Risk Factors and Predictors of Heart Failure: from Incidence to Prognosis

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Ιθάκη

Σα βγεις στον πηγαιμό για την Ιθάκη, να εύχεσαι νάναι μακρύς ο δρόμος, γεμάτος περιπέτειες, γεμάτος γνώσεις. Τους Λαιστρυγόνας και τους Κύκλωπας, τον θυμωμένο Ποσειδώνα μη φοβάσαι, τέτοια στον δρόμο σου ποτέ σου δεν θα βρείς, αν μέν' η σκέψις σου υψηλή, αν εκλεκτή συγκίνησις το πνεύμα και το σώμα σου αγγίζει. Τους Λαιστρυγόνας και τους Κύκλωπας, τον άγριο Ποσειδώνα δεν θα συναντήσεις, αν δεν τους κουβανείς μες στην ψυχή σου, αν η ψυχή σου δεν τους στήνει εμπρός σου.

Να εύχεσαι νάναι μακρύς ο δρόμος. Πολλά τα καλοκαιρινά πρωϊά να είναι που με τι ευχαρίστησι, με τι χαρά θα μπαίνεις σε λιμένας πρωτοειδωμένους· να σταματήσεις σ' εμπορεία Φοινικικά, και τες καλές πραγμάτειες ν' αποκτήσεις,
σεντέφια και κοράλλια, κεχριμπάρια κ' έβενους, και ηδονικά μυρωδικά κάθε λογής, όσο μπορείς πιο άφθονα ηδονικά μυρωδικά· σε πόλεις Αιγυπτιακές πολλές να πας, να μάθεις και να μάθεις απ' τους σπουδασμένους.

Πάντα στον νου σου νάχεις την Ιθάκη. Το φθάσιμον εκεί είν' ο προορισμός σου. Αλλά μη βιάζεις το ταξίδι διόλου. Καλλίτερα χρόνια πολλά να διαρκέσει· και γέρος πια ν' αράξεις στο νησί, πλούσιος με όσα κέρδισες στον δρόμο, μη προσδοκώντας πλούτη να σε δώσει η Ιθάκη.

Η Ιθάκη σ' έδωσε το ωραίο ταξίδι. Χωρίς αυτήν δεν θάβγαινες στον δρόμο. Αλλο δεν έχει να σε δώσει πια.

Κι αν πτωχική την βρεις, η Ιθάκη δεν σε γέλασε. Ετσι σοφός που έγινες, με τόση πείρα, ήδη θα το κατάλαβες η Ιθάκες τι σημαίνουν.

Κωνστάντινος Π. Καβαφης, 1911

Ithaca

When you set out on your journey to Ithaca, pray that the road is long, full of adventure, full of knowledge. The Lestrygonians and the Cyclops, the angry Poseidon - do not fear them: You will never find such as these on your path, if your thoughts remain lofty, if a fine emotion touches your spirit and your body. The Lestrygonians and the Cyclops, the fierce Poseidon you will never encounter, if you do not carry them within your soul, if your soul does not set them up before you.

Pray that the road is long. That the summer mornings are many, when, with such pleasure, with such joy you will enter ports seen for the first time; stop at Phoenician markets, and purchase fine merchandise, mother-of-pearl and coral, amber and ebony, and sensual perfumes of all kinds, as many sensual perfumes as you can; visit many Egyptian cities, to learn and learn from scholars.

Always keep Ithaca in your mind. To arrive there is your ultimate goal. But do not hurry the voyage at all. It is better to let it last for many years; and to anchor at the island when you are old, rich with all you have gained on the way, not expecting that Ithaca will offer you riches.

Ithaca has given you the beautiful voyage. Without her you would have never set out on the road. She has nothing more to give you.

And if you find her poor, Ithaca has not deceived you. Wise as you have become, with so much experience, you must already have understood what Ithacas mean.

Konstantinos P. Kavafis, 1911

To Evi, the love of my life
and, to Melina and Ioanna, the meaning of it

ABSTRACT

Background: Heart failure (HF) is a major public health problem affecting at least 26 million people worldwide and one of the leading causes of disability and death.

Aims: To identify characteristics associated with improved or worsened prognosis in patients with established HF and to study factors associated with higher risk for the incidence of HF in the general population.

Methods and Results: This thesis consists of four papers. Paper I was designed to study the impact of different dose levels of beta-blockers (BBs) and angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs) on long-term mortality in elderly patients with HF with reduced ejection fraction (EF). The study cohort included 184 HF patients aged ≥80 years with EF ≤40%. The target ACEI/ARB dose was associated with reduced all-cause mortality compared to <50% of target dose. There were no significant differences in survival between the different BB doses. In Paper II, a comparison of the prevalence and prognostic contribution to mortality of non-cardiac comorbidities was conducted between HF patients with EF <50% and ≥50%. Data from the Swedish Heart Failure Registry between May 2000 and December 2012 were used. Stroke, anemia, gout, and cancer were all associated with higher mortality in both phenotypes with similar impact, whereas diabetes, renal failure, and liver disease had a higher impact in patients with EF <50%. Pulmonary disease was more prominent in patients with EF ≥50%. In Paper III, the predictive value of different biomarkers for HF incidence was examined. The study cohort was a randomly selected sample of men born in 1943 who were followed up over 21 years. N-terminal pro B-type natriuretic peptide (NT-proBNP) ≥25ng/L and high-sensitivity C-reactive protein (hs-CRP) >3mg/L at age 50 years were associated with higher odds of incident HF. Paper IV studied and compared risk factors and incidence of HF in middle-aged men born 30 years apart. The study population consisted of a sample of men born in 1943 (described in Paper III) and a similar sample of men born in 1913. The impact of different factors on the risk of developing HF was examined. Eighty men born in 1913 (9.4%) and 42 men born in 1943 (5.3%) developed HF during follow-up with an adjusted hazard ratio comparing the two cohorts of 0.46 (95% confidence interval 0.28–0.74, p=0.002). In both cohorts, higher body mass index, higher diastolic blood pressure, treatment for hypertension, and onset of atrial fibrillation, ischemic heart disease, or diabetes mellitus were associated with higher risk of HF. Higher heart rate was associated with an increased risk only in men born in 1913, whereas higher systolic blood pressure, smoking, higher glucose, higher cholesterol, and physical inactivity were associated with an increased HF risk in men born in 1943. The relative importance of atrial fibrillation as a risk factor decreased, whereas that of systolic blood pressure and physical inactivity increased in men born in 1943 compared with men born in 1913.

Conclusions: Titration to the target ACEI/ARB dose is beneficial with respect to mortality in elderly patients with HF. Non-cardiac comorbidities contribute significantly to mortality in both HF phenotypes with some notable differences. NT-proBNP and hs-CRP have a predictive value for the incidence of HF in middle-aged men. The incidence of HF in middle-aged men has decreased during the past 30 years and, in the meantime, the risk profile for HF has also changed.

Keywords: Heart failure, prognosis, characteristics, risk factors, incidence, prediction

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LIST OF PAPERS

This thesis is based on the work contained in the following papers, which are referred to in the text by their Roman numerals.

Paper I Barywani SB, Ergatoudes C, Schaufelberger M, Petzold M, Fu ML. Does the target dose of neurohormonal blockade matter for outcome in Systolic heart failure in octogenarians?
Int J Cardiol. 2015;187:666-72

Paper II Ergatoudes C, Schaufelberger M, Andersson B, Pivodic A, Dahlström U, Fu M. Non-cardiac comorbidities and mortality in patients with heart failure with reduced vs. preserved ejection fraction: a study using the Swedish Heart Failure Registry.
Clin Res Cardiol. 2019;108:1025-33

Paper III Ergatoudes C, Thunström E, Hansson PO, Morales D, Mandalenakis Z, Rosengren A, Zhong Y, Caidahl K, Fu M. Natriuretic and Inflammatory Biomarkers as Risk Predictors of Heart Failure in Middle-Aged Men From the General Population: A 21-Year Follow-Up.
J Card Fail. 2018;24:594-600

Paper IV Ergatoudes C, Hansson PO, Svärdsudd K, Rosengren A, Thunström E, Caidahl K, Pivodic A, Fu M. Incidence rates and risk factors of heart failure: comparing two cohorts of middle-aged men born 30 years apart.
Submitted

SVENSK SAMMANFATTNING

Bakgrund: Hjärtsvikt (HF) är ett stort folkhälsoproblem som drabbar minst 26 miljoner människor världen över och är en ledande orsak till funktionsnedsättning och mortalitet.

Syfte: Att identifiera tillstånd som är förknippade med förbättrad eller förvärrad prognos hos patienter med etablerad HF och att studera faktorer som är associerade med högre risk för incidens av HF i den allmänna populationen.

Metoder och Resultat: Avhandlingen består av fyra delarbete. Arbete I var utformat för att studera effekten av olika dosnivåer av beta-blockerare (BB) och angiotensin konverterings enzym hämmare (ACEIs) på mortalitet hos äldre patienter med HF med reducerad ejektionsfraktion (EF). Studiekohorten var 184 HF patienter i åldern ≥80 med HF och EF ≤40%. Måldosen ACEis var associerad med lägre mortalitet jämfört med <50% av måldosen. Inga signifikanta skillnader i överlevnad hittades mellan BBs-dosgrupperna. I Arbete II genomfördes en jämförelse för prevalensen och för den prognostiska betydelsen av icke-kardiella komorbiditeter på mortalitet mellan patienter med HF med EF <50% och HF med EF ≥50%. Data från det svenska hjärtsviktregistret mellan maj 2000 och december 2012 analyserades. Stroke, anemi, gikt och cancer var alla förknippade med högre mortalitet i båda fenotyperna med liknande effekt, medan diabetes, njursvikt och leversjukdom hade en högre påverkan på mortalitet hos patienter med EF <50%. Lungsjukdom var mer framträdande hos patienter med EF ≥50%. I arbete III undersöktes det prediktiva värdet av olika biomarkörer för uppkomst av HF hos 50-åriga män. Studiekohorten var ett slumpmässigt urval av män födda 1943 som följdes upp under 21 år. N-terminal pro b-type natriuretic peptide (NT-proBNP) ≥25ng/L och high-sensitivity C-reactive protein (hs-CRP) >3mg/L vid 50 års ålder var associerat med högre odds för insjuknande i HF. Arbete IV studerade och jämförde riskfaktorer och incidensen av HF hos 2 kohorter av medelålders män födda 30 år från varandra. Kohorten av män födda 1943 (beskrivet i Arbete III) och ett liknande urval av män födda 1913 utgjorde den studiepopulationen. Effekterna av olika faktorer på risken för att utveckla HF undersöktes. Åttio män födda 1913 (9.4%) och 42 män födda 1943 (5.3%) utvecklade hjärtsvikt under uppföljningstiden, justerad hazard ratio (födda 1943 vs 1913): 0.46 (95% konfidensintervall 0.28–0.74, p=0.002). I båda kohorterna var högre kroppsmasseindex, högre diastoliskt blodtryck, behandling för högt blodtryck, förekomst av förmaksflimmer, ischemisk hjärtsjukdom och diabetes mellitus associerade med högre risk för HF. Högre hjärtfrekvens var förknippad med en ökad risk endast hos män födda 1913 medan högre systoliskt blodtryck, rökning, högre glukos, högre kolesterol och fysisk inaktivitet var förknippade med högre risk hos män födda 1943. Den relativa betydelsen av förmaksflimmer som riskfaktor har minskat medan betydelsen av systoliskt blodtryck och fysisk inaktivitet har ökat i kohort 1943 jämfört med 1913.

