Opportunities and challenges of real-world data in heart failure

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Opportunities and challenges of real-world data in heart failure

Kansen en uitdagingen van real-world data in hartfalen
(met een samenvatting in het Nederlands)

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Contents

CHAPTER 1

GENERAL INTRODUCTION

Healthcare data has entered a new era, with increasing amounts of real-world clinical data (RWD) electronically collected, stored, linked and analysed due to the digitization of healthcare information and interest in precision medicine.[1,2] Using RWD for research purposes is generating a great deal of real-world evidence (RWE). One explanation for the increased interest in RWD is that it can be used to answer different research questions compared to randomized clinical trials (RCTs). We can learn different things from real world-patients that we cannot learn from trial patients.

The traditional levels of evidence-based medicine are commonly displayed in the form of a pyramid, with case reports at the base, case-control and cohort studies in the middle and at the top RCTs and meta-analyses. We can deduct from this structure that the higher the quality of the study design, the more confidence we have in making clinical decisions based on the results of that study. However, there are some pragmatic limitations of RCTs inherent to their design.[3] A clear reason is the generalisability of RCTs to real-world situations. Health care systems are complex and challenging and not always can we use rigorous treatment regimens or apply conventional models to predict outcomes on diverse patient populations.[4] Additionally, some research questions cannot be answered by RCTs, such as the uptake of a new medicine in clinical practice over time or the economic cost associated with this. These types of research questions require sources of RWD. This is the driving force to enhance conventional evidence-based medicine with evidence from RWD.[5]

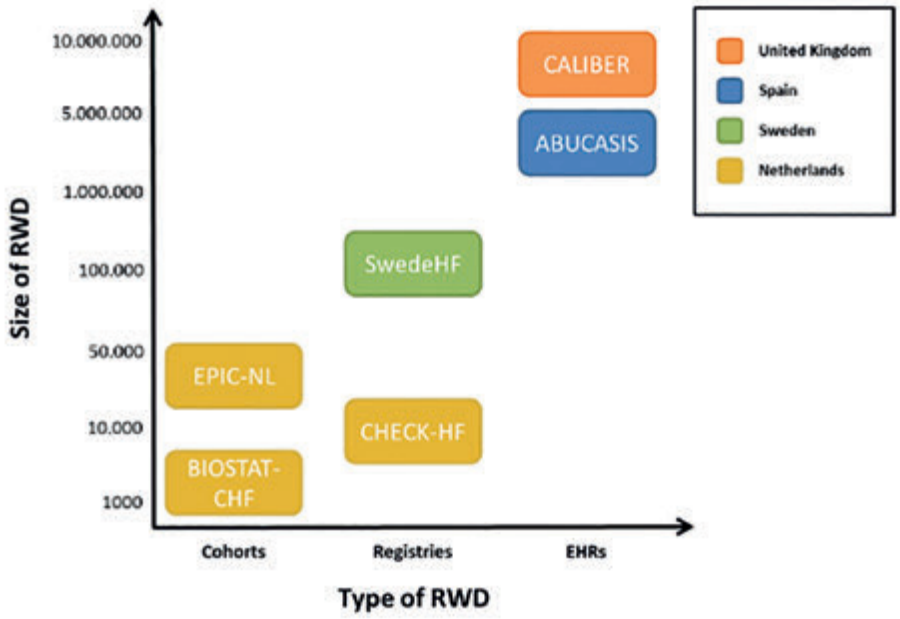
Sources of real-world data

There are many different sources and types of RWD.[5,6] We can discern sources that collect data for research, clinical or administrative purposes.[7] One of the clinical RWD sources are healthcare databases with electronic health records (EHRs), which are systems that gather records of routine clinical and laboratory healthcare data collected during usual clinical practice and could be used to study the epidemiology of a disease. There are also insurance databases, which are set up by health insurers for administrative purposes, but could be used to study medication uptake, treatment patterns or the economic cost of healthcare. A more research based form of RWD are patient registries, that collect information on specific patients with characteristics in common, for example heart failure, to be used for observational studies. Lastly, a source

where big data is gathered for research purposes, are the general population cohorts and biobanks.

Since a wide variety of RWD sources are used for research purposes throughout this thesis, they have been summarized in **Figure 1**. This thesis will demonstrate the potential opportunities and challenges of RWD by means of electronic health records (EHRs), disease registries and cohort studies.

Figure 1. Sources of real-world data within this thesis.



CALIBER = CArdiovascular disease research using LInked Bespoke studies and Electronic health Records; ABUCASIS = Valencian Health Agency's universal health care system; SwedeHF = Swedish Heart Failure registry; CHECK-HF = Chronisch Hartfalen ESC-richtlijn Cardiologische praktijk Kwaliteitsproject-HartFalen; EPIC-NL = European Prospective Investigation into Cancer and nutrition Netherlands and BIOSTAT-CHF =The BIOlogy Study to TAilored Treatment in Chronic Heart Failure.

The potential of real-world healthcare data

Access to the sources in **Figure 1** provides a large network of RWD across Europe. This abundance of routine clinical care data could be used for a wide variety of research purposes and has the potential to answer scientific questions we have not been able to assess before.[7] The large sample sizes allow for

increased ability to investigate outcomes and diseases or subgroups within populations and to track patients over time and through different linked data settings. Detailed information is available on drug prescription, allowing the estimation of drug treatment in a broader, heterogeneous population under real-world conditions.[5] Additionally, it could help in designing and selecting the right patients for RCTs.[8]

However, several requirements have to be met in order to access the full potential of RWD. Since most RWD is not primarily collected for research purposes, such as EHR or insurance claim data, which traditionally had more clinical and administrative purposes, the quality might not be of the same standard as in conventional research settings.[5–7] Before RWD can be used to generate RWE, it has to be cleaned, structured, standardised and missing data needs to be handled appropriately. Once these initial requirements have been addressed, RWE can be achieved at a higher level of reliability, efficiency and consistency.

Real-world data in heart failure

RWD has successfully been embraced in a number of research fields. For example, in oncology, cancer centres have been collecting data on real-world patients in cancer registries for decades. RWD is also of interest in the field of cardiovascular disease (CVD), and in particular in heart failure.[9] Heart failure is a chronic, heterogeneous syndrome. This heterogeneity is currently hindering the progress in conventional evidence-based research. Therefore, due to the nature of this disease, it is an attractive example to show the opportunities, and challenges of RWD.

Phenotyping heart failure

The most commonly used clinical parameter to distinguish subphenotypes of heart failure is left ventricular ejection fraction (EF). Based on EF, patients are classified into heart failure with reduced ejection fraction (HFrEF; EF <40%), mid-range ejection fraction (HFmrEF; EF 40–49%) or preserved ejection fraction (HFpEF; EF >50%).[10] A challenge we have to overcome within RWD is the lack of phenotypic depth of the information available; in the case of heart failure EF is often missing or not documented.[11] This limits the use of RWD in current heart failure research. From an optimistic perspective, this can also be seen as an opportunity to think outside of the box to find other ways to study different heart failure disease trajectories. Several researchers have used the flexibility of RWD

to look for answers, either by attempting to find new echography parameters or allocate patients to different subgroups with advanced techniques.[12–14]

Difference between trial patient and real-world patient

Heart failure patients are treated with guideline-recommended therapies, based on evidence from RCTs.[10] However, patients selected to participate in RCTs may not be representative of the whole spectrum of patients seen in clinical practice. Especially women, elderly and patients with higher EF are underrepresented in RCTs but make up a large proportion of real-world patients.[15,16] In a typical HF trial population approximately 70% of patients enrolled are male, ejection fraction is lower and the median age is 65 years. In a real-world population where the median age of heart failure patients is nearly 80 years old, 50% of patients are female and ejection fraction is higher. There is a clear mismatch between these settings.[15] RWD therefore provides the opportunity to study a more diverse and realistic patient population and include those patients underrepresented in RCTs.[15,16]

Heterogeneity of the disease

The heterogeneity of heart failure is a major roadblock in conventional evidence-based medicine. Other research fields have dealt with heterogeneity far more effectively than in heart failure. For example, in oncology, where different markers are used to phenotype patients accordingly, such as type of cancer, size of tumour, presence of metastases, biomarkers, histologic or genetic markers and so on.[19] Thus far the one size fits all approach has worked for HFrEF. In patients with HFrEF, neurohormonal activation as a response to the inability of the heart's pump function to meet the body's metabolic demand has been well recognised as the main driver of adverse remodelling and poor outcomes. In particular, drugs influencing the sympathetic nervous system (i.e. beta-blockers) or the renin-angiotensin-aldosterone-system (i.e. ACE-inhibitors/angiotensin receptor blockers (ARBs)) have been shown to dramatically improve survival on a group level.[10] However, shared pathophysiological mechanisms have not been found in patients with HFpEF. The heterogeneity in HFpEF has most likely attributed to the failure of clinical trials to establish a clinically relevant effect of interventions in HFpEF patients.[17,18] As a result, particularly in this group, heterogeneity appears to exist beyond EF. Therefore, it is suggested that we identify clusters within HFpEF patients to classify patients better.[12,20,21] Patient clusters that are most likely to benefit from targeted interventions could be identified through phenotyping, a data driven approach that assigns (novel) classifications based on patterns within clinical information. RWD provides the opportunity to perform these kind of advanced analyses.

Aim of this thesis

The aim of this thesis is to assess the potential of RWD in heart failure research in four specific fields addressing the topics of heterogeneity, real-world patients and phenotyping: risk factors, treatment, prognosis and phenotyping.

I. *Risk factors*: Can we adequately verify traditional risk factors for heart failure in RWD. Are we able to identify less know risk factors or combinations of risk factors that have a major impact on preventing risk of heart failure in the general population?

II. *Treatment*: Can we identify undertreated subgroups of heart failure patients in RWD? Are heart failure treatments associated with better survival in an elderly population (patients underrepresented in RCTs)?

III. *Prognosis*: Can we use RWD to investigate potential differences in prognosis between European countries? Are changes in circulating biomarkers associated with prognosis to identify new surrogate endpoints for heart failure trials?

IV. *Phenotyping*: Are we able to address the heterogeneity of HFpEF and missing information of RWD by applying advanced methods to subphenotype heart failure patients more precisely?

Outline of this thesis

Chapter 2 verifies and identifies (un)known risk factors for heart failure across age- and sex-specific strata in EHRs. In **Chapter 3**, Life's Simple 7 metrics from the American Heart Association, a measure for healthy lifestyle, and the risk of heart failure in the general population is discussed.

Chapter 4 describes the temporal patterns in treatment for unselected heart failure patients over almost 15 years of follow-up in EHRs. In **Chapter 5**, the benefit of beta-blocker use in elderly HFrEF patients (i.e. those patients underrepresented in clinical trials) is examined with a propensity score matched study for all-cause and cardiovascular mortality and heart failure hospitalisation.

Chapter 6 explores whether big data could be used to find new surrogate markers for prognosis in HFrEF patients with enhancing an existing prediction model with biomarker data, in particular change in biomarkers levels. **Chapter 7** addresses

differences in characteristics, treatment and survival of heart failure patients in three European countries by using RWD: Spain, Sweden and the United Kingdom.

Chapter 8 describes an algorithm to predict missing heart failure classification in EHRs; it predicts phenotype status (HFrEF, HFmrEF or HFpEF) in patients with unknown EF. In **Chapter 9**, heterogeneous HFpEF patients are clustered with an advanced model to discern clinically useful clusters for trial design.

In the last chapter of this thesis concluding remarks will be provided in the general discussion (**Chapter 10**). It describes challenges and opportunities for RWD in heart failure research.

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PART I – RISK FACTORS FOR HEART FAILURE

CHAPTER 2

RISK FACTORS FOR INCIDENT HEART FAILURE IN AGE AND SEX SPECIFIC STRATA: A POPULATION-BASED COHORT USING LINKED ELECTRONIC HEALTH RECORDS

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Abstract

Aim. Several risk factors for incident heart failure (HF) have been previously identified, however large electronic health records (EHR) datasets may provide the opportunity to examine the consistency of risk factors across different subgroups from the general population.

Methods and Results. We used linked EHR data from 2000 to 2010 as part of the UK-based CALIBER resource to select a cohort of 871,687 individuals 55 years or older and free of HF at baseline. The primary endpoint was the first record of HF from primary or secondary care. Cox proportional hazards analysis was used to estimate hazard ratios for associations between risk factors and incident HF, separately for men and women and by age category: 55–64, 65–74, and >75 years. During 5.8 years of median follow-up, a total of 47 987 incident HF cases were recorded. Age, social deprivation, smoking, sedentary lifestyle, diabetes, atrial fibrillation, chronic obstructive pulmonary disease, body mass index, haemoglobin, total white blood cell count and creatinine were associated with HF. Smoking, atrial fibrillation and diabetes showed stronger associations with incident HF in women compared to men.

Conclusions. We confirmed associations of several risk factors with HF in this large population-based cohort across age and sex subgroups. Mainly modifiable risk factors and comorbidities are strongly associated with incident HF, highlighting the importance of preventive strategies targeting such risk factors for HF.

Introduction

Heart failure (HF) is one of the leading causes of morbidity and mortality and is one of the initial presentations of cardiovascular disease (CVD).[1] The lifetime risk in individuals aged 55 years and older is about one in five and the 5-year survival ranges from 20-50% after first diagnosis.[2–4]

In recent decades, several risk factors for developing HF have been established, such as high blood pressure (BP), diabetes, smoking and obesity.[5–8] The contribution of these risk factors may differ substantially, considering the age and clinical presentation of CVDs differ greatly amongst men and women.[1] Therefore, the associations of such risk factors with HF should be evaluated separately in men and women across a range of age groups.

Furthermore, management of well-known risk factors could be partly responsible for a declining incidence of HF.[9] However, as 'classic' risk factors such as hypertension are successfully treated by BP-lowering medication to decrease CVD risk, in a population where such strategies are implemented, the equilibrium between risk factors, dependent on age, sex and risk factor distribution, could have shifted, and relatively less know risk factors could emerge.

Previous studies of risk factors for HF may lack data richness or sheer volume for a thorough assessment of differences in the contribution of risk factors across different patient groups of interest (notably strata of age and sex).[10–12] Very large databases of electronic health records (EHR) may provide the opportunity to study risk factors among age- and sex-specific groups of patients in the general population.

In the current study we studied a large population-based cohort using EHR, with a highly heterogeneous HF phenotype, to identify risk factors for developing HF and to compare these risk factors between men and women across different age groups.[13]

Methods

Study population

A cohort of 871,687 individuals was constructed from the CALIBER resource (CArdiovascular research using LInked Bespoke studies and Electronic health

Records), which links four sources of EHR in England: primary care records from the Clinical Practice Research Datalink (CPRD), secondary care hospital discharges in Hospital Episodes Statistics (HES), disease registration in the Myocardial Ischaemia National Audit Project (MINAP) registry and the national death registration in the Office for National Statistics (ONS) registry.[13]

Individuals were included if they were 55 years or older between 1 January 2000 and 25 March 2010, if they had been registered with a general practitioner for at least 1 year, in a practice that had at least 1 year of up-to-standard data recording in CPRD. The last date of the previously mentioned occasions was considered cohort entry date (index date).

We excluded individuals with a history of HF in CPRD, HES or MINAP before their index date. Individuals were censored at first diagnosis of HF, death, de-registration from a practice, last practice data collection or at the study end date, whichever occurred first. The study flow diagram of participants can be found in **Figure S1.**

Study approval was granted by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency (protocol 14_ 246) and the MINAP Academic Group.

Risk factors

Risk factors included in this study were: age, sex, ethnicity, social deprivation, body mass index (BMI), physical activity, smoking, diastolic BP (DBP), systolic BP (SBP), lipid measures (total cholesterol and triglyceride), physiological markers [albumin, creatinine, platelets and white blood cell (WBC) count], comorbidities [diabetes, hypertension, atrial fibrillation (AF) and chronic obstructive pulmonary disease (COPD)] and prescriptions of BP-lowering and lipid-regulating drugs.

Baseline risk factors were identified as the closest measurement to index date up to 3 years before and 1 year after index date. All determinants were recorded during consultations in CPRD or HES. Reported ethnicity was used to classify individuals as Caucasian, black, Asian or other. Social deprivation was measured as quintiles of the index of multiple deprivation, a score calculated based on seven indices of deprivation: income, employment, health and disability, education, barrier to housing and services, crime and living environment.[14] Furthermore we classified hypertension as three SBP measurements >140

mmHg and/or use of BP lowering medication, obesity as a BMI measurement > 30 kg/m^2, smoking status as never, ex- or current smokers and patient's level of physical activity as recorded in primary care was classified as sedentary lifestyle or active lifestyle. Definitions of all risk factors can be found at https://www.caliberresearch.org/portal/.

Endpoints

The primary endpoint was incident HF and was based on the first record of HF from CPRD or HES.[4] Events in CPRD were defined by a diagnosis of HF or diagnosis of chronic left ventricular dysfunction on echocardiogram with READ codes, and in HES by a diagnosis of HF with ICD-10. Secondary endpoint was the first record of HF, excluding patients with a previous myocardial infarction (MI) event at baseline. READ and ICD-10 codes for HF and MI definitions can be found in **Table S1.**

Statistical analysis

Incidence rates of HF (per 1000 person-years of follow-up) were estimated by calendar time including 95% confidence intervals (CI), stratified by sex and age category: 55–64 years, 65–74 years and >75 years.

Missing data in the all baseline risk factors were imputed, except comorbidities and prescriptions, using multiple imputation, from the *mice* algorithm in the statistical software package R. We stratified imputations by sex and age category and created 10 imputed datasets. Analyses were performed on the imputed datasets separately and results were pooled using Rubin's rules. Multivariable Cox proportional hazards analysis was used to estimate hazard ratios (HRs) for associations between baseline risk factors and incident HF, separately by sex and age categories for all baseline risk factors. The proportional hazards assumption was verified by assessment of the Schoenfeld residuals. For our secondary analysis we repeated the above analysis in a subset of individuals without a history of MI. The Bonferroni correction was used to account for multiple testing. We tested for interaction with age categories (55–64 years, 65–74 years and >75 years) and sex for all associations presented.

We estimated the population attributable risk (PAR) of risk factors for incident HF for: social deprivation, smoking, sedentary lifestyle, obesity and diabetes. To assess the impact of these risk factors we estimated the PAR (95% CI) with the standard formula: PAR = [P(F)*(HR-1)] / [1+P(F)*(HR-1)] where P(F) is the

prevalence of the risk factor in the population and HR the hazard ratio of disease due to that risk factor.[15]

In sensitivity analyses, we compared the results after multiple imputation to those based on a complete case analysis and to a subset of individuals not using BP-lowering medication at baseline. Furthermore, we compared inter-practice/hospital variation in a frailty Cox proportional hazards model where practice was a random effects variable and we compared associations of risk factors for incident HF stratified by endpoints from different sources of EHR (CPRD and HES). All analyses were performed using R version 3.2.3.

Results

Baseline characteristics

The study cohort included 871,687 individuals aged 55 years or older of whom 47,987 (5.5%) individuals developed incident HF during a median follow up of 5.8 years [interquartile range (IQR) 2.7;9.9], with a median time to event of 3.7 years [IQR 1.8;6.4]. A Kaplan-Meier time-to-event plot for incident HF can be found in the supplementary **Figure S2**. Baseline characteristics are presented separately for men (**Table 1**) and women (**Table 2**), stratified by age and incident HF development. Compared to individuals without HF, incident HF patients more often had a higher social deprivation, sedentary lifestyle, higher BMI, higher SBP and higher creatinine levels, and were more often smokers at baseline. Comorbidities more often occurred in incident HF patients than individuals without HF at baseline; this was similar for both men and women.

Table 1. Baseline characteristics stratified by age and heart failure status in men

	55 – 64 years		65 – 74 years		> 75 years	
	Incident HF patients	Individuals without HF	Incident HF patients	Individuals without HF	Incident HF patients	Individuals without HF
Number of patients	5,408	252,290	8,047	80,369	9,859	48,672
Demographics						
Ethnicity (% Caucasian)	96.1	95.1	96.6	95.8	98.2	97.4
Most deprived fifth (%)*	26.2	17.2	22.8	18.1	19.4	19.3
Lifestyle (%) †						
Smoking						
Current Smoking	32.4	27.9	19.7	18.8	12.5	13
Ex-smoker	31.9	29.3	38.7	36.5	39.5	38.7
Never smoked	35.7	42.8	41.6	44.7	48	48.3
Sedentary lifestyle	43.5	36.4	48.1	41.2	62.3	58.1
Clinical measures in mean (sd) or median [IQR] †						
Body Mass Index (kg/m2)	28.5 (5.2)	27.5 (4.5)	27.3 (4.4)	26.6 (4.0)	25.7 (4.0)	25.1 (3.9)
Total cholesterol (mmol/L)	5.4 (1.2)	5.5 (1.0)	5.2 (1.0)	5.3 (1.0)	5.1 (1.0)	5.1 (1.0)
Triglycerides (mmol /L)	1.9 (1.4)	1.8 (1.2)	1.7 (1.1)	1.7 (1.0)	1.5 (0.9)	1.5 (0.9)
SBP (mmHg)	142.0 (19.3)	138.4 (16.9)	146.7 (19.2)	145.4 (18.3)	147.9 (19.8)	146.5 (19.5)
DBP (mmHg)	83.5 (10.2)	83.2 (9.5)	81.4 (9.6)	82.0 (9.4)	79.8 (9.8)	79.6 (9.7)
Heamoglobin (g/dL)	14.7 (1.4)	14.8 (1.2)	14.2 (1.6)	14.3 (1.5)	13.5 (1.7)	13.5 (1.7)
Platelets (10^9/L)	240.7 [80.5]	243.0 [77.4]	229.3 [82.1]	231.1 [80.9]	226.8 [87.1]	230.1 [89.3]
Total WBC count (10^9 / L)	7.5 (2.4)	7.0 (2.2)	7.5 (2.6)	7.2 (2.5)	7.6 (2.8)	7.5 (2.7)
Albumin (g/L)	41.8 (3.9)	42.4 (3.6)	40.8 (3.9)	40.9 (3.9)	39.3 (4.3)	39.2 (4.4)
Creatinine (micromol/L)	94.4 [21.6]	93.0 [18.25]	100.0 [25.0]	98.0 [22.35]	104.2 [30.5]	108.3 [35.0]

Table 1. Continued

	55 – 64 years		65 – 74 years		> 75 years	
	Incident HF patients	Individuals without HF	Incident HF patients	Individuals without HF	Incident HF patients	Individuals without HF
Comorbidity (%) §						
Atrial fibrillation	6.5	0.9	8.8	2.4	11.1	4.6
COPD	22.4	10.2	25.4	13.8	27.7	18.1
Diabetes mellitus	5.5	1.6	5.3	2.3	3.7	2.4
Myocardial infarction	5.3	0.9	4.2	1.3	3.8	1.5
Hypertension	72.1	54.9	80.0	71.6	80.8	72.9
Obesity	42.6	26.6	24.0	17.4	13.7	10.3
Medication use (%) ¤						
Blood pressure lowering medication	37.3	15.9	48.7	26.4	59.0	34.9
Lipid regulating drugs	29.6	13.6	26.2	17.2	11.5	10.7

*assessed by index of multiple deprivation † measurement closest to and within 3 years before baseline. § denotes prior medical history of given comorbidity 3 years before baseline, ¤ prescription use 3 years before baseline. SD = Standard Deviation; LDL = Low Density Lipoprotein; HDL = High Density Lipoprotein ; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; total WBC count = total White Blood Cell count; eGFR = estimated Glomerular Filtration Rate; COPD = Chronic Obstructive Pulmonary Disease.

Table 2. Baseline characteristics stratified by age and heart failure status in women

	55 – 64 years		65 – 74 years		> 75 years	
	Incident HF patients	Individuals without HF	Incident HF patients	Individuals without HF	Incident HF patients	Individuals without HF
Number of patients	2,878	254,486	6,624	94,568	15,171	93,315
Demographics						
Ethnicity (% Caucasian)	94.8	94.5	96.7	96.0	98.8	98.2
Most deprived fifth (%)*	29.4	16.4	25.4	18.6	22.2	19.1
Lifestyle (%) †						
Smoking						
Current Smoking	26.2	21.3	16.5	14.4	7.3	7.4
Ex-smoker	23.3	21.1	23.8	22.5	20.7	20.4
Never smoked	50.5	57.6	59.7	63.1	72.0	72.2
Sedentary lifestyle	52.8	41.7	60.3	51.3	75.5	71.3
Clinical measures in mean (sd) or median [IQR]†						
Body Mass Index (kg/m2)	29.8 (7.2)	27.3 (5.7)	28.1 (5.8)	26.8 (5.2)	25.5 (5.0)	24.7 (4.7)
Total cholesterol (mmol/L)	5.8 (1.2)	5.8 (1.1)	5.9 (1.2)	6.0 (1.1)	5.8 (1.2)	5.8 (1.2)
Triglycerides (mmol /L)	1.8 (1.1)	1.5 (0.9)	1.8 (1.0)	1.6 (0.9)	1.7 (1.1)	1.6 (0.9)
SBP (mmHg)	144.0 (19.5)	136.3 (17.5)	150.7 (19.8)	147.3 (18.7)	152.0 (20.9)	149.5 (20.8)
DBP (mmHg)	82.8 (9.8)	81.3 (9.2)	82.5 (9.7)	82.4 (9.3)	81.2 (9.9)	80.5 (10.0)
Heamoglobin (g/dL)	13.4 (1.3)	13.5 (1.1)	13.2 (1.4)	13.3 (1.3)	12.7 (1.5)	12.7 (1.5)
Platelets (10^9/L)	268.1 [85.2]	268.7 [87.1]	263.8 [91.2]	263.5 [88.5]	260.6 [96.7]	264.0 [97.4]
Total WBC count (10^9 / L)	7.3 (2.3)	6.7 (2.0)	7.3 (2.4)	7.0 (2.3)	7.5 (2.6)	7.3 (2.5)
Albumin (g/L)	41.2 (3.8)	41.9 (3.5)	40.5 (3.8)	40.7 (3.8)	39.0 (4.4)	38.9 (4.5)
Creatinine (micromol/L)	78.9 [18.8]	76.7 [16.5]	84.0 [23.2]	81.0 [20.0]	90.2 [29.3]	86.2 [25.6]

Table 2. Continued

	55 – 64 years		65 – 74 years		> 75 years	
	Incident HF patients	Individuals without HF	Incident HF patients	Individuals without HF	Incident HF patients	Individuals without HF
Comorbidity (%) §						
Atrial fibrillation	5.4	0.4	7.7	1.4	10.9	3.7
COPD	29.4	13.1	27.4	14.1	24.6	15.2
Diabetes mellitus	6.5	1.1	4.9	1.7	3.4	1.9
Myocardial infarction	2.6	0.2	2.6	0.5	2.3	0.9
Hypertension	82.6	47.6	81.7	72.3	70.2	75.3
Obesity	42.6	26.6	32.4	23.1	16.8	12.7
Medication use (%) ¤						
Blood pressure lowering medication	47.2	18.9	58.6	31.8	69.1	44.2
Lipid regulating drugs	22.9	9.4	21.6	14.3	8.8	8.7

*assessed by index of multiple deprivation † measurement closest to and within 3 years before baseline. § denotes prior medical history of given comorbidity 3 years before baseline, ¤ prescription use 3 years before baseline. SD = Standard Deviation; LDL = Low Density Lipoprotein; HDL = High Density Lipoprotein; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; total WBC count = total White Blood Cell count; eGFR = estimated Glomerular Filtration Rate; COPD = Chronic Obstructive Pulmonary Disease.

Incidence rates

Incidence rates of HF events per 1000 person-years varied between sexes and age categories. Overall, incidence rates in men were higher than in women (**Figure 1**). Incidence rates were stable over calendar time for men and women aged 55–64 years with a mean incidence rate per 1000 person-years of 3.6 and 1.9, respectively; these incidence rates increased with older age to an average of 13.6 for men and 9.2 for women at age 65–74 years. The highest incidence rate per 1000 person-years was observed for the age category >75 years with a mean incidence rate per 1000 person-years of 34.4 for men and 28.0 for women.

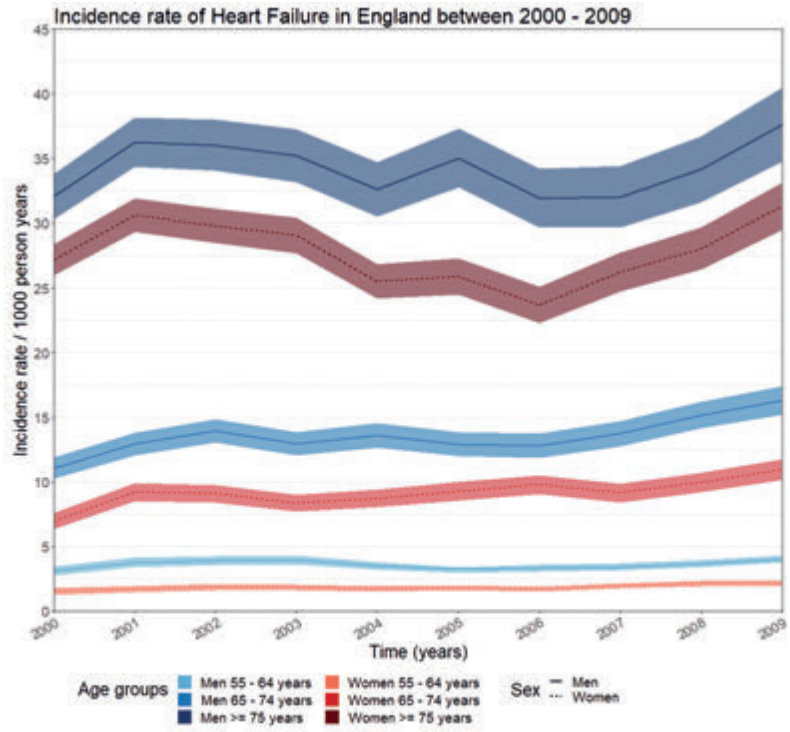
Risk factors for incident heart failure

Results from the multivariable Cox proportional hazard models show that diabetes, AF and COPD had the strongest associations with incident HF in men and an even stronger association with HF in women in all age categories, with associations attenuating with older age (p-value for interaction with age <0.05). In men, we found associations with HF for age, lowest quintile of social deprivation, BMI, haemoglobin, total WBC count and creatinine in all age categories (**Figure 2**). The associations of age, social deprivation, smoking and BP all attenuated in older men (p-value for interaction with age <0.05), whereas the association of sedentary lifestyle with incident HF was stronger in the older age categories compared to 55–64 year olds (p-value for interaction with age <0.05).

We found similar associations for women, age, lowest quintile social deprivation, current smoking, sedentary lifestyle, BMI, haemoglobin, total WBC count and creatinine were associated with incident HF in all age categories. However, compared to men, women showed stronger associations of creatinine, diabetes, AF and COPD, these were associated with incident HF in all age categories (**Figure 2**, p-value for interaction with sex < 0.05). Similar to men, associations of social deprivation, smoking, BP and diabetes attenuated in older women (p-value interaction with age <0.05).

We found no associations with incident HF in either men or women for platelets, total plasma cholesterol, triglycerides or albumin (**Figure 2**). We found an association for SBP (per 20 mmHg) for the youngest age category in women (1.11 [95% CI 1.05-1.18]), but not for men.

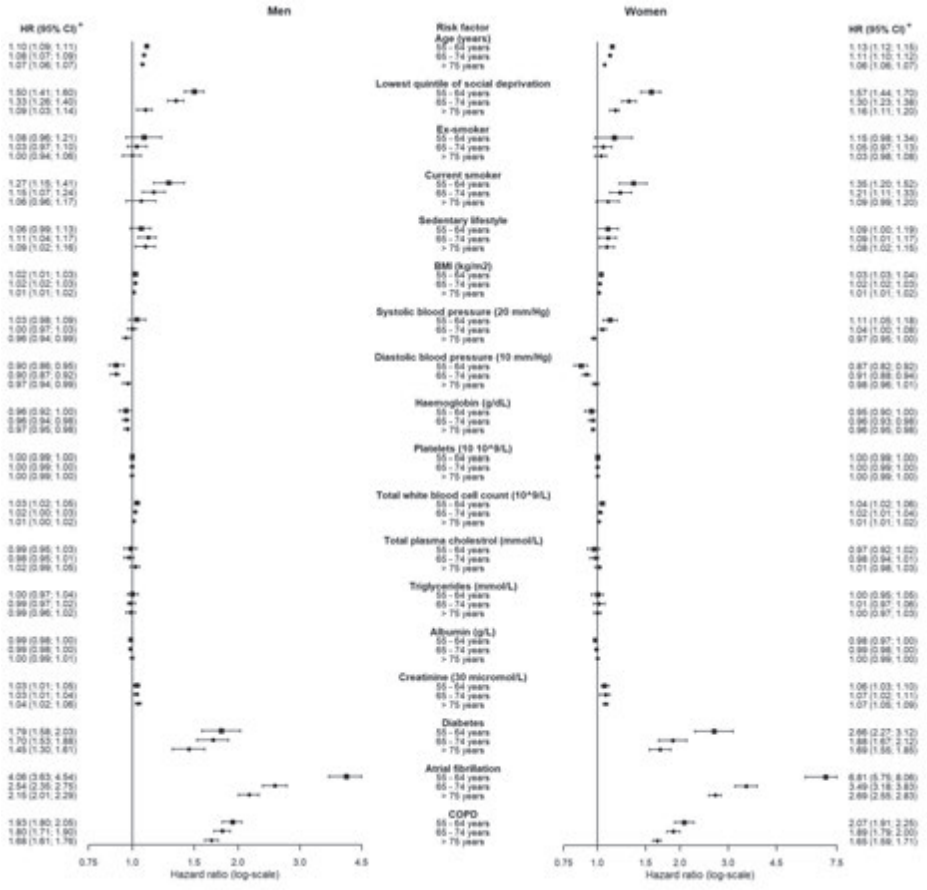
Figure 1. Incidence rate (per 1000 person years) of heart failure in England between 2000 and 2009 stratified by age category and sex.



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Men 55 - 64 years	287	402	472	533	513	502	552	601	676	767
Men 65 - 74 years	692	819	880	798	818	753	729	768	823	841
Men >= 75 years	1297	1385	1275	1127	941	909	760	709	688	671
Women 55 - 64 years	142	183	229	251	254	284	293	349	405	425
Women 65 - 74 years	504	683	680	620	638	666	694	639	683	721
Women >= 75 years	1942	2108	1931	1739	1406	1314	1119	1163	1146	1141

Incidence rate / 1000 person years with 95% confidence interval (band), table with absolute number of cases stratified by age category and sex.

Figure 2. Forest plot of multivariable hazard ratios (95% CI) of risk factors for incident heart failure, stratified by age and sex



Results of the multivariable model showing independent hazard ratios (HRs) of other variables shown and further adjusted for ethnicity, blood pressure lowering medication and lipid regulating drugs and stratified by age and sex. Square boxes = 55 – 64 years, circle boxes = 65 – 74 years and diamond boxes = > 75 years. Hazard ratio (95% CI) = Hazard ratio (95% Confidence Interval). * Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold). Patient events men: Age category 55-64 years n (events) = 257,698 (5,408), age category 65-74 years n (events) = 88,416 (8,047), age category >75 years n (events) = 58,531 (9,859). Patient events women: Age category 55-64 years n (events) = 257,364 (2,878), age category 65-74 years n (events) = 101,192 (6,624), age category >75 years n (events) = 108,486 (15,171).

Furthermore, SBP was inversely associated in the oldest age category for both sexes (0.96 [95% CI 0.94-0.99] and 0.97 [95% CI 0.96-1.00] respectively). DBP (per 10 mmHg) was inversely associated with incident HF in the two younger age categories, whereas no association in the oldest age group was observed (**Figure 2**). Overall results from the multivariable Cox proportional hazard model, men and women and all ages combined, are shown in supplementary **Figure S3**. When patients with and without a history of MI were analysed, similar HRs were found for the associations between risk factors and incident HF in men and women (supplementary **Figure S4** and **S5**), with a trend towards a positive association of total cholesterol with HF, though not significant. When we added history of MI to the main model, it did not change the observed associations of other risk factors (data not shown). When we compared individuals using BP-lowering medication with those who were not, we observed an attenuation of most associations in individuals not prescribed BP-lowering medication, except for SBP and diabetes, the associations of these risk factors with incident HF became stronger in all age categories for both men and women (supplementary **Figure S6** and **S7**).

Relative contribution of modifiable risk factors and comorbidities

The largest proportion of male HF cases that could be prevented was if COPD, AF and hypertension would not occur in the population (**Table 3**). A smaller proportion of cases could be prevented by the modifiable lifestyle factors obesity, diabetes and current smoking.

Relative contributions of risk factors to incident HF appeared to be stronger in women compared to men. In women, the largest proportion of HF cases that could be prevented by modifiable risk factors were COPD and AF, but not hypertension. Similar to men, obesity and diabetes could prevent a smaller proportion of HF cases (**Table 4**). In both men and women, the relative contributions attenuated with older age, whereas the relative contribution of sedentary lifestyle remained similar across age categories.

Table 3. Relative contributions of risk factors for incident heart failure stratified by age in men

Age category	Risk Factors	Hazard ratio (95% CI)*	Prevalence	Relative contribution (95% CI)
55 - 64 years	COPD	1.93 (1.81; 2.06)	0.22	17.24 (15.36; 19.19)
	Atrial fibrillation	4.04 (3.62; 4.52)	0.07	16.50 (14.55; 18.62)
	Obesity	1.21 (1.11; 1.31)	0.48	9.07 (4.97; 12.84)
	Sedentary lifestyle	1.06 (0.99; 1.14)	0.44	2.54 (-0.44; 5.74)
	Diabetes	1.85 (1.64; 2.10)	0.06	4.47 (3.40; 5.70)
	Current-smokers	1.27 (1.14; 1.40)	0.32	8.04 (4.34; 11.47)
	Hypertension	1.14 (1.07; 1.22)	0.72	9.17 (4.80; 13.69)
65 - 74 years	COPD	1.81 (1.72; 1.90)	0.25	17.06 (15.46; 18.61)
	Atrial fibrillation	2.54 (2.35; 2.75)	0.09	11.93 (10.62; 13.34)
	Obesity	1.25 (1.18; 1.34)	0.24	5.66 (4.14; 7.54)
	Sedentary lifestyle	1.11 (1.05; 1.18)	0.48	5.03 (2.35; 7.97)
	Diabetes	1.73 (1.57; 1.92)	0.05	3.72 (2.93; 4.65)
	Current-smokers	1.15 (1.07; 1.24)	0.20	2.87 (1.36; 4.51)
	Hypertension	1.03 (0.97; 1.09)	0.80	n.e.
> 75 years	COPD	1.69 (1.61; 1.76)	0.28	16.05 (14.45; 17.39)
	Atrial fibrillation	2.16 (2.02; 2.30)	0.11	11.41 (10.17; 12.61)
	Obesity	1.15 (1.07; 1.25)	0.14	2.01 (0.95; 3.31)
	Sedentary lifestyle	1.09 (1.03; 1.16)	0.62	5.31 (1.83; 9.06)
	Diabetes	1.45 (1.31; 1.62)	0.04	1.64 (1.13; 2.24)
	Current-smokers	1.05 (0.95; 1.16)	0.19	n.e.
	Hypertension	1.10 (1.05; 1.15)	0.81	7.48 (3.88; 10.81)

* Independent HRs of other variables shown and further adjusted for age, haemoglobin, platelets, total white blood cell count, total cholesterol, triglycerides, albumin, creatinine, ethnicity, smoking habits, index of multiple deprivation, blood pressure lowering medication and lipid lowering drugs. N.E.= not estimable, Obesity = Body Mass Index ≥ 30 kg/m^2, 95% CI = 95% Confidence Interval. Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

Table 4. Relative contributions of risk factors for incident heart failure stratified by age in women

Age category	Risk Factors	Hazard ratio (95% CI)*	Prevalence	Relative contribution (95% CI)
55 - 64 years	COPD	2.07 (1.91; 2.25)	0.29	23.93 (21.11; 26.87)
	Atrial fibrillation	6.78 (5.73; 8.01)	0.05	23.79 (20.35; 27.46)
	Obesity	1.39 (1.25; 1.54)	0.43	14.25 (9.62; 18.70)
	Sedentary lifestyle	1.12 (1.03; 1.22)	0.52	5.96 (1.56; 10.41)
	Diabetes	2.77 (2.36; 3.24)	0.07	10.32 (8.12; 12.71)
	Current-smokers	1.33 (1.18; 1.49)	0.26	7.96 (4.50; 11.38)
	Hypertension	1.09 (1.00; 1.19)	0.83	n.e.
65 - 74 years	COPD	1.89 (1.79; 2.00)	0.27	19.61 (17.79; 21.51)
	Atrial fibrillation	3.49 (3.18; 3.83)	0.08	16.09 (14.37; 17.89)
	Obesity	1.25 (1.17; 1.34)	0.32	7.49 (5.22; 9.92)
	Sedentary lifestyle	1.10 (1.02; 1.18)	0.60	5.69 (1.19; 9.79)
	Diabetes	1.91 (1.70; 2.15)	0.05	4.27 (3.32; 5.02)
	Current-smokers	1.21 (1.11; 1.32)	0.24	3.35 (1.78; 5.02)
	Hypertension	0.98 (0.92; 1.04)	0.82	n.e.
> 75 years	COPD	1.65 (1.59; 1.71)	0.25	13.79 (12.67; 14.87)
	Atrial fibrillation	2.69 (2.55; 2.84)	0.11	15.56 (14.45; 16.71)
	Obesity	1.14 (1.08; 1.20)	0.17	2.30 (1.33; 3.25)
	Sedentary lifestyle	1.09 (1.02; 1.16)	0.76	6.36 (1.49; 10.78)
	Diabetes	1.70 (1.56; 1.86)	0.03	2.32 (1.87; 2.84)
	Current-smokers	1.08 (0.99; 1.19)	0.07	n.e.
	Hypertension	1.02 (0.99; 1.07)	0.70	n.e.

* Independent HRs of other variables shown and further adjusted for age, haemoglobin, platelets, total white blood cell count, total cholesterol, triglycerides, albumin, creatinine, ethnicity, smoking habits, index of multiple deprivation, blood pressure lowering medication and lipid lowering drugs. N.E.= not estimable, Obesity = Body Mass Index ≥ 30 kg/m^2, 95% CI = 95% Confidence Interval. Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

Sensitivity analysis

Patient characteristics were similar between imputed data and complete case data for men and women (supplementary **Table S2** and **S3**). Sensitivity analysis showed that a complete case analysis yielded similar directions of associations for risk factors with incident HF in both men and women (supplementary **Table S4** and **S5**); however, associations were attenuated in the imputed data analysis. General practice variability had no effect on the overall associations in men and

women (supplementary **Table S6** and **S7**), since the random effects models resulted in near identical estimates to our main analysis. Lastly, analyses stratified by different sources of EHR showed that the associations of social deprivation, current smoking and diabetes with incident HF were stronger in HES cases compared to CPRD, whereas the association of AF was stronger in younger (55 – 65 years) men and women in CPRD compared to HES (supplementary **Table S8** and **S9**). Overall, the analyses were comparable with our main analysis.

Discussion

In this large population-based cohort study using linked EHRs, we investigated the association of risk factors with the development of HF. We found independent associations of diabetes, AF, COPD, age, social deprivation, modifiable lifestyle factors and inflammatory markers, but not SBP, with incident HF, in a population using BP-lowering and lipid-regulating medication.

In England, we found higher incidence rates for men and elderly (>75 years) which were stable in the period of 2000 - 2005, though increasing from 2006 onwards for all categories. Previous studies have reported sex- and/or age-specific incidence rates of HF and indicate that the incidence of HF is stable over time, whereas others suggest it might be increasing or even decreasing.[16–21] These differences might be reflected in a varying follow-up time, diverse patient populations, diversity in quality of data, lack of distinction of incidence rates based on both age and gender and regional or cultural differences underlying these incidence rates.

Risk factors for incident heart failure

We confirmed several associations of risk factors with HF, such as diabetes, BMI and smoking. Our study supports and contributes to previous studies in CALIBER,[21–24] which have shown associations of these risk factors with a range of CVDs. We observed similar patterns of association between men and women as well as attenuation of the associations of risk factors with HF at older age. Compared to men, women showed stronger associations of modifiable lifestyle factors, such as smoking, a sedentary lifestyle and diabetes, with incident HF. This could reflect a different aetiology between men and women in the development of HF.

We found no, or weak, independent association between SBP and incident HF in our multivariable analyses. This contrasts with papers reporting on the association of SBP with incident HF.[5,6] However, similar associations between SBP and incident HF, as previously reported,[6] could be reproduced by excluding individuals using BP-lowering medication in our analyses. This reinforces the importance of treating high BP accordingly.

Our results show that in a population with high prescription rates of BP-lowering medication, smaller independent associations of other risk factors become more evident. For example, we found levels of total WBC count independently associated with HF, this could indicate an underlying inflammatory process leading to HF.[26,27] Inflammation could be triggered by comorbidities such as diabetes or obesity or via endothelial dysfunction and atherosclerosis from an underlying heart disease; however it remains to be investigated how inflammation and HF interact exactly. Similar results have recently been reported for other CVDs.[24] Additionally, we found an association of creatinine and an inverse association of haemoglobin with incident HF. Low haemoglobin, or anaemia, and raised creatinine levels are frequently observed among HF patients and are associated with worse outcomes and increased mortality.[28,29] Lastly, our results show an inverse association of DBP with incident HF. This is likely due to reversed causality induced by the relatively old age of our study population (median age 61.5 years [IQR 55–71.9]); it is known that DBP is lower in elderly and is associated with worse survival.[30,31]

Observing the substantial prevalence of modifiable risk factors and comorbidities, such as COPD, AF, obesity, a sedentary lifestyle and smoking, our results suggest that preventive strategies could be an opportunity to reduce the risk of developing incident HF. Previous research has already shown that adherence to a healthy lifestyle reduces the lifetime risk of HF.[32,33] Future studies should verify these results in population-based studies and focus should be directed to implicating effective preventive strategies in clinical practice.

Study strengths & limitations

Strengths of this study are the linkage of multiple EHR sources, which allowed for the collection of a large representative sample of 871,687 individuals across England and studying a large population of HF patients. Previous studies have shown the feasibility and validity of routinely collected data in CPRD and HES.[34,35] However, several limitations of this study should be considered when

interpreting these findings. First, due to the nature of EHR, the accuracy and amount of detailed information recorded is limited, though findings based on the multiple imputed dataset showed a similar direction of association compared to complete-case analysis. Residual confounding may still exist. Second, we were unable to differentiate between HF phenotypes, since there was no access to detailed echocardiography estimates to assess systolic function. This is likely to conceal a greater degree of heterogeneity. Third, all measurements are prone to measurement error and/or misclassification. To define HF we used data from 2 different EHR sