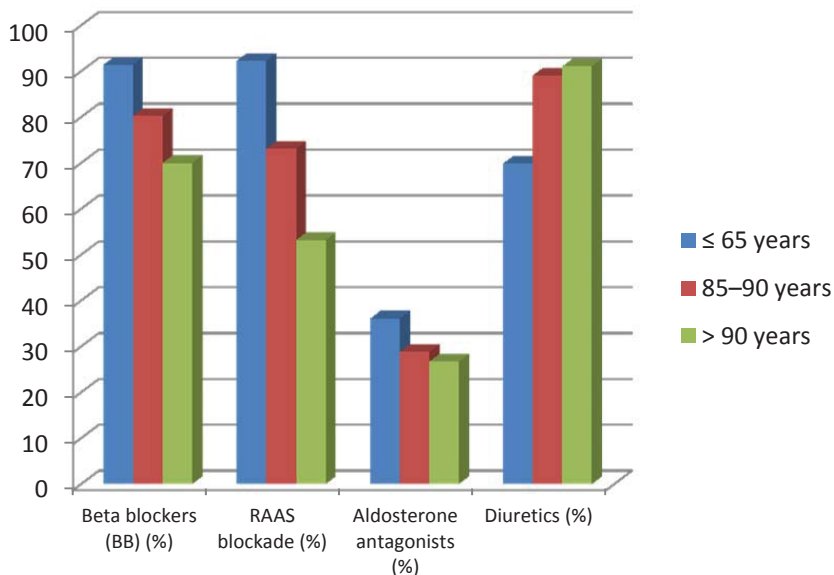


Figure 4. Percentage of medication use in different age categories.

Study II

The mean age in the cohort was 70 ± 11 years. There were differences in clinical characteristics between HFpEF and HFReEF. The HFpEF group had more female patients and less ischemic heart disease than the HFReEF group. RDW values were higher in patients with heart failure compared with the gray zone and normal groups. However, there was no significant difference in RDW or NT-proBNP levels between HFReEF and HFpEF. Moreover, we observed a positive correlation between NT-proBNP levels and RDW levels but an inverse correlation between LVEF and RDW levels. The prevalence of HFReEF was higher in the upper RDW quartiles (Figure 5). In our study, stroke was inversely correlated to RDW. A history of myocardial infarction was 3 times more common in patients with the highest RDW levels. Even though the patients with HFReEF and HFpEF had higher RDW levels the confidence intervals were wide and most patients in these groups still had normal levels of RDW (Figure 6). However, the patients with the highest RDW levels were generally sicker than those with lower levels, with more co-morbidities.

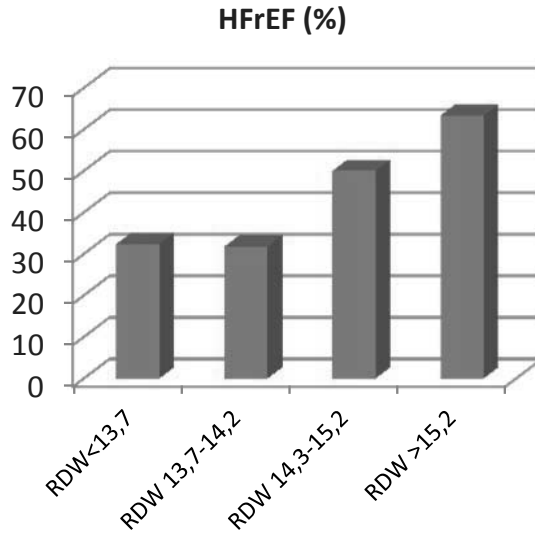


Figure 5. Percentage of HFrEF patients within each RDW quartile.

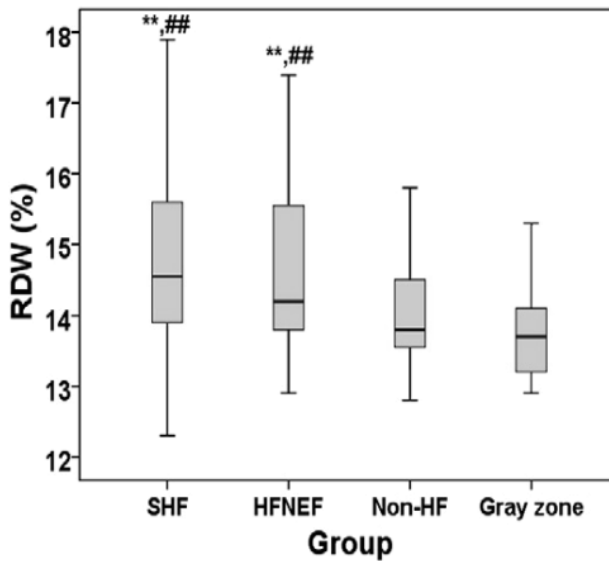


Figure 6. Box-plot of RDW levels in different patient groups. (Eur J Int Med 23(2012) p. 606)

Study III

The mean age was 78.8 ± 3.8 years in this cohort and 24% were female. In total, there was 42% MACE and 25% were diagnosed with post-ACS heart failure which was the most common MACE. After 3 years of follow-up 11% of the patients had died and 77% of patients living at the end of the follow-up responded to the quality of life questionnaires. In general, the quality of life was comparable to healthy individuals the same age in the Swedish population (8930 healthy individuals responding to the SF-36 for the validation of the Swedish version of SF-36) [83, 84]. Moreover, the >80 year old ACS patients had a higher quality of life than their counterparts in the normal population (Figure 7). However, post-ACS heart failure patients and patients with MACE had a lower quality of life. Furthermore, we found that even though post-ACS heart failure patients received guideline recommended treatment, heart failure treatment seldom reached target dose and mineral corticoid receptor antagonists were rarely used.

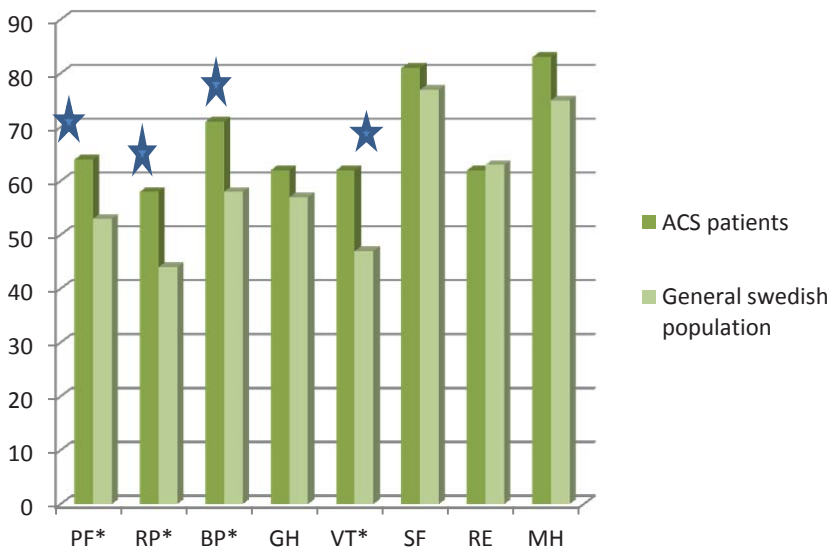


Figure 7. Differences in quality of life between ACS patients >80 years old and the general Swedish population. Stars show significant differences in QoL. Abbreviations: PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health.

Study IV

The mean age of the cohort was 72.7 ± 14 years and 40% were female. We found that all heart failure groups had higher 5 year mortality rates than the non-HF group. However, the HF_rEF group had the highest mortality rate. There was no significant difference in mortality between HF_mrEF and HF_pEF although there was a trend towards higher mortality in HF_mrEF (HR 1.43, CI 0.98-2.10 p=0.06) (Figure 8). Moreover, all three categories had different factors influencing mortality rates. The use of loop diuretics was shown to be a predictor of mortality in HF_pEF and HF_mrEF. ACEI were associated with lower mortality in HF_pEF and HF_mrEF. In HF_mrEF hypertension was protective, in HF_pEF statins were associated with lower mortality and in HF_rEF anticoagulation was protective, although 45% of the HF_rEF patients had a history of atrial fibrillation. In addition, diabetes mellitus and LBBB were predictors of mortality in HF_rEF, while pulmonary disease and cancer were predictors of all-cause mortality in HF_pEF.

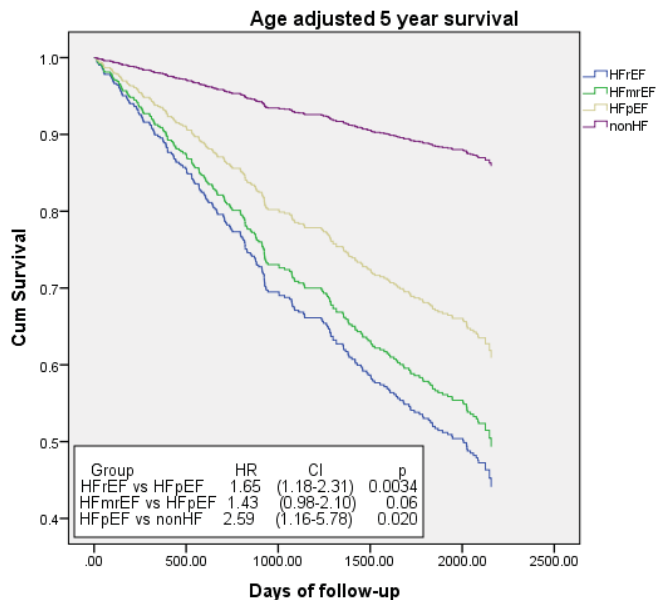


Figure 8. Kaplan-meyer curves of age adjusted survival in different patient categories along with Hazard ratios (HR), Confidence interval (CI) and p-value.

DISCUSSION

Clinical phenotype and co-morbidity in heart failure in the elderly

The elderly heart failure population not only carries a higher risk for adverse outcome but also has a distinct clinical phenotype compared with the younger heart failure population. However, most studies on HF have been conducted in the younger population, despite the fact that most of heart failure occurs in the elderly [9]. Although there have been some studies on this elderly population, these studies either had smaller sample sizes or excluded many co-morbidities [35, 36, 127-131].

By access to The Swedish Heart Failure Registry, the largest national heart failure registry in the world, and our hospital cohorts in this thesis, we have demonstrated that the elderly heart failure patients have clinical characteristics that differ from those of the younger population. In general, elderly heart failure patients are more women, have lower BMI, higher systolic blood pressure, lower diastolic blood pressure, more left bundle branch block, more than twice as many patients with HFpEF, more cardiovascular co-morbidities (ischaemic heart disease, hypertension and atrial fibrillation) and more non-cardiovascular co-morbidities (anaemia, pulmonary disease, stroke and renal insufficiency). For instance, moderate renal insufficiency kept increasing from 11% in patients ≤ 65 years to 90% in patients > 85 years. Likewise, the incidence of anaemia increased from 22% in patients ≤ 65 years to 44% in patients > 85 years.

The most striking clinical feature in the elderly heart failure population compared with the younger population is co-morbidity. In our study we confirmed that cardiovascular and non-cardiovascular co-morbidities significantly increased in elderly patients compared with those younger. This was true for all co-morbidities except for diabetes. This is in accordance with previous studies that also showed a lower frequency of diabetes in the elderly [36, 39, 49, 128, 132]. A possible reason for this could be that patients with diabetes rarely live long enough to reach high age.

The clinical phenotype of HFpEF has received increasing attention in the last 2 decades. This is because HFpEF is a heterogeneous clinical syndrome characterized by cardiovascular, metabolic, and pro-inflammatory diseases associated with advanced age and extra-cardiac co-morbidities. This heterogeneity of the HFpEF syndrome may explain why diagnosing and treating HFpEF is so challenging and clinical trials in HFpEF have failed thus far. Therefore, the future therapeutic approach in HFpEF should be aimed at targeting a specific HFpEF phenotype, instead of the ‘one-size-fits-all’ approach, which has been proven to be unsuccessful in clinical trials in the last decades. Accordingly, it is highly clinically relevant to identify different clinical phenotypes in HFpEF.

In this thesis we have studied the clinical phenotype of HFpEF based on The Swedish Heart failure Registry and hospital cohorts in both a prospective and a retrospective manner. We have demonstrated that, being different from patients with HFrfEF, patients with HFpEF are more often female and have more often hypertension and atrial fibrillation but less ischemic heart disease. In general, there are more non-cardiac co-

morbidities in HFpEF whereas more cardiac co-morbidities in HFrEF. Our findings are in accordance with other studies [36, 37, 39, 133] and support the growing recognition that HFrEF and HFpEF are different clinical entities with different underlying mechanisms [134-136].

Biomarkers as a prognostic tool in heart failure in the elderly

Heart failure is mostly a complex geriatric syndrome that causes considerable mortality, morbidity and reduced functioning. Pathophysiologically, heart failure has multiple precipitating causes and predisposing risk factors, which makes prognostic models for predicting outcome challenging. In the case of HFpEF, almost half of the patients have mortality due to non-cardiovascular causes [13, 85-90, 93]. Therefore, in contrast to the younger heart failure population, the risk of death in elderly patients with HF can only be partly explained by established mortality risk factors, such as NYHA class, NT-proBNP and LVEF. That is why a multi-biomarker strategy has received increasing attention. NT-proBNP is one of those generally accepted prognostic biomarkers in younger patients with HF. However, as shown in a study by Bjurman et al, in the elderly, NT-proBNP levels only predict mortality well at very high levels [137]. Therefore, perhaps a combination of other biomarkers is needed for an accurate prognostic model for predicting prognosis, but further studies are needed on the subject. RDW has also been previously studied as a marker for increased mortality in cardiovascular disease and heart failure [110-122]. However, the relationship between RDW and NT-proBNP in addition to LVEF has not been studied previously in different categories of heart failure.

In this study, we explored the associations between the RDW, LVEF and biomarkers simultaneously in a hospital population referred for echocardiography because of suspected HF. In contrast to many previous studies, all patients in our study were assessed by echocardiography, electrocardiogram, blood sampling and clinical examination within 24 h from the time point when echocardiography was performed. In addition, patients with HFpEF and an uncertain HFpEF diagnosis were included to simulate the real-life challenge when HF is suspected in patients with LVEF over 50%.

Our findings extend previous observations by showing that older patients with HFpEF have mean RDW levels similar to what is observed in HFrEF patients. However, despite the elevated mean RDW levels in HFpEF, there was no significant association between the frequencies of HFpEF patients across the RDW quartiles. This lack of an association between the RDW levels and the frequency of HFpEF could indicate that the RDW elevating mechanisms are different in HFpEF compared with HFrEF. Moreover, the elevated RDW in HFrEF and HFpEF cannot be exclusively due to anemia since the frequency of anemia was not different among the four study groups, indicating that there are other mechanisms, in addition to anemia, contributing to the high RDW levels in HFrEF and HFpEF. However, anemia might be involved since it occurs often in heart failure.

There was an inverse correlation between RDW and LVEF across RDW quartiles. RDW was higher among patients with a low LVEF and among patients with higher

NT-proBNP values and previous myocardial infarction. These findings are in agreement with previous observations that showed a relationship between elevated RDW and elevated NT-proBNP [119, 138], history of myocardial infarction [139], diabetes, smoking and severe kidney dysfunction [112, 120-122, 138, 140].

Previous studies have also found a correlation between LVEF and RDW in HF_{rEF} [119]. However, most heart failure patients still had normal RDW levels according to the reference range for the lab, thus possibly decreasing the usability of RDW as a lone predictor for prognosis. However, values above 14.4% have previously been demonstrated to be enough to be an independent predictor of mortality in heart failure patients [122], and in our study most of the heart failure patients had values above that. Therefore, it is reasonable to assume that the usefulness of RDW as a marker of mortality is probably highest when combined with other markers of mortality such as NT-proBNP and co-morbidities.

Prognosis of post-ACS heart failure in the elderly

Patients with coronary artery disease complicated by heart failure face a higher risk of in-hospital and post-discharge fatal and nonfatal ischemic and arrhythmic events. Over the past 2 decades the prognosis of patients after acute myocardial infarction (AMI) has markedly improved. Changes in baseline population characteristics as well as a decrease in infarct size due to salvage of myocardium have resulted in a decrease in the prevalence of HF after ACS. According to a recent study by access to Swedeheart, a marked decrease was found in the incidence of HF complicating AMI between 1996 and 2008. However, HF continues to worsen the early-, intermediate-, and long-term adverse prognosis after AMI [72].

However, despite this advancement in management, age and co-morbidities in the elderly impair the prognosis of ACS. As a matter of fact, a significant proportion of patients with coronary artery disease are elderly. In the meantime, in octogenarians with ACS, PCI was shown to be associated with improved survival from all-cause death over 5 years of follow-up [141]. Therefore, there are multiple factors, both favorable and unfavorable, for prognosis in elderly patients with ACS. However, data on long-term prognosis with special emphasis on heart failure after ACS in the elderly are limited. Moreover, no information on quality of life (QoL) was available in the elderly ACS cohort.

Given the limited data on outcome and QoL in elderly patients with ACS who receive reperfusion therapy, as well as the multi-factorial nature of the prognosis of the elderly population, we conducted a prospective observational study examining outcome and QoL in elderly ACS patients undergoing coronary angiography. For this purpose, a 3-year follow-up after inclusion was performed comprising a physical examination, a personal interview and QoL questionnaire.

In our study, 25% of patients with ACS still develop post-ACS heart failure. However, only 18% of them are early onset and therefore, when compared to some other studies, the incidence has decreased [70-72] as would be expected with improved treatment over the years with percutaneous coronary angioplasty and improved medical treat-

ment. However, when the additional patients with late onset post ACS heart failure are added, the prevalence is similar to earlier studies. Late occurrences of post ACS heart failure can however often be missed and thus prevalence may be underestimated. Moreover, post-ACS heart failure patients scored lower on the quality of life questionnaire than those who did not have heart failure. However, the 3 year mortality in our study was only 11% and the patients had in general the same quality of life as an age-matched healthy Swedish population. This low mortality rate could be explained by the fact that the incidence of sudden cardiac death after acute MI has declined after the introduction of modern treatment with medical therapy and revascularization [142-146]. Furthermore, post ACS heart failure patients often do not receive target dose beta blockers, ACEI/ARBs and mineral corticoid receptor antagonists indicating potential for further improvement in secondary prevention and individualized care.

Prognosis of HFrEF and HFpEF in the elderly

Previous studies have shown inconsistent results when it comes to mortality in HFpEF compared with HFrEF. One possible reason for this divergency in prognosis between HFrEF and HFpEF in previous studies could be due to different inclusion criteria applied, for example cut-off values for LVEF in HFpEF have varied from 40 to 55% [16, 34, 86, 91, 92]. In this thesis, 2 heart failure guidelines by The ESC were used: one from 2012 and another from 2016. The 2012 ESC guideline set the cut-off for LVEF at 50% for the diagnosis of HFpEF and referred to EF 35-50% as a grey area [58] whereas the 2016 ESC guidelines refer to EF 40-49% as a mid-range ejection fraction group (HFmrEF) [40].

Based on The ESC heart failure guideline 2016 for diagnosis, we found that HFrEF has the highest mortality compared with HFpEF and HFmrEF. However, HFpEF and HFmrEF also carry high mortality rates. This is in accordance with some previous studies [13, 86, 87, 90]. Interestingly, there was no difference in mortality rates between HFpEF and HFmrEF, even if there was a trend towards a higher mortality in HFmrEF. To our knowledge, our study is probably the first to make a direct comparison among HFrEF, HFmrEF and HFpEF shortly after the current ESC heart failure guidelines 2016 was published [40].

Furthermore, we found different prognostic factors in all three categories of HF. In HFpEF non-cardiovascular co-morbidities like pulmonary disease and cancer were predictors of mortality while in HFrEF diabetes and LBBB were predictors of mortality, and diabetes has been shown to be a predictor in previous studies [147]. Hypertension was a predictor of survival in HFmrEF while statins predicted survival in HFpEF and anticoagulants in HFrEF. Furthermore, statins have previously been found to predict survival in HFpEF [148-150]

HFmrEF is a newly defined subtype of HF and limited studies are available. In our study, the HFmrEF group had some characteristics similar to HFpEF but most variables were more like HFrEF. For example, the HFmrEF group had high cardiovascular co-morbidities and diabetes similar to HFrEF, but in the meantime had a high prevalence of obesity and atrial fibrillation like the HFpEF group. This highly suggests different entities for these three heart failure categories. The HFmrEF group is

currently poorly studied and further studies are needed to further discern if this heart failure category is indeed a category on its own.

Treatment of heart failure in the elderly

First-line pharmacotherapy in HFrEF consists of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) if the patient is intolerant to ACEI, and β -blockers (BBs). Guidelines for treatment of heart failure in the adult give a general treatment recommendation irrespective of age despite the fact that most studies were carried out in the younger population. However, in the real world, elderly heart failure patients receive less treatment with life-saving therapy. As shown in our studies, the older heart failure patients received less treatment with ACEI/ARB, beta blockers and mineral corticoid receptor antagonist. However this does not necessarily mean that heart failure was sub-optimally treated in the elderly. This is because heart failure therapy must be individualized, particularly in the elderly. For instance, according to guidelines, the abovementioned life saving medications should be commenced at a low dose and up-titrated to the target dose.

However, doses recommended by guidelines are often not achieved in daily clinical practice, and regularly cannot be achieved in the elderly. In view of the gap between the widespread use of lower doses of ACEI/ARBs or BBs in clinical practice in elderly patients with heart failure and the target dose recommended by guidelines, there is a fundamental issue to be solved: which dose level is optimal in the elderly? An individualized, highest tolerable dose as we use in our daily clinical practice, or a target dose as recommended by the guidelines?

A recent study in our group from a nurse-based Heart Failure Outpatient Clinic has demonstrated that, in patients with HFrEF who were on treatment with BB or ACEI/ARB in 95% of cases, only 53% received the target dose of ACEIs/ARBs and 21% received the target dose of BB despite up-titration over the span of 6 months [151]. The main causes for not reaching the target dose of ACEIs/ARBs were symptomatic hypotension (41%), elevated creatinine (43%), and elevated potassium (11%). For BBs, the main reasons for not reaching the target dose were symptomatic bradycardia (53%), symptomatic hypotension (46%), and worsening pulmonary obstruction symptoms (1%) [151].

HFpEF represents a greater challenge because there is no proven treatment that improves mortality and morbidity, despite efforts in the past two decades. The current treatment options serve mainly to relieve symptoms. For example, diuretics are used to control sodium and water retention. Adequate treatment of hypertension, diabetes mellitus and myocardial ischaemia is important, as is control of the ventricular rate in patients with atrial fibrillation. One of the ongoing trials in HFpEF is OPTIMIZE-HFpEF in our group. The purpose of this trial is to test the hypothesis that a systematic screening for and optimized management of co-morbidities in HFpEF will relieve symptoms and improve overall prognosis. The rationale is that since HFpEF in the elderly is characterized by multiple co-morbidities that cause progression of HFpEF, that the optimal management of co-morbidities is a feasible therapeutic target [152].

Limitations

This thesis is based on a mixture of different study populations. There were limitations regardless of registry-based population or hospital cohort.

Regarding registry based study population (paper I), the most severe limitation is the low representation from primary care. Moreover, not all hospitals and outpatient clinics in Sweden have registered their patients in the registry, so only 54,3 % of the Swedish heart failure population was included in the registry in the latest yearly report [64]. Also, some variables are underreported. For example, only 5% of the data set was completely filled for both depression and malignancy.

In addition, diagnosis was reported individually by physicians from participating registration sites. With the consideration that natriuretic peptide testing was not widely used, a diagnosis of HF in the absence of natriuretic peptide testing and/or echocardiography is questionable in particular in the oldest population where co-morbidity (e.g. pulmonary disease) is easily wrongly diagnosed as HF because of similar symptoms. However, as the registry population is very large without a known selection of patients it should for the most part be a good representation of the Swedish heart failure population.

Regarding our prospective hospital cohort (Paper II), it was conducted during 2009–2010. At that time there was a diagnostic uncertainty with regards to HFpEF. In order to make the HFpEF diagnosis certain, we used a higher NT-proBNP cut-off value of 1500 ng/L to avoid over-diagnosis. This was based on the consideration that in our hospital cohort, NT-proBNP-elevating conditions like atrial fibrillation and renal failure were common. Moreover, in contrast to other studies, the patients were not optimally treated at the time of inclusion, which may result in higher NT-proBNP levels relative to previous studies on stable HF patients. Nevertheless, our diagnostic criteria in paper II is not only different from paper I but also different from paper IV where the 2016 ESC guidelines were strictly applied.

In the ACS prospective study the cohort was selected by clinicians in the daily practice and thus there could be a selection bias excluding frail patients. There was even a selection bias in the way patients were only included during normal office hours and therefore inclusion was not entirely consecutive. Besides, the cohort is relatively small.

The cohort for study IV is spread in age, so the non-HF group is younger than the heart failure groups. This could cause an exaggeration of the differences in mortality rates and therefore direct comparison is difficult even if we tried adjusting for age.

In Addition as with all observational studies, a cause-effect relationship cannot be proven with the results and can only be hypothesis generating. Moreover, despite adjustment with cox-regression models, it is still impossible to rule out confounding from unmeasured variables in the MACE or the mortality analysis.

Strengths

This thesis has several strengths.

In terms of study design, this thesis has its advantage by combining 1) large sample sized registry database and well validated hospital cohort, and 2) prospective observations and retrospective studies. By doing so this thesis is able to present a true picture of the elderly heart failure population. Moreover the thesis has its strength by choosing long-term outcome as an endpoint in contrast to prior available studies. Last but not least, this thesis was probably the 1st to compare prognosis between HF_rEF, HF_{mr}EF and HF_pEF shortly after the latest ESC heart failure guideline 2016 was published in May 2016.

In terms of patient population, this thesis has its strength by studying heart failure population in the elderly with focus on clinical phenotype and prognosis, which are fundamental for our better understanding of this complex geriatric syndrome.

CONCLUSIONS

- Heart failure in the elderly is a unique clinical entity not only with regards to clinical characteristics but also on prognosis and its influencing factors. In the elderly, co-morbidities not only more often accompany heart failure but also affect clinical phenotype and prognosis, and should therefore be regarded as an important part of heart failure.
- RDW as a part of a multi-biomarker strategy has its potential to be useful in prognostic models for heart failure together with clinical variables.
- The rate of post ACS heart failure declined but is still common despite advanced treatment suggesting a definite need for further improved tailored care in this elderly ACS cohort.
- HFrEF still has a higher mortality rate than HFpEF and HFmrEF despite continuous improvement in therapy in the last decades. Moreover, factors influencing mortality are different in different categories of heart failure

FUTURE PERSPECTIVES

This thesis is dealing with an important issue in our society, namely heart failure in the elderly population, since the disease causes a high burden which adversely affects individuals, families, and society. One of the many challenges is poor understanding of this complex geriatric syndrome. In addition, this health problem has been inadequately studied despite the fact that the main body of the heart failure population is the elderly.

Based on findings from this thesis and others there is a greater heterogeneity in clinical phenotype and prognosis in heart failure in the elderly. This emphasizes the urgent need of an in-depth study of the clinical characteristics, pathophysiology and prognosis in different heart failure categories (HF_rEF, HF_{mr}EF and HF_pEF) in order to develop effective therapy in the future.

Our finding on highly prevalent co-morbidities in heart failure in the elderly highlights the importance of the multidisciplinary management. In this regard, early detection and treatment of co-morbidities is essential as long as we believe that co-morbidity is an important part of the heart failure syndrome and contributes to the progression of heart failure.

Prevention is no doubt the best treatment in the case of heart failure. Most of heart failure develops because of hypertension and ischemic heart disease. Despite great achievement in both primary and secondary prevention of cardiovascular disease and heart failure in the last decades, post-ACS heart failure still occurs in about 1 of 5 patients. The present thesis has not only demonstrated that there is urgent need for further improvement in this regard but also that there is substantial potential to achieve our goal.

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