Slutsatser: Upptitrering till måldos av ACEI är fördelaktig för överlevnad hos äldre patienter med HF och EF <40%. Icke kardiella komorbiditeter har ett signifikant bidrag till dödligheten i båda HF-fenotyperna med några skillnader. NT-proBNP och hs-CRP har ett prediktivt värde för uppkomst av HF hos medelålders män. Incidensen av hjärtsvikt hos medelålders män har minskat de senaste 30 åren och under tiden har riskprofilen för hjärtsvikt också förändrats.

CONTENTS

ABBREVIATIONS

ACEI	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin II receptor blocker
BB	Beta-blocker
BP	Blood pressure
BMI	Body mass index
CI	Confidence interval
DBP	Diastolic blood pressure
EF	Ejection fraction
HF	Heart failure
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
hs-CRP	High-sensitivity C-reactive protein
IL-6	Interleukin-6
MRA	Mineralocorticoid receptor antagonist
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
OR	Odds ratio
ROC	Receiver operating characteristic
SBP	Systolic blood pressure
SD	Standard deviation
SwedeHF	Swedish Heart Failure Registry
TIA	Transient ischemic attack

INTRODUCTION

"The very essence of cardiovascular practice is the early detection of heart failure"
Sir Thomas Lewis, 1933

Definition of heart failure

Heart failure (HF) is a complex clinical syndrome, for which several definitions have been proposed. The European Society of Cardiology defines HF as a clinical syndrome characterized by symptoms such as shortness of breath, persistent coughing or wheezing, ankle swelling, and fatigue that may be accompanied by the following signs: jugular venous pressure, pulmonary rales, increased heart rate, and peripheral edema (Table 1).[1]

According to Braunwald's Heart Disease,[2] HF is defined as 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.

Table 1. Symptoms of heart failure

• Shortness of breath (dyspnea)	• Fatigue	• Weakness
• Swelling (edema) in legs and ankles	• Rapid heartbeat	• Persistent cough or wheezing
• Increased need to urinate at night (nocturia)	• Reduced ability to exercise	• Dyspnea when lying down (orthopnea)

History of heart failure

Descriptions of HF exist from ancient Egypt, Greece, and India. An Egyptian dignitary who died 3,500 years and was discovered in 1904 in the Egyptian city of Luxor (the mummy of Nebiri) may be the oldest known victim of HF. Histology of the lungs showed the presence of pulmonary edema, which was likely due to HF, as histochemical staining of lung tissue ruled out other diseases as a cause of 'fluid in the air spaces of the lung', including tuberculosis, granulomas, or bacterial infections.[3]

A description of rales is found in the Hippocratic corpus: "When the ear is held to the chest, and one listens for some time, it may be heard to see the inside like the boiling of vinegar". It also discussed a way to drain this fluid through a hole drilled in a rib.[4]

Important elements in the history of HF over the centuries that followed are presented in the Table 2.[5]

Table 2. History of major milestones in heart failure

1628	William Harvey described the circulation
1785	William Withering published an account of the medical use of digitalis
1895	Willem Einthoven invented the first practical electrocardiogram
1895	Wilhelm Conrad Roentgen discovered X-rays
1918	Ernest Henry Starling published the Frank-Starling law of the heart
1954	Inge Edler and Hellmuth Hertz used ultrasound to image cardiac structures
1967	Christiaan Barnard performed the first human heart transplant
1987	CONSENSUS-I Study showed survival benefit of ACEIs in heart failure
1995	European Society of Cardiology published the first guidelines for heart failure

Classification of heart failure related to ejection fraction

Left ventricular ejection fraction (EF) is used for the classification of HF into different categories. EF defines as the fraction of chamber volume ejected in systole (stroke volume) in relation to the volume of the blood in the ventricle at the end of diastole (end-diastolic volume). The American Society of Echocardiography and the European Association of Cardiovascular Imaging consider a normal EF and normal range as 62% (52–72%) in men and 64% (54–74%) in women.[6]

HF with preserved EF (HFpEF) is characterized by EF ≥50% and additional obligatory criteria including diastolic abnormalities on echocardiography[7] in both European and American guidelines.[1, 8] EF <50% is considered reduced and this type of HF was until recently defined as HF with reduced EF (HFrEF). However, the definition of patients with EF in the range of 40–49% has been considered a 'grey area', which was defined as HF with mid-range EF (HFmrEF) in the latest update of European Society of Cardiology guidelines (Table 3).[1]

Epidemiology of heart failure

HF is a major public health problem affecting more than 26 million people worldwide.[9, 10] According to data from the Framingham Heart Study, the lifetime risk for developing HF at 40 years of age is approximately 20% for both men and women.[11] In Sweden, the prevalence of HF is estimated to be about 2% and increases with age, rising to ≥10% in those over 70 years.[12, 13] Data from 2.1 million Swedish inhabitants show that the mean age at first diagnosis of HF was 77 years[12] and the incidence was

Table 3. Definition of heart failure according to 2016 European Society of Cardiology guidelines

Criteria	Type of heart failure		
	HFrEF	**HFmrEF**	**HFpEF**
1	Symptoms/signs	Symptoms/signs	Symptoms/signs
2	EF <40%	EF 40–49%	EF ≥50%
3	–	1. Elevated levels of natriuretic peptide 2. At least one additional criterion a. Relevant heart structure heart disease (LVH and/or LAE) b. Diastolic dysfunction	1. Elevated levels of natriuretic peptide 2. At least one additional criterion a. Relevant heart structure heart disease (LVH and/or LAE) b. Diastolic dysfunction

EF, ejection fraction; HFmrEF, heart failure with mid-range EF; HFpEF, heart failure with preserved EF; HFrEF, heart failure with reduced ejection fraction; LAE, left atrial enlargement; LVH, left ventricular hypertrophy.

3.8/1000 person-years. The epidemiology of HF is evolving. Data suggests that the incidence of HF peaked in the mid-1990s and has since declined, except in younger individuals where the incidence has increased.[14-16] Increased life expectancy and improved HF management have led to an increased HF prevalence. It is estimated that the prevalence of HF will increase by 46% from 2012 to 2030.[17]

The proportion of patients with HFrEF compared to those with HFpEF varies significantly between studies. Approximately half of patients with HF have preserved EF, although the percentage of HFpEF ranges significantly depending on the definition applied and the population studied.[18-23]

Guideline-directed medical therapy of heart failure

Neurohormonal blockers such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-blockers (BBs), and mineralocorticoid receptor antagonists (MRAs) have been proven to decrease morbidity and mortality in HFrEF and are therefore recommended by guidelines as the cornerstone in therapy for HFrEF patients.[24-31]

In patients who remain symptomatic despite optimal treatment with ACEI/ARB, BB, and MRA, sacubitril/valsartan is recommended as a replacement for an ACEI/ARB to further reduce the risk of hospitalization and death as well as to improve symptomatic relief and quality of life.[32] In the case of a resting heart rate ≥70/min in sinus rhythm despite optimal treatment including BB, ivabradine should be considered.[33]

In addition to pharmacologic therapy, cardiac resynchronization therapy and implantable cardioverter defibrillator therapy are key components in the management of HFrEF. Implantable cardioverter defibrillators are recommended for secondary prevention in patients with a history of ventricular tachycardia as well as primary prevention in symptomatic patients with EF ≤35% despite optimal medical treatment.

Cardiac resynchronization therapy has been shown to reduce morbidity and mortality in selected patients with HF[34] and should be considered in symptomatic patients with EF ≤35% despite optimal medical treatment when QRS duration is ≥130 msec.

On the contrary, no treatment has yet been shown, convincingly, to reduce mortality in patients with HFpEF or HFmrEF (patients with HFmrEF have generally been included in trials of patients with HFpEF).[35-41] All outcome trials in HFpEF to date have failed to demonstrate survival benefit, despite robust evidence of prognostic benefit using the same agents in HFrEF. However, it is worth mentioning that recent *post-hoc* analyses have suggested benefits from medical treatment may be present in patients with HFmrEF.[39, 42,43]

Challenges of applying guideline-directed medical therapy in clinical practice

The first step in the therapeutic algorithm recommended by guidelines for patients with symptomatic HFrEF is the initiation of an ACEI (or an ARB if the patient is ACEI intolerant) and a BB at low doses with subsequent titration to maximum tolerated evidence-based doses.[1] However, observational studies in the real-world setting demonstrate that only around one-third of HF patients receive the target dose of either ACEI/ARB and/or BB.[44, 45] Likewise, in the Swedish Heart Failure Registry (SwedeHF) only two-thirds reached ≥50% of the target dose for either ACEI or BB.[46] Furthermore, there is a limited number of studies examining the association between medication dose and outcome in HF patients. These studies suggest an outcome benefit by using higher compared to lower doses of ACEIs, ARBs, or BBs.[47-50]

To date, most clinical trials have been conducted primarily in relatively young patients with HF. However, compared with participants in studies, HF patients in daily clinical practice are often older with several comorbidities and have a low tolerability for different medical treatments. Is guideline-directed medical therapy equally beneficial in elderly compared to younger HF patients? Evidence regarding the optimal dose in this group of patients is limited. The question raised is whether the dose-related benefit for prognosis suggested by the available studies in HFrEF patients also applies for elderly patients in the real-world setting.

Comorbidities in heart failure

Comorbidity refers to chronic conditions that coexist with the condition being described. A commonly used classification is cardiac (ischemic heart disease, atrial fibrillation, etc.) and non-cardiac diseases. Both types of comorbidities accompany HF with higher frequency in these patients compared to age-matched controls.[51] Non-cardiac comorbidities are highly prevalent: 75% of HF patients have at least one comorbidity[51] and about 40% of them have ≥5, with renal disease, anemia, and diabetes mellitus being the most common.[52]

There is a growing recognition that the burden of comorbidities increases the risk of mortality and decreases quality of life,[53-55] suggesting that targeting comorbidities as a part of HF care may be beneficial for prognosis.[56]

Compared to patients with HFrEF, those with HFpEF are more frequently women, older, have a higher prevalence of obesity and atrial fibrillation, and have a lower incidence of ischemic heart disease.[57-60] Previous studies suggest a higher prevalence of non-cardiac illnesses among HFpEF compared to HFrEF patients,[61-63] leading to the belief that comorbidities might play a more significant role in HFpEF.[64] However, recent studies demonstrate similar prevalence between these two HF phenotypes.[51, 65] Few studies have compared the relative impact of non-cardiac comorbidities on prognosis in patients with HFrEF compared to HFpEF and available results have been inconsistent.[61, 66-70]

Prognosis in heart failure

The improved management of HF has reduced mortality rates by as much as 50% over the past decades, although both short- and long-term mortality rates remain high.[71, 72] In fact, men and women with a diagnosis of HF seem to have worse survival than patients with one of several common cancers.[73] The 1-year mortality rate for HF patients in Sweden in 2016 was 16.8% according to the SwedeHF annual report.[46] Approximately 50% of patients diagnosed with HF die within 5 years.[73, 74]

The survival of HF patients is influenced by several factors including age, sex, the cause of HF, and hospitalizations. The mortality rate in treated patients with HF increases with advancing age in both sexes.[75] Prognosis has generally been better in women than men. In the Framingham Study, the median survival time after diagnosis was 3.2 years in women and 1.7 years in men.[75] The etiology of HF may be predictive of long-term outcome. Peripartum cardiomyopathy has better prognosis compared to patients with ischemic heart disease or infiltrative myocardial disease, such as amyloidosis.[76] Furthermore, the need for hospitalization is an important marker of poor prognosis.[77]

Does prognosis differ between HFrEF and HFpEF? To date, mortality rates reported in studies for HFrEF compared to HFpEF are strongly influenced by the study population, the inclusion criteria applied, and the definitions used for the two HF phenotypes. A meta-analysis of randomized trials found a higher mortality rate in HFrEF,[78] while epidemiological studies demonstrated similar mortality rates.[79-81] However, a study that included all patients hospitalized at Sahlgrenska University Hospital/Östra for HF between May 2007 and April 2008 showed that patients with HFpEF have a better long-term prognosis.[82] The majority of deaths in both categories are cardiovascular deaths. However the proportion of deaths that are cardiovascular related is higher in HFrEF than in HFpEF.[83-85]

Risk-factors for the development of heart failure

The major efforts in HF research to date have focused on treatment, outcomes, and prognosis as well as the structured management of patients with the clinical syndrome of HF. In order to highlight the importance of HF prevention, the American Heart Association and American College of Cardiology have proposed a classification scheme for HF to include “Stage-A” patients, i.e., those who do not have structural heart disease but are at risk for developing HF.[8]

A variety of factors are known to be associated with higher risk of developing HF, ranging from lifestyle characteristics (smoking, physical inactivity) to common medical conditions (hypertension, ischemic heart disease, atrial fibrillation, diabetes mellitus, obesity).[86-90] Ways to reduce the risk of HF are summarized in Table 4.

Table 4. Ways to reduce the risk of heart failure

Lifestyle factors	Medical conditions
• Physical activity	• Treat high blood pressure
• Healthy weight	• Treat atrial fibrillation
• No smoking	• Control diabetes
• Healthy eating	• Maintain healthy cholesterol levels

The Framingham Heart Study is a landmark achievement that has provided significant evidence about the incidence and the risk profile of HF in the general population. Investigations have found that hypertension and coronary heart disease are the two most common conditions preceding the onset of HF and, in addition, diabetes mellitus and electrocardiographic left ventricular hypertrophy are also associated with higher risk of developing HF.[91] A recognized limitation in Framingham Heart Study is that emerging risk factors were not incorporated, such as bodyweight and physical inactivity, as well as the lack of randomization of the study cohort.

Changes in lifestyle, new medications, and advances in medical technology during the past half century have likely affected the prevalence of cardiovascular risk factors as well as modifying the prognosis of the majority of cardiovascular diseases. Population-based observational studies have examined the secular trends of cardiovascular risk factors and have reported significant changes.[92-95] During this time period, serum total cholesterol levels, systolic and diastolic blood pressure, and smoking have decreased, while the prevalence of obesity has escalated.[95, 96] Meanwhile, the prognosis of several cardiovascular diseases, with ischemic heart disease probably being the most applicable example, has been greatly improved. The mortality rate from ischemic heart disease has decreased dramatically in the past four decades in developed countries.[97, 98] A similar trend in ischemic heart disease was observed in two cohorts of middle-aged men living in Gothenburg born 30 years apart.[99]

It is, however, worth mentioning that secondary prevention after myocardial infarction remains suboptimal. In a study from our group only 3.5% of patients achieved six pre-specified prevention goals 2 years after acute myocardial infarction and non-fatal cardiovascular events occurred in 46.5% of the participants.[100] A reasonable question is whether the above-described changes in cardiovascular risk factors and diseases have an impact on the incidence and risk profile of HF in the contemporary era with gradually improved primary and secondary cardiovascular prevention (despite remaining suboptimal).

Biomarkers as predictors of incident heart failure

An increasing number of enzymes, hormones, peptides, and proteins, which are referred to as biomarkers, appear to be associated with HF. Measuring their concentrations in the circulation can be a convenient and non-invasive approach to provide important information about disease severity and helps in the detection, diagnosis, prognosis, and management of the disease.[101] These biomarkers may reflect different mechanisms that seem to coexist in the complex pathophysiology of HF such as myocyte stress, inflammation, myocyte injury, oxidative stress, and sustained neurohormonal overactivation.[102]

Natriuretic peptides, as indicators of hemodynamic stress, have an essential role in HF diagnosis as well as the evaluation of HF treatment.[103-107] N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) is probably the most widely used biomarker and is included in the diagnostic algorithm suggested in the most recent European guidelines.[1] Even inflammation seems to be important in the pathogenesis and progression of HF.[108] Available data suggest that elevated circulating inflammatory cytokines and high-sensitivity C-reactive protein (hs-CRP) are associated with worse prognosis in patients with established HF.[109-114] Another protein associated with worse prognosis in HF is cystatin C, a well-known biomarker of renal function which also indicates the level of oxidative stress in the human body.[115]

Compared to prognostic studies of biomarkers in HF, studies regarding the predictive value of biomarkers for incident HF in the general population are scarce.[68, 116] How useful are biomarkers as predictors of incident HF? There have been some studies about the identification of risk factors for HF and risk assessment scores have been developed.[89, 117] However, these scores were based on specific subgroups (e.g., elderly, patients with hypertension), so they cannot be applied in a general population, and furthermore, the majority of them have not been externally validated. In addition, it is known that HF can occur in individuals in the absence of any known risk factors. Furthermore, asymptomatic left ventricular dysfunction frequently antecedes HF but routine echocardiography is very expensive for use as a screening method. Since different biomarkers represent different pathophysiological mechanisms involved in HF, it is assumed that a panel of such biomarkers may facilitate the identification of individuals at risk for HF at an early stage. The role of a single biomarker as a predictor of HF incidence has been examined. In the Framingham Study, interleukin-6 (IL-6) was associated with a higher risk of HF in patients without prior myocardial infarction.[116] However, studies using a panel of biomarkers reflecting different pathophysiological mechanisms in a general population for incident HF are sparse.

"Prevention is better than cure"

Desiderius Erasmus

AIMS

General aims

The general aims of this thesis are: 1) to study the association between different characteristics and prognosis in patients with established HF; and 2) to study characteristics associated with higher risk for the incidence of HF in the general population.

Specific aims

- To examine whether elderly patients with HF and EF ≤40% treated with ≥50% of ACEI/ARB and/or BB target dose have better prognosis in terms of mortality compared to those receiving <50% of target dose, despite maximum titration. In addition, to study whether the target dose outperforms all other doses (Paper I).

- To compare the prevalence and prognostic contributions of non-cardiac comorbidities to all-cause mortality in patients with EF <50% and ≥50%. In addition, to examine whether an increasing number of non-cardiac comorbidities is associated with a higher risk of mortality and if this risk is similar in the two HF phenotypes. Finally, to examine possible variations in the impact of each comorbidity on mortality over a 12-year study period (Paper II).

- To evaluate whether biomarkers proven to be useful prognostic predictors in patients with established HF could predict the onset of HF in middle-aged men from the general population during a 21-year follow-up (Paper III).

- To compare the incidence and risk factors of HF in middle-aged men from the general population born 30 years apart, in 1913 and 1943, respectively (Paper IV).

SUBJECTS AND METHODS

Paper I

Study population

This was a retrospective study of 184 consecutive HF patients aged ≥80 years and EF ≤40% referred to two outpatient cardiology departments (Sahlgrenska University Hospital/Sahlgrenska and Sahlgrenska University Hospital/Östra) between January 2000 and January 2008.

Methods

One inclusion criterion was the titration of ACEI/ARB and/or BB to either maximal tolerated dose or target dose for guideline-recommended HF medications. This was performed by our HF specialist nurses over 3–6 months. Titration ended after reaching target dose or the highest tolerated dose. Target doses for ACEIs, ARBs, and BBs were based on the European Society of Cardiology guideline recommendations.[118]

The study cohort was divided into three groups according to ACEI/ARB and/or BB doses: low, intermediate, and target dose (<50% of target dose, ≥50% to <target dose, and target dose, respectively), Figure 1. The primary outcome was 5-year all-cause mortality and secondary outcomes were 5-year cardiac mortality and hospitalization due to worsening HF.

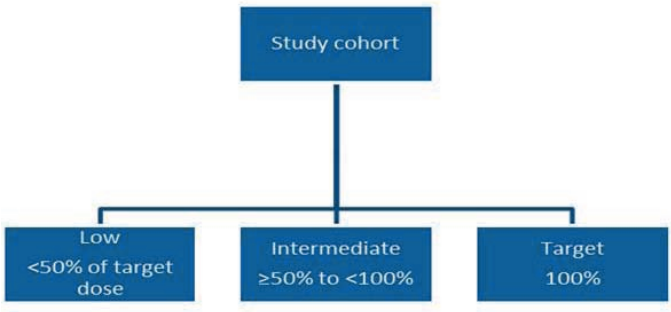

Figure 1. Definition of target dose strata.

Statistical analysis

Cox proportional hazards regression analysis was used to analyze possible associations between the three different doses of each agent (ACEI/ARB and/or BB) and survival. Kaplan-Meier analysis and univariate Cox proportional-hazard regression analysis were used to build multivariate models.

Paper II

Study population

All patients registered in SwedeHF between May 2000 and December 2012 constituted the study population. Exclusion criteria were: 1) death during hospitalization; 2) incomplete information about EF; and 3) existence of valvular disease with clinical significance as reported in the SwedeHF, Figure 2.

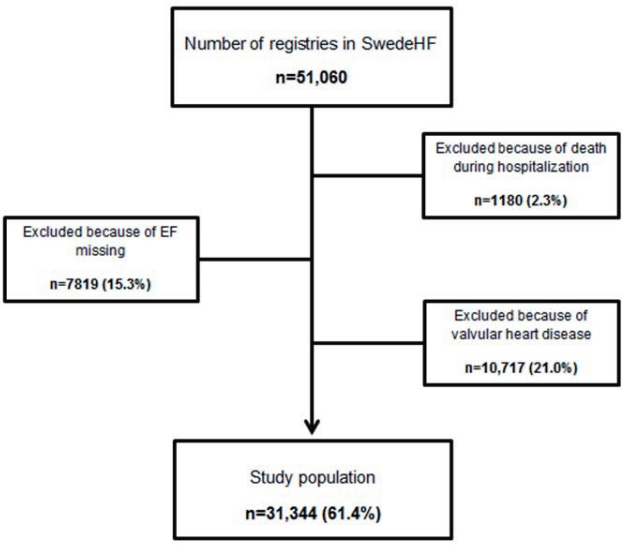

Figure 2. Patient flow chart.

Methods

Data were collected from the SwedeHF, which was linked with the National Patient Register and the Cause of Death Register. The study cohort was divided into two groups, HFrEF and HFpEF. HFrEF was defined as EF <50% and HFpEF as EF ≥50% according to the definitions in the 2012 European Society of Cardiology guidelines.[118] The ten non-cardiac comorbidities included in the investigation were: hypertension, diabetes, stroke/transient ischemic attack (TIA), anemia, renal failure, pulmonary disease, liver disease, sleep apnea, gout, and cancer within the previous 3 years. The primary outcome was all-cause mortality until December 31, 2012.

Statistical analysis

Multivariate Cox regression analyses were performed for the different variables at the index date, calculating hazard ratios (HRs) with 95% confidence intervals (CIs) for mortality. To examine trends over time for the contribution to mortality by each comorbidity, similar model analyses were performed separately for HFrEF and HFpEF, but also including five consecutive periods (2000–2004, 2005–2006, 2007–2008, 2009–2010, and 2011–2012) and the interaction between comorbidity and periods.

Paper III

Study population

A randomly selected sample of half of all men born in 1943 and living in the city of Gothenburg, Sweden, were invited in 1993 to participate in the study named "Men Born In 1943", a longitudinal, prospective cohort study investigating cardiovascular risk factors and diseases. Of the 1463 men invited, 798 (55%) accepted participation and underwent a health examination at entry. Men who were alive and still resident in Sweden were invited to a second examination in 2003 and a third examination in 2014.

Methods

The three examinations included a physical examination, blood testing, and questionnaires concerning medical history, lifestyle, physical activity, and mental wellbeing. In addition, echocardiographic assessment was included in the 2014 examination. A panel of biomarkers, (NT-proBNP, hs-CRP, IL-6, and cystatin C) were analyzed. HF during follow-up was identified through a combination of three procedures: 1) a data file with the personal identification number of the men run against the National Patient Register and the Swedish National Cause of Death Registry; 2) a review of medical records from additional cases identified at the examinations; and 3) results from the echocardiographic examination in 2014.

Statistical analysis

Multivariate logistic regression models were used to examine the association of each biomarker with the incidence of HF adjusted for body mass index (BMI) and hypertension. Odds ratios (ORs) with 95% CIs were presented along with the area under the receiver operating characteristic (ROC) curve as a measure of predictive performance. For NT-proBNP, IL-6, and cystatin C, median levels were applied as cut-off levels. For hs-CRP, cut-off levels were set to 1 and 3mg/L in accordance with previous studies.

Paper IV

Study population

Two population samples of men born in 1913 and 1943 were first examined at age 50 years in 1963 and 1993, respectively, and followed longitudinally over 21 years. For the sample of men born in 1913, repeated examinations were conducted in 1967, 1973, and 1980. For the sample of men born in 1943, the methodology has been described in Paper III.

Methods

The same study protocol was used for both cohorts and included physical examination and questionnaires concerning medical history, lifestyle, physical activity, and mental wellbeing as well as blood samples at baseline. The definition of HF used in both cohorts was: 1) hospitalization with a diagnosis of HF either as a principal or a

secondary diagnosis; or 2) death with an underlying cause of HF reported in the Swedish National Cause of Death Registry.

Statistical analysis

Cox proportional hazards regression analysis was used to examine the impact of different factors on the risk of developing HF and to compare the impact of these factors between the two cohorts. Analysis was performed using both characteristics at baseline (at 50 years of age) and time-dependent variables (atrial fibrillation, diabetes mellitus, and ischemic heart disease). HR per unit increase in standard deviation (SD) was used to rank the importance of risk factors in each cohort. Multivariate models were then built in a stepwise procedure using the results from the univariate analyses.

Methodology summary for Papers I–IV

An overview of the methodology for Papers I–IV is given in Table 5.

Table 5. Methodology overview

	Paper I	**Paper II**	**Paper III**	**Paper IV**
Study design	Retrospective	Retrospective	Longitudinal	Longitudinal
Study population	HF patients EF ≤40%, age ≥80 years	HF patients SwedeHF	Randomly selected population sample	Two randomly selected population samples born 30 years apart
Comparison	HF medication High *vs* low doses	HF phenotypes HFrEF *vs* HFpEF	Biomarkers High *vs* low levels	Risk factors Presence *vs* absence
Outcomes	All-cause mortality Cardiac mortality HF hospitalization	All-cause mortality	Incident HF	Incident HF
Statistical analysis	Cox regression analysis	Cox regression analysis	Logistic regression analysis	Cox regression analysis

EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved EF; HFrEF, heart failure with reduced ejection fraction; SwedeHF, Swedish Heart Failure Registry.

Ethics

All the study protocols in this thesis were approved by the Ethical Committee at the University of Gothenburg and conformed to the principles outlined in the 1964 Declaration of Helsinki and its subsequent amendments except for the first examination of the cohort of men born in 1913 in 1963 where only oral informed consent was given.

RESULTS

Paper I

A total of 184 patients fulfilled the inclusion criteria and constituted the study cohort. The mean age of the patients was 83 years. After titration, only 14% of patients were treated with the target doses of both ACEI/ARB and BB. The target dose of ACEI/ARB was achieved in 53% of patients and that of BB by 21% (Table 6).

Table 6. Doses after titration

Drugs	No. of patients (%)		
	Low dose (<50% of target)	Intermediate dose (≥50% to <target)	Target (100%)
ACEI/ARB	47 (26)	39 (21)	98 (53)
BB	92 (50)	54 (29)	38 (21)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta-blocker.

The study results are summarized in Table 7. The 5-year all-cause mortality was 77% and 5-year all-cause mortality was 61%. There were no significant differences in non-cardiac mortality and non-cardiac hospital admissions between the three different dose-groups of ACEI/ARB and/or BB.

Table 7. Main study results

	HR (95% CI)	p-value
All cause mortality: target *vs* low dose ACEI/ARB	0.6 (0.4–0.9)	0.03
Cardiac cause mortality: target *vs* low dose ACEI/ARB	0.5 (0.2–0.8)	0.005
All cause mortality: target *vs* low dose BB	0.7 (0.5–1.2)	0.2
Cardiac mortality: target *vs* low dose BB	0.7 (0.4–1.4)	0.4

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta-blocker; CI, confidence interval; HR, hazard ratio.

For ACEI/ARBs, the target dose was associated with reduced all-cause and cardiac mortality compared to <50% of target dose (HR 0.6, 95% CI 0.4–0.9; p=0.03). No significant differences were found between target dose and intermediate dose or between intermediate dose and lower dose.

For BBs, there were no significant differences in survival between the three groups. It is, however, important to mention that there were no significant differences in heart rate after titration of BB between the three dose groups.

Paper II

Between May 2000 and December 2012, 31,344 patients (79.3% HFrEF, 20.7% HFpEF) in the SwedeHF were retained for analysis after exclusions.

Patients with HFpEF were older (mean age 77 *vs* 71 years), more likely to be women (53% *vs* 31%), and had a higher prevalence of atrial fibrillation and a lower prevalence of ischemic heart disease compared to those with HFrEF. Patients with preserved EF had a higher prevalence of all non-cardiac comorbidities except for renal failure, which had a similar age-adjusted prevalence in both groups. The prevalence of non-cardiac comorbidities is summarized in Table 8.

Table 8. Prevalence of non-cardiac comorbidities

Variable	No. of patients (%)			Age-adjusted p-value
	Total (n = 31,344)	HFrEF (n = 24,856)	HFpEF (n = 6488)	
Hypertension	21,684 (69.2)	16,418 (66.1)	5266 (81.2)	<0.0001
Diabetes	8732 (27.9)	6780 (27.3)	1952 (30.1)	<0.0001
Stroke/TIA	5041 (16.1)	3778 (15.2)	1263 (19.5)	0.0003
Anemia	11,231 (35.8)	8399 (33.8)	2832 (43.7)	<0.0001
Renal failure	14,706 (47.1)	11,155 (45.0)	3551 (54.9)	0.47
Lung disease	8954 (28.6)	6676 (26.9)	2278 (35.1)	<0.0001
Liver disease	501 (1.6)	370 (1.5)	131 (2.0)	<0.0001
Sleep apnea	1132 (3.6)	835 (3.4)	297 (4.6)	<0.0001
Gout	1329 (4.2)	998 (4.0)	331 (5.1)	0.026
Cancer within previous 3 years	4108 (13.1)	3094 (12.4)	1014 (15.6)	0.0042

HFpEF, heart failure with preserved EF; HFrEF, heart failure with reduced ejection fraction; TIA, transient ischemic attack.

All-cause mortality until December 31, 2012 was 34.3% in the HFrEF group and 40.3% in HFpEF group. The age-adjusted mortality rate was 11.1 (CI 95% 10.9–11.4) and 10.6 (CI 95% CI 10.1–11.0) per 100 person-years, respectively. The association between comorbidities and mortality is summarized in Table 9.

Table 9. Association between comorbidities and mortality

Variable	HFrEF		HFpEF		p-value for interaction with EF
	HR (95% CI)	p-value	HR (95% CI)	p-value	
Hypertension	0.96 (0.91–1.00)	0.051	0.85 (0.77–0.93)	0.0007	0.0063
Diabetes	1.57 (1.50–1.65)	<0.0001	1.39 (1.27–1.51)	<0.0001	0.0002
Stroke/TIA	1.36 (1.29–1.43)	<0.0001	1.30 (1.19–1.43)	<0.0001	0.10
Anemia	1.70 (1.63–1.78)	<0.0001	1.65 (1.53–1.79)	<0.0001	0.42
Renal failure	1.65 (1.57–1.73)	<0.0001	1.44 (1.32–1.57)	<0.0001	0.0031
Lung disease	1.46 (1.40–1.53)	<0.0001	1.66 (1.54–1.80)	<0.0001	0.0066
Liver disease	2.13 (1.83–2.47)	<0.0001	1.42 (1.09–1.85)	0.0084	0.015
Sleep apnea	1.11 (0.96–1.27)	0.15	1.17 (0.94–1.45)	0.16	0.83
Gout	1.57 (1.43–1.72)	<0.0001	1.38 (1.17–1.62)	0.0001	0.051
Cancer within previous 3 years	1.35 (1.28–1.43)	<0.0001	1.35 (1.22–1.49)	<0.0001	0.84

CI, confidence interval: EF, ejection fraction; HFpEF, heart failure with preserved EF; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; TIA, transient ischemic attack.

Stroke, anemia, gout, and cancer had a similar impact on mortality in both phenotypes, whereas diabetes, kidney failure, and liver disease had a higher impact on mortality in HFrEF patients. Pulmonary disease was more prominent in those with HFpEF. Sleep apnea was not associated with a worsened prognosis in either group.

An increased number of comorbidities was associated with higher risk of mortality in both HF phenotypes according to multivariate survival analysis without significant differences for the impact on mortality between the two HF phenotypes. The adjusted HR for patients with one comorbidity *vs* no comorbidities was 1.37 (95% CI 1.20–1.57) for HFrEF and 1.60 (95% CI 1.07–2.38) for HFpEF. Adjusted HR for patients with seven comorbidities was 7.63 (95% CI 5.55–10.50) for HFrEF and 6.59 (95% CI 3.89–11.16) for HFpEF.

During follow-up (2000–2012), no statistically significant interaction was found between periods and the effect of each comorbidity on mortality.

Paper III

In total, 85 of 747 (11.4%) of the participants developed HF during the 21-year follow-up. Thirteen of the 85 patients (15.2%) died by the end of the study. More than half of the HF cases (55%) were diagnosed at the last examination in 2014 when an echocardiographic examination was performed. The majority (37 of 47, 78.7%) of the new cases had HFpEF.

According to logistic regression analysis, biomarkers associated with higher OR for developing HF were NT-proBNP and hs-CRP. No association was observed for IL-6 or cystatin-C and HF (Table 10).

Table 10. Association between biomarkers and heart failure

Variable	Value	OR (95% CI)	p-value
NT-proBNP, ng/L	≥25	2.09 (1.30–3.36)	0.0024
hs-CRP, mg/mL	>1	1.72 (1.02–2.90)	0.040
hs-CRP, mg/mL	>3	2.61 (1.59–4.29)	0.0002
IL-6, ng/L	>1.88	1.50 (0.94–2.39)	0.089
Cystatin C, mg/L	>0.89	1.15 (0.73–1.83)	0.54

CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; OR, odds ratio.

For the combination of NT-proBNP ≥25ng/L and hs-CRP >3mg/L, the estimated OR was 2.82 (95% CI 1.53–5.18). A model including BMI, hypertension, NT-proBNP, and hs-CRP was built with stepwise logistic regression analysis. The probability of developing HF in individuals with NT-proBNP ≥25ng/L, hs-CRP >3mg/L, BMI ≥25kg/m^2, and hypertension was 0.33 (95% CI 0.23–0.45). On the contrary, the probability was only 0.04 (95% CI 0.02–0.07) for those with normal BMI, normal blood pressure, NT-proBNP <25ng/L, and hs-CRP ≤3mg/L.

Paper IV

The incidence of HF in men born in 1943 living in Gothenburg was 5.3% (42 of 793), whereas that for men born in 1913 was 9.4 % (80 of 855). The event rates were 2.67% (95% CI 1.97–3.62) and 4.95 (95% CI 3.98–6.16) per 1000 person-years for the 1943 and 1913 cohorts, respectively.

After adjusting for baseline characteristics, men born in 1943 had a 54% lower risk of developing HF compared to men born 30 years earlier (HR 0.46, 95% CI 0.28–0.74, p=0.002).

Characteristics associated with higher HF risk in both cohorts were higher BMI, higher diastolic blood pressure, treatment for hypertension, onset of atrial fibrillation, ischemic heart disease, and diabetes mellitus. Higher heart rate was associated with an increased risk only in men born in 1913, whereas higher systolic blood pressure (SBP), smoking, higher glucose levels, higher total cholesterol levels, and physical inactivity were associated with a higher risk of HF for men born in 1943 (Table 11).

Table 11. Risk factors for heart failure

Men born in 1913		Men born in 1943	
Risk factor	**HR (95% CI)**	**Risk factor**	**HR (95% CI)**
BMI	1.11 (1.04–1.19)	BMI	1.19 (1.11–1.28)
DBP	1.09 (1.00–1.18)	DBP	1.18 (1.03–1.35)
BP medication use	4.31 (1.58–11.79)	BP medication use	4.20 (1.94–9.09)
Atrial fibrillation	29.17 (17.40–48.90)	Atrial fibrillation	13.98 (7.43–26.32)
Ischemic heart disease	7.95 (4.81–13.12)	Ischemic heart disease	6.23 (3.28–11.83)
Diabetes mellitus	2.18 (1.04–4.53)	Diabetes mellitus	3.28 (1.60–6.71)
Heart rate ≤66/min	0.85 (0.67–1.06)	SBP ≤130 mmHg	0.91 (0.61–1.35)
Heart rate >66/min	1.20 (1.08–1.34)	SBP >130 mmHg	1.45 (1.18–1.78)
		Smoking	2.84 (1.18–6.85)
		Glucose level	1.33 (1.22–1.46)
		Cholesterol level	1.34 (1.01–1.78)
		Physical inactivity	2.31 (1.18–4.51)

BMI, body mass index; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; SBP, systolic blood pressure.

The comparison of the impact of different characteristics on HF between the two cohorts showed that the importance of atrial fibrillation as a risk factor for HF has decreased and that of SBP and physical inactivity has increased in men born in 1943 compared to those born thirty years earlier (Table 12).

Table 12. Secular trends in risk factors for heart failure

Risk factor	HR (95% CI)		Interaction p-value
	Men born in 1913	Men born in 1943	
Atrial fibrillation	29.17 (17.40–48.90)	13.98 (7.43–26.32)	0.031
SBP ≤130 mmHg	1.09 (0.75–1.59)	0.91 (0.61–1.35)	0.52
SBP >130 mmHg	1.10 (0.97–1.24)	1.45 (1.18–1.78)	0.021
Physical inactivity	1.02 (0.64–1.64)	2.31 (1.18–4.51)	0.048

CI, confidence interval; HR, hazard ratio; SBP, systolic blood pressure.

DISCUSSION

Neurohormonal blockade: does the dose matter in elderly patients with HFrEF?

The results from Paper I suggest that the target dose of ACEIs or ARBs is associated with lower all-cause and cardiac mortality in elderly patients with HF and EF <40%. However, the target dose was achievable in only half of the patients. On the other hand, the target dose of BB was not associated with benefits in terms of either all-cause or cardiac mortality.

In clinical practice, an HF patient is commonly older than participants in randomized clinical trials. The average age seen in most landmark HF trials is somewhere between 60 and 70 years.[24, 25, 27, 29, 33] Hence, the evidence for treating elderly patients is mostly extrapolated from cohorts that are two decades younger. In fact, some trials excluded patients >80 years of age.[25, 26] In addition, the treatment of HF in the elderly can be challenged by the presence of multiple comorbidities, polypharmacy, lower tolerability, and a lack of social support.[119]

Our study cohort should be regarded as representative of real-world clinical settings. All patients were subjected to optimal dose titration, implying that dose levels should be the highest tolerable as all patients were referred to specialist HF outpatient clinics where titration of HF medication was conducted by HF specialist nurses in cooperation with a cardiologist over a maximum period of 6 months.

After titration, 53% of the participants were treated with the target dose of ACEI/ARB and only 21% with the target dose of BB. The target dose for both agents was only achievable for 14% of patients. The dose levels in our study are comparable to those of previous studies despite our cohort being older and with more comorbidities. In the Improve-HF Study, the target dose of ACEI/ARB and BB were achieved in 38% and 30% of participants, respectively.[45]

Achieving the target dose of ACEI/ARB was associated with reduced mortality compared to a low dose. This finding is accordance with previous studies[47, 48, 50] and implies the value of titrating of this medication to improve prognosis, even in elderly patients. With respect to BBs, no statistically significant differences in survival were observed between the three dose groups. A possible explanation is that the mean heart rate after titration was similar across groups. Therefore, achieving an optimal heart rate may be more important for outcome than the dose itself, which is in line with previous studies.[120, 121]

The importance of non-cardiac comorbidities for mortality in HF: are there any differences between HFrEF and HFpEF?

By access to SwedeHF, our data confirms the high burden of non-cardiac comorbidities in both HFrEF and HFpEF patients. With the exception of renal failure where the

age-adjusted prevalence was similar between groups, non-cardiac comorbidities were more common in patients with HF and preserved EF. Our findings are in line with previous publications with more women, higher mean age, higher prevalence of atrial fibrillation, and lower prevalence of ischemic heart disease in HFpEF compared to HFrEF patients.[57, 58] After adjustment for age, patients with HFpEF had a slightly lower mortality rate.

Our study not only confirms previous observations that non-cardiac illnesses confer significant risk for mortality in HF patients[53] but also extends present knowledge by demonstrating some notable differences on the impact between the two HF phenotypes in contrast to some previous studies.[67, 69, 122]

The relative contribution to mortality was similar comparing HFrEF and HFpEF for stroke/TIA, anemia, gout, and cancer. Diabetes mellitus, renal failure, and liver disease were more prominent in patients with HFrEF, while pulmonary disease was more prominent in patients with HFpEF. Hypertension seems to be a protective factor for mortality in both HF groups, with a slightly higher impact in HFpEF patients. A possible explanation for the protective nature of hypertension is that it reflects the beneficial effect of antihypertensive treatment on mortality. Sleep apnea was not associated with a higher risk for mortality in either group. The low prevalence of sleep apnea reported in the registry (3.6%), which is much lower than previously reported,[51, 123] raises the suspicion of either under-diagnosis or low reporting rates in the registry.

No significant variations in the trend was observed with respect to the impact of comorbidities on mortality between 2000 and 2012 despite treatment for some of these comorbidities having improved over this period of time.[93, 124, 125] One reason might be that the period that was investigated was too short to show changes in the impact of comorbidities on mortality in HF patients. Another reason is, perhaps, that the improved therapy of non-cardiac comorbidities is not sufficient to improve HF outcome or that the management of these comorbidities remains suboptimal in many HF patients. In addition, it is possible that many of the non-cardiac comorbidities remain under-diagnosed and under-treated: therefore, they negatively affect prognosis continuously or many of the non-cardiac comorbidities are diagnosed too late to modify prognosis.

Biomarkers as predictors of HF: is it possible to make risk stratification of incident HF over 20 years?

The results from Paper III suggest that both NT-proBNP and hs-CRP can act as predictors for the development of HF over 20 years in middle-aged men from the general population. A combination of both biomarkers in combination with clinical variables such as hypertension and BMI >25 kg/m^2 can enhance the predictive value. To our knowledge, our study had the longest follow-up (21 years) compared to previous studies. Our results confirm those from a previous study in 2010 of a Swedish cohort where both biomarkers predicted the incidence of HF.[68] However, the association in our cohort was found with the same biomarkers but at much lower levels.

On the basis of our findings, we may speculate that the mechanisms by which brain natriuretic peptide is secreted (such as wall stretching and neurohormonal activation) are probably present at a very early stage and, together with other mechanisms (such as inflammation), constitute the initial pathophysiology underlying HF. The predictive value of NT-proBNP and hs-CRP was present even in those at 50 years of age and with a history of cardiovascular events, such as myocardial infarction and atrial fibrillation, according to the sensitivity analysis.

Incidence and risk factors of HF: have they changed the past 30 years?

Paper IV demonstrates that men born in 1943 had half the risk of HF development after 50 years of age compared to those born 30 years earlier. In addition, the risk profile of HF has also changed. Atrial fibrillation, obesity, ischemic heart disease, diabetes, and hypertension remain important risk factors. The relative importance of atrial fibrillation as a risk factor for HF decreased considerably in men born in 1943, whereas SBP and physical inactivity during leisure time proved to be more important as risk factors for HF in this cohort.

The reported decreased incidence of HF in our study is consistent with other studies, suggesting a decrease in the incidence of HF since the mid-1990s.[14-16] This finding might be explained by continuous improvements in both modifications of risk factors and therapy of several cardiovascular diseases. The later cohort in our study had lower mean systolic and diastolic blood pressure, lower percentage of smokers, and lower cholesterol levels compared to the older cohort. Our hypothesis about improved management of cardiovascular diseases as a possible explanation for the decreased HF incidence is supported by the fact that 83% of participants with atrial fibrillation in the older cohort developed subsequent HF, whereas only 20% of those with atrial fibrillation in the later cohort had new-onset HF. Likewise, for ischemic heart disease, the proportion of men with new-onset HF has decreased from 20% in the older cohort to 13% in the later cohort.

The comparison of the impact of each risk factor on the incidence of HF between the two cohorts showed that the relative importance of atrial fibrillation as a risk factor has decreased, probably because of its improved management in recent years including better rhythm and rate control as well as the use of ablation as a treatment option. The relative importance of SBP and of physical inactivity has increased in men born 1943 compared to those born 30 years earlier. SBP was found to be associated with higher risk only in the later cohort and at levels above 130 mmHg, suggesting that a target of SBP of below 130 mmHg when treating hypertension could be beneficial for the prevention of HF. The association of a high physical activity level with a low incidence of HF has been demonstrated previously.[87] In our study, data about physical activity was only available for leisure time and not for work-related physical activity. A possible explanation for why physical inactivity during leisure time seems to be of greater importance for the development of HF in men born in 1943 is that these men were probably generally less physically active during working hours than those born 30 years earlier.

Strengths and limitations

One of the strengths in Paper I is the real-life cohort of elderly patients with HF, which allows us to study the impact of the dose effect of HF medication on mortality after optimal dose titration. However, the fact that all patients included come from specialist clinics is a limitation for the generalizability of the results to patients who do not have follow-up at specialist HF outpatient clinics. Another strength is that the data was validated by review from a medical journal. The low number of patients included in the analysis is a limitation as well as the lack of randomization and the retrospective nature of the study.

The strengths of Paper II are the large sample size in a real-world cohort and that the data were linked to the Swedish national health data registries, which are obligatory for all health providers in Sweden and cover a long follow-up period. Like many other registry studies, a limitation of our study is the risk of confounding and selection bias. Not all care providers register HF patients in the SwedeHF, so we cannot exclude the scenario that care providers who do not include patients in the registry are less successful with HF care. Both confounding and selection bias affect the extrapolation of the results. Furthermore, the limited information about comorbidities and, in particular, the lack of information about the severity or staging of comorbidities is a restriction for further assessing the contribution of each comorbidity to mortality.

A strength of Paper III is the use of a random population-based approach and, moreover, the long duration of longitudinal follow-up. The collection of data about HF through review of medical records, the use of the National Patient Register, and the echocardiographic examination all helped to reduce the risk of misclassification of the outcome. Once again, the relative low number of participants is a limitation as it is the absence of women. Another limitation is that echocardiographic examinations were not performed at baseline. Thus, the possibility cannot be fully excluded that some participants already had heart dysfunction when they were initially included in the study as 50-year-olds.

A major strength of Paper IV is that two representative population samples of the same age and from the same geographic region were investigated using the same methodology. The long follow-up duration with a minimal loss of patients during follow-up further strengthens the study. As mentioned above, the low number of participants and the absence of women are limitations. The fact that the rates of participation were 88% in men born in 1913 and 55% in men born in 1943 might have affected the results.

CONCLUSIONS

- Achieving the target dose of ACEI/ARB is associated with lower all-cause and cardiac mortality compared to those who received a low dose (<50% of target dose) in elderly patients with HF and EF <40%. With respect to BBs, no statistically significant differences in survival were observed between target dose groups.

- Non-cardiac comorbidities had a significant impact on mortality in HF patients regardless of EF but with some notable intergroup differences. An increased number of comorbidities was associated with a higher risk of mortality in both HFrEF and HFpEF phenotypes. No change was found in the trend of the prognostic impact of the comorbidities on HF over the study period despite improvements in HF therapy and treatment of comorbidities.

- NT-proBNP ≥25 ng/L and elevated hs-CRP levels in men aged 50 years were predictive biomarkers for the incidence of HF over a 21-year follow-up.

- The incidence of HF has decreased in middle-aged men living in Gothenburg during the past three decades and there has been consequential changes in the risk profile for the development HF. However, atrial fibrillation, obesity, ischemic heart disease and hypertension remain important risk factors.

CLINICAL IMPLICATIONS

This thesis covers a significant challenge in the management of HF, namely the prognosis of HF as well as the prediction of HF in the general population.

The patients included in Paper I are very commonly encountered in daily clinical practice and how to treat them optimally remains a challenge, even for specialist HF physicians. It is not unusual that these patients receive lower than target doses of HF medications or even no dosing at all. Our results suggest that titration to the target dose of ACEI/ARBs appears beneficial with respect to outcome and should not, therefore, be neglected by physicians. With respect to BB treatment, it appears that heart rate is more important than the final dose. BBs are probably the most effective agents for heart rate control. Therefore, it is reasonable to regulate heart rate in HF, preferably by use of appropriate BB doses until an optimal heart rate is achieved.

Our findings in Paper II add important information about the significant contribution of non-cardiac comorbidities to mortality in both HFrEF and HFpEF. This is an important message as there is a misperception that comorbidities are more of a driving factor for worsening prognosis in patients with HFpEF compared to those with HFrEF. On the basis of our findings, a greater focus on the early recognition and treatment of comorbidities in both HF phenotypes is justified.

Paper III demonstrated the predictive value of low levels of NT-proBNP and hsCRP for the incidence of HF in middle-aged men. The clinical relevance is that the use of biomarkers in combination with certain clinical characteristics such as hypertension and BMI as risk factors may improve the identification of individuals from the general population at a higher risk of HF development, thus enabling early preventive measures.

The results from Paper IV suggest that the improved management of risk factors and of cardiovascular diseases, such as atrial fibrillation, has led to a decreased incidence of HF. However, the incidence of HF remains high, risk factors are not optimally managed, and new risk factors are emerging. Therefore, we are still facing serious challenges about how to further modify risk factors such as atrial fibrillation, ischemic heart disease, diabetes mellitus, and hypertension as well as how to manage new risk factors in order to prevent the development of HF in the future.

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REFERENCES

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH and van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *European journal of heart failure*. 2016;18:891-975.

2. Zipes DP, Libby P, Bonow RO, Mann DL and Tomaselli GF. *Braunwald's Heart Disease E-Book: A Textbook of Cardiovascular Medicine*: Elsevier Health Sciences; 2018.

3. Bianucci R, Loynes RD, Sutherland ML, Lallo R, Kay GL, Froesch P, Pallen MJ, Charlier P and Nerlich AG. Forensic Analysis Reveals Acute Decompensation of Chronic Heart Failure in a 3500-Year-Old Egyptian Dignitary. *Journal of forensic sciences*. 2016;61:1378-81.

4. Katz Arnold M. The "Modern" View of Heart Failure. *Circulation: Heart Failure*. 2008;1:63-71.

5. Davis RC, Hobbs FD and Lip GY. ABC of heart failure. History and epidemiology. *BMJ (Clinical research ed)*. 2000;320:39-42.

6. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W and Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *European heart journal cardiovascular Imaging*. 2015;16:233-70.

7. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA and Waggoner AD. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*. 2016;29:277-314.

8. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJV, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WHW, Tsai EJ and Wilkoff BL. 2013 ACCF/AHA Guideline for the Management of Heart Failure. *A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines*. 2013;62:e147-e239.

9. Savarese G and Lund LH. Global Public Health Burden of Heart Failure. *Cardiac failure review*. 2017;3:7-11.

10. Mosterd A and Hoes AW. Clinical epidemiology of heart failure. *Heart (British Cardiac Society)*. 2007;93:1137-1146.

11. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ and Levy D. Lifetime Risk for Developing Congestive Heart Failure. *Circulation*. 2002;106:3068-3072.

12. Zarrinkoub R, Wettermark B, Wandell P, Mejhert M, Szulkin R, Ljunggren G and Kahan T. The epidemiology of heart failure, based on data for 2.1 million inhabitants in Sweden. *European journal of heart failure*. 2013;15:995-1002.

13. Parén P, Schaufelberger M, Björck L, Lappas G, Fu M and Rosengren A. Trends in prevalence from 1990 to 2007 of patients hospitalized with heart failure in Sweden. *European journal of heart failure*. 2014;16:737-742.

14. Teng TH, Finn J, Hobbs M and Hung J. Heart failure: incidence, case fatality, and hospitalization rates in Western Australia between 1990 and 2005. *Circulation Heart failure*. 2010;3:236-43.

15. Yeung DF, Boom NK, Guo H, Lee DS, Schultz SE and Tu JV. Trends in the incidence and outcomes of heart failure in Ontario, Canada: 1997 to 2007. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2012;184:E765-73.

16. Barasa A, Schaufelberger M, Lappas G, Swedberg K, Dellborg M and Rosengren A. Heart failure in young adults: 20-year trends in hospitalization, aetiology, and case fatality in Sweden. *Eur Heart J*. 2014;35:25-32.

17. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, Nichol G, Pham M, Piña IL, Trogdon JG, American Heart Association Advocacy Coordinating C, Council on Arteriosclerosis T, Vascular B, Council on Cardiovascular R, Intervention, Council on Clinical C, Council on E, Prevention and Stroke C. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circulation Heart failure*. 2013;6:606-619.

18. Chen YT, Vaccarino V, Williams CS, Butler J, Berkman LF and Krumholz HM. Risk factors for heart failure in the elderly: a prospective community-based study. *The American journal of medicine*. 1999;106:605-12.

19. Ceia F, Fonseca C, Mota T, Morais H, Matias F, de Sousa A and Oliveira A. Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. *European journal of heart failure*. 2002;4:531-9.

20. Hellermann JP, Jacobsen SJ, Reeder GS, Lopez-Jimenez F, Weston SA and Roger VL. Heart failure after myocardial infarction: prevalence of preserved left ventricular systolic function in the community. *American heart journal*. 2003;145:742-8.

21. Abhayaratna WP, Smith WT, Becker NG, Marwick TH, Jeffery IM and McGill DA. Prevalence of heart failure and systolic ventricular dysfunction in older Australians: the Canberra Heart Study. *The Medical journal of Australia*. 2006;184:151-4.

22. Mureddu GF, Agabiti N, Rizzello V, Forastiere F, Latini R, Cesaroni G, Masson S, Cacciatore G, Colivicchi F and Uguccioni M. Prevalence of preclinical and clinical heart failure in the elderly. A population-based study in Central Italy. *European journal of heart failure*. 2012;14:718-729.

23. van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA and Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. *European journal of heart failure*. 2016;18:242-52.

24. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *The New England journal of medicine*. 1987;316:1429-35.

25. Yusuf S, Pitt B, Davis CE, Hood WB and Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *The New England journal of medicine*. 1991;325:293-302.

26. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet (London, England)*. 1999;353:2001-7.

27. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet (London, England)*. 1999;353:9-13.

28. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J and Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *The New England journal of medicine*. 1999;341:709-17.

29. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK and DeMets DL. Effect of carvedilol on survival in severe chronic heart failure. *The New England journal of medicine*. 2001;344:1651-8.

30. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S and Pfeffer MA. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet (London, England)*. 2003;362:767-71.

31. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ and Pitt B. Eplerenone in patients with systolic heart failure and mild symptoms. *The New England journal of medicine*. 2011;364:11-21.

32. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K and Zile MR. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. *New England Journal of Medicine*. 2014;371:993-1004.

33. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G and Tavazzi L. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet (London, England)*. 2010;376:875-85.

34. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA, 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D and Zareba W. Cardiac-resynchronization therapy for the prevention of heart-failure events. *The New England journal of medicine*. 2009;361:1329-38.

35. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B and Ostergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet (London, England)*. 2003;362:777-81.

36. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C and Ptaszynska A. Irbesartan in patients with heart failure and preserved ejection fraction. *The New England journal of medicine*. 2008;359:2456-67.

37. van Veldhuisen DJ, Cohen-Solal A, Bohm M, Anker SD, Babalis D, Roughton M, Coats AJ, Poole-Wilson PA and Flather MD. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). *J Am Coll Cardiol*. 2009;53:2150-8.

38. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S and McKinlay SM. Spironolactone for heart failure with preserved ejection fraction. *The New England journal of medicine*. 2014;370:1383-92.

39. Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, Manzano L, McMurray JJV, Ruschitzka F, van Veldhuisen DJ, von Lueder TG, Böhm M, Andersson B, Kjekshus J, Packer M, Rigby AS, Rosano G, Wedel H, Hjalmarson Å, Wikstrand J, Kotecha D and Beta-blockers in Heart Failure Collaborative G. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *European heart journal*. 2018;39:26-35.

40. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L and Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J*. 2006;27:2338-45.

41. Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, Love TE, Aronow WS, Adams KF, Jr. and Gheorghiade M. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial. *Circulation*. 2006;114:397-403.

42. Lund LH. Heart Failure with Mid-range Ejection Fraction: Lessons from CHARM. *Cardiac failure review*. 2018;4:70-72.

43. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, O'Meara E, Shah SJ, McKinlay S, Fleg JL, Sopko G, Pitt B and Pfeffer MA. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J*. 2016;37:455-62.

44. Maggioni AP, Dahlström U, Filippatos G, Chioncel O, Leiro MC, Drozdz J, Fruhwald F, Gullestad L, Logeart D, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors A, Nielsen OW, Zannad F, Tavazzi L and ESC obotHFAot. EURObservational Research Programme: The Heart Failure Pilot Survey (ESC-HF Pilot). *European journal of heart failure*. 2010;12:1076-1084.

45. Gheorghiade M, Albert NM, Curtis AB, Thomas Heywood J, McBride ML, Inge PJ, Mehra MR, O'Connor CM, Reynolds D, Walsh MN, Yancy CW and Fonarow GC. Medication Dosing in Outpatients With Heart Failure After Implementation of a Practice-Based Performance Improvement Intervention: Findings From IMPROVE HF. *Congestive Heart Failure*. 2012;18:9-17.

46. Vasko P JÅ, Dahlström U. RiksSvikt Årsrapport 2016.

47. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, Young S and Shusterman N. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation*. 1996;94:2807-16.

48. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JGF, Horowitz JD, Massie BM, Rydén L, Thygesen K and Uretsky BF. Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure. *Circulation*. 1999;100:2312-2318.

49. Wikstrand J, Hjalmarson A, Waagstein F, Fagerberg B, Goldstein S, Kjekshus J and Wedel H. Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure:

analysis of the experience in metoprolol CR/XL randomized intervention trial in chronic heart failure (MERIT-HF). *J Am Coll Cardiol*. 2002;40:491-8.

50. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, Riegger GA, Malbecq W, Smith RD, Guptha S and Poole-Wilson PA. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet (London, England)*. 2009;374:1840-8.

51. van Deursen VM, Urso R, Laroche C, Damman K, Dahlström U, Tavazzi L, Maggioni AP and Voors AA. Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. *European journal of heart failure*. 2014;16:103-111.

52. Braunstein JB, Anderson GF, Gerstenblith G, Weller W, Niefeld M, Herbert R and Wu AW. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol*. 2003;42:1226-33.

53. van Deursen VM, Damman K, van der Meer P, Wijkstra PJ, Luijckx GJ, van Beek A, van Veldhuisen DJ and Voors AA. Co-morbidities in heart failure. *Heart failure reviews*. 2014;19:163-72.

54. Mentz RJ and Felker GM. Noncardiac Comorbidities and Acute Heart Failure Patients. *Heart Failure Clinics*. 2013;9:359-367.

55. Mentz RJ, Kelly JP, von Lueder TG, Voors AA, Lam CSP, Cowie MR, Kjeldsen K, Jankowska EA, Atar D, Butler J, Fiuzat M, Zannad F, Pitt B and O'Connor CM. Noncardiac Comorbidities in Heart Failure With Reduced Versus Preserved Ejection Fraction. *Journal of the American College of Cardiology*. 2014;64:2281-2293.

56. Fu M, Zhou J, Thunstrom E, Almgren T, Grote L, Bollano E, Schaufelberger M, Johansson MC, Petzold M, Swedberg K and Andersson B. Optimizing the Management of Heart Failure With Preserved Ejection Fraction in the Elderly by Targeting Comorbidities (OPTIMIZE-HFPEF). *Journal of cardiac failure*. 2016;22:539-44.

57. Hogg K, Swedberg K and McMurray J. Heart failure with preserved left ventricular systolic function. *epidemiology, clinical characteristics, and prognosis*. 2004;43:317-327.

58. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW and Young JB. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. *J Am Coll Cardiol*. 2007;50:768-77.

59. Zhang J, Begley A, Jackson R, Harrison M, Pellicori P, Clark AL and Cleland JGF. Body mass index and all-cause mortality in heart failure patients with normal and reduced ventricular ejection fraction: a dose-response meta-analysis. *Clinical research in cardiology : official journal of the German Cardiac Society*. 2019;108:119-132.

60. Holmström A, Sigurjonsdottir R, Edner M, Jonsson Å, Dahlström U and Fu MLX. Increased comorbidities in heart failure patients ≥ 85 years but declined from >90 years: data from the Swedish Heart Failure Registry.. *International journal of cardiology*. 2013;167:2747-2752.

61. Ather S, Chan W, Bozkurt B, Aguilar D, Ramasubbu K, Zachariah AA, Wehrens XHT and Deswal A. Impact of Noncardiac Comorbidities on Morbidity and Mortality in a Predominantly Male Population With Heart Failure and Preserved Versus Reduced Ejection Fraction. *Journal of the American College of Cardiology*. 2012;59:998-1005.

62. Campbell RT, Jhund PS, Castagno D, Hawkins NM, Petrie MC and McMurray JJ. What have we learned about patients with heart failure and preserved ejection fraction from DIG-PEF, CHARM-preserved, and I-PRESERVE? *J Am Coll Cardiol*. 2012;60:2349-56.

63. Yancy CW, Lopatin M, Stevenson LW, De Marco T and Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol*. 2006;47:76-84.

64. Shah SJ and Gheorghiade M. Heart failure with preserved ejection fraction: treat now by treating comorbidities. *Jama*. 2008;300:431-3.

65. Fu M, Ahrenmark U, Berglund S, Lindholm CJ, Lehto A, Broberg AM, Tasevska-Dinevska G, Wikstrom G, Agard A and Andersson B. Adherence to optimal heart rate control in heart failure with reduced ejection fraction: insight from a survey of heart rate in heart failure in Sweden (HR-HF study). *Clinical research in cardiology : official journal of the German Cardiac Society*. 2017;106:960-973.

66. Felker GM, Shaw LK, Stough WG and O'Connor CM. Anemia in patients with heart failure and preserved systolic function. *American heart journal*. 2006;151:457-62.

67. MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, Solomon SD, Granger CB, Swedberg K, Yusuf S, Pfeffer MA and McMurray JJ. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J*. 2008;29:1377-85.

68. Smith JG, Newton-Cheh C, Almgren P, Struck J, Morgenthaler NG, Bergmann A, Platonov PG, Hedblad B, Engström G and Wang TJ. Assessment of conventional cardiovascular risk factors and multiple biomarkers for the prediction of incident heart failure and atrial fibrillation. *Journal of the American College of Cardiology*. 2010;56:1712-1719.

69. Iorio A, Senni M, Barbati G, Greene SJ, Poli S, Zambon E, Di Nora C, Cioffi G, Tarantini L, Gavazzi A, Sinagra G and Di Lenarda A. Prevalence and prognostic impact of non-cardiac co-morbidities in heart failure outpatients with preserved and reduced ejection fraction: a community-based study. *European journal of heart failure*. 2018.

70. Riedel O, Ohlmeier C, Enders D, Elsasser A, Vizcaya D, Michel A, Eberhard S, Schlothauer N, Berg J and Garbe E. The contribution of comorbidities to mortality in hospitalized patients with heart failure. *Clinical research in cardiology : official journal of the German Cardiac Society*. 2018;107:487-497.

71. Laribi S, Aouba A, Nikolaou M, Lassus J, Cohen-Solal A, Plaisance P, Pavillon G, Jois P, Fonarow GC, Jougla E and Mebazaa A. Trends in death attributed to heart failure over the past two decades in Europe. *European journal of heart failure*. 2012;14:234-9.

72. Gabet A, Juilliere Y, Lamarche-Vadel A, Vernay M and Olie V. National trends in rate of patients hospitalized for heart failure and heart failure mortality in France, 2000-2012. *European journal of heart failure*. 2015;17:583-90.

73. Mamas MA, Sperrin M, Watson MC, Coutts A, Wilde K, Burton C, Kadam UT, Kwok CS, Clark AB, Murchie P, Buchan I, Hannaford PC and Myint PK. Do patients have worse outcomes in heart failure than in cancer? A primary care-based cohort study with 10-year follow-up in Scotland. *European journal of heart failure*. 2017.

74. Taylor CJ, Ordóñez-Mena JM, Roalfe AK, Lay-Flurrie S, Jones NR, Marshall T and Hobbs FDR. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population based cohort study. *BMJ (Clinical research ed)*. 2019;364:l223.

75. Ho KK, Anderson KM, Kannel WB, Grossman W and Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation*. 1993;88:107-15.

76. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, Baughman KL and Kasper EK. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *The New England journal of medicine*. 2000;342:1077-84.

77. Solomon SD, Dobson J, Pocock S, Skali H, McMurray JJ, Granger CB, Yusuf S, Swedberg K, Young JB, Michelson EL and Pfeffer MA. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation*. 2007;116:1482-7.

78. Meta-analysis Global Group in Chronic Heart F. The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *European Heart Journal*. 2012;33:1750-1757.

79. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL and Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *New England Journal of Medicine*. 2006;355:251-259.

80. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y and Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. *The New England journal of medicine*. 2006;355:260-9.

81. Senni M, Gavazzi A, Oliva F, Mortara A, Urso R, Pozzoli M, Metra M, Lucci D, Gonzini L, Cirrincione V, Montagna L, Di Lenarda A, Maggioni AP and Tavazzi L. In-hospital and 1-year outcomes of acute heart failure patients according to presentation (de novo vs. worsening) and ejection fraction. Results from IN-HF Outcome Registry. *International journal of cardiology*. 2014;173:163-9.

82. Kontogeorgos S, Thunstrom E, Johansson MC and Fu M. Heart failure with preserved ejection fraction has a better long-term prognosis than heart failure with reduced ejection fraction in old patients in a 5-year follow-up retrospective study. *International journal of cardiology*. 2017;232:86-92.

83. Henkel DM, Redfield MM, Weston SA, Gerber Y and Roger VL. Death in heart failure: a community perspective. *Circulation Heart failure*. 2008;1:91-7.

84. Adabag S, Smith LG, Anand IS, Berger AK and Luepker RV. Sudden cardiac death in heart failure patients with preserved ejection fraction. *Journal of cardiac failure*. 2012;18:749-54.

85. Hamaguchi S, Kinugawa S, Sobirin MA, Goto D, Tsuchihashi-Makaya M, Yamada S, Yokoshiki H and Tsutsui H. Mode of death in patients with heart failure and reduced vs. preserved ejection fraction: report from the registry of hospitalized heart failure patients. *Circulation journal : official journal of the Japanese Circulation Society*. 2012;76:1662-9.

86. Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, Kitzman DW, Gardin JM, Rutledge JE and Boineau RC. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol*. 2000;35:1628-37.

87. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C and Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. *Archives of internal medicine*. 2001;161:996-1002.

88. Wilhelmsen L, Rosengren A, Eriksson H and Lappas G. Heart failure in the general population of men--morbidity, risk factors and prognosis. *Journal of internal medicine*. 2001;249:253-61.

89. Butler J, Kalogeropoulos A, Georgiopoulou V, Belue R, Rodondi N, Garcia M, Bauer DC, Satterfield S, Smith AL, Vaccarino V, Newman AB, Harris TB, Wilson PW and Kritchevsky SB. Incident heart failure prediction in the elderly: the health ABC heart failure score. *Circulation Heart failure*. 2008;1:125-33.

90. Dunlay SM, Weston SA, Jacobsen SJ and Roger VL. Risk factors for heart failure: a population-based case-control study. *The American journal of medicine*. 2009;122:1023-1028.

91. Ho KK, Pinsky JL, Kannel WB and Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol*. 1993;22:6a-13a.

92. Eriksson M, Holmgren L, Janlert U, Jansson JH, Lundblad D, Stegmayr B, Soderberg S and Eliasson M. Large improvements in major cardiovascular risk factors in the population of northern Sweden: the MONICA study 1986-2009. *Journal of internal medicine*. 2011;269:219-31.

93. Gregg EW, Li Y, Wang J, Rios Burrows N, Ali MK, Rolka D, Williams DE and Geiss L. Changes in Diabetes-Related Complications in the United States, 1990–2010. *New England Journal of Medicine*. 2014;370:1514-1523.

94. Borodulin K, Vartiainen E, Peltonen M, Jousilahti P, Juolevi A, Laatikainen T, Mannisto S, Salomaa V, Sundvall J and Puska P. Forty-year trends in cardiovascular risk factors in Finland. *European journal of public health*. 2015;25:539-46.

95. Zhong Y, Rosengren A, Fu M, Welin L, Welin C, Caidahl K, Mandalenakis Z, Dellborg M, Svardsudd K and Hansson PO. Secular changes in cardiovascular risk factors in Swedish 50-year-old men over a 50-year period: The study of men born in 1913, 1923, 1933, 1943, 1953 and 1963. *European journal of preventive cardiology*. 2017;24:612-620.

96. Vartiainen E, Laatikainen T, Peltonen M, Juolevi A, Mannisto S, Sundvall J, Jousilahti P, Salomaa V, Valsta L and Puska P. Thirty-five-year trends in cardiovascular risk factors in Finland. *International journal of epidemiology*. 2010;39:504-18.

97. Berg J, Björck L, Lappas G, O'Flaherty M, Capewell S and Rosengren A. Continuing decrease in coronary heart disease mortality in Sweden. *BMC cardiovascular disorders*. 2014;14:9.

98. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, Ferranti Sd, Després J-P, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW and Turner MB. Executive Summary: Heart Disease and Stroke Statistics—2016 Update. *Circulation*. 2016;133:447-454.

99. Fu M, Rosengren A, Thunstrom E, Mandalenakis Z, Welin L, Caidahl K, Pivodic A, Zhong Y, Ergatoudes C, Morales D, Welin C, Svardsudd K, Dellborg M and Hansson PO. Although Coronary Mortality Has Decreased, Rates of Cardiovascular Disease Remain High: 21 Years of Follow-Up Comparing Cohorts of Men Born in 1913 With Men Born in 1943. *Journal of the American Heart Association*. 2018;7.

100. Ergatoudes C, Thunstrom E, Rosengren A, Bjorck L, Bengtsson Bostrom K, Falk K and Fu M. Long-term secondary prevention of acute myocardial infarction (SEPAT) - guidelines adherence and outcome. *BMC cardiovascular disorders*. 2016;16:226.

101. Braunwald E. Biomarkers in heart failure. *The New England journal of medicine*. 2008;358:2148-59.

102. deFilippi CR and Seliger SL. A Multibiomarker Approach to Heart Failure Prognostication: A Work in Progress. *JACC Heart failure*. 2017;5:265-267.

103. Vorovich E, French B, Ky B, Goldberg L, Fang JC, Sweitzer NK and Cappola TP. Biomarker predictors of cardiac hospitalization in chronic heart failure: a recurrent event analysis. *Journal of cardiac failure*. 2014;20:569-76.

104. Troughton R, Michael Felker G and Januzzi JJL. Natriuretic peptide-guided heart failure management. *European Heart Journal*. 2014;35:16-24.

105. Troughton RW, Frampton CM, Brunner-La Rocca H-P, Pfisterer M, Eurlings LWM, Erntell H, Persson H, O'Connor CM, Moertl D, Karlström P, Dahlström U, Gaggin HK, Januzzi JL, Berger R, Richards AM, Pinto YM and Nicholls MG. Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis. *European Heart Journal*. 2014;35:1559-1567.

106. Volpe M, Carnovali M and Mastromarino V. The natriuretic peptides system in the pathophysiology of heart failure: from molecular basis to treatment. *Clinical Science*. 2016;130:57-77.

107. Chow SL, Maisel AS, Anand I, Bozkurt B, de Boer RA, Felker GM, Fonarow GC, Greenberg B, Januzzi JL, Jr., Kiernan MS, Liu PP, Wang TJ, Yancy CW and Zile MR. Role of Biomarkers for the Prevention, Assessment, and Management of Heart Failure: A Scientific Statement From the American Heart Association. *Circulation*. 2017.

108. Anker SD and von Haehling S. Inflammatory mediators in chronic heart failure: an overview. *Heart (British Cardiac Society)*. 2004;90:464-70.

109. Seta Y, Shan K, Bozkurt B, Oral H and Mann DL. Basic mechanisms in heart failure: the cytokine hypothesis. *Journal of cardiac failure*. 1996;2:243-9.

110. Yin WH, Chen JW, Jen HL, Chiang MC, Huang WP, Feng AN, Young MS and Lin SJ. Independent prognostic value of elevated high-sensitivity C-reactive protein in chronic heart failure. *American heart journal*. 2004;147:931-8.

111. Anand IS, Latini R, Florea VG, Kuskowski MA, Rector T, Masson S, Signorini S, Mocarelli P, Hester A, Glazer R and Cohn JN. C-Reactive Protein in Heart Failure. *Prognostic Value and the Effect of Valsartan*. 2005;112:1428-1434.

112. Hartford M, Wiklund O, Mattsson Hulten L, Persson A, Karlsson T, Herlitz J and Caidahl K. C-reactive protein, interleukin-6, secretory phospholipase A2 group IIA and intercellular adhesion molecule-1 in the prediction of late outcome events after acute coronary syndromes. *Journal of internal medicine*. 2007;262:526-36.

113. Araujo JP, Lourenco P, Azevedo A, Frioes F, Rocha-Goncalves F, Ferreira A and Bettencourt P. Prognostic value of high-sensitivity C-reactive protein in heart failure: a systematic review. *Journal of cardiac failure*. 2009;15:256-66.

114. Mann DL. Innate immunity and the failing heart: the cytokine hypothesis revisited. *Circ Res*. 2015;116:1254-68.

115. Gao C, Zhong L, Gao Y, Li X, Zhang M and Wei S. Cystatin C levels are associated with the prognosis of systolic heart failure patients. *Archives of cardiovascular diseases*. 2011;104:565-71.

116. Vasan RS, Sullivan LM, Roubenoff R, Dinarello CA, Harris T, Benjamin EJ, Sawyer DB, Levy D, Wilson PW and D'Agostino RB. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. *Circulation*. 2003;107:1486-91.

117. Kannel WB, D'Agostino RB, Silbershatz H, Belanger AJ, Wilson PW and Levy D. Profile for estimating risk of heart failure. *Archives of internal medicine*. 1999;159:1197-204.

118. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT and Ponikowski P. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *European journal of heart failure*. 2012;14:803-69.

119. Cacciatore F, Abete P, Mazzella F, Viati L, Della Morte D, D'Ambrosio D, Gargiulo G, Testa G, Santis D, Galizia G, Ferrara N and Rengo F. Frailty predicts long-term mortality in elderly subjects with chronic heart failure. *European journal of clinical investigation*. 2005;35:723-30.

120. Bohm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, Lerebours G and Tavazzi L. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet (London, England)*. 2010;376:886-94.

121. Gelbrich G, Edelmann F, Inkrot S, Lainscak M, Apostolovic S, Neskovic AN, Waagstein F, Loeffler M, Anker SD, Dietz R and Dungen HD. Is target dose the treatment target? Uptitrating beta-blockers for heart failure in the elderly. *International journal of cardiology*. 2012;155:160-6.

122. Smith DH, Thorp ML, Gurwitz JH, McManus DD, Goldberg RJ, Allen LA, Hsu G, Sung SH, Magid DJ and Go AS. Chronic kidney disease and outcomes in heart failure with preserved versus reduced ejection fraction: the Cardiovascular Research Network PRESERVE Study. *Circulation Cardiovascular quality and outcomes*. 2013;6:333-42.

123. Herrscher TE, Akre H, Overland B, Sandvik L and Westheim AS. High prevalence of sleep apnea in heart failure outpatients: even in patients with preserved systolic function. *Journal of cardiac failure*. 2011;17:420-5.

124. Kinlay S. Changes in stroke epidemiology, prevention, and treatment. *Circulation*. 2011;124:e494-6.

125. McAlister FA, Wilkins K, Joffres M, Leenen FH, Fodor G, Gee M, Tremblay MS, Walker R, Johansen H and Campbell N. Changes in the rates of awareness, treatment and control of hypertension in Canada over the past two decades. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2011;183:1007-13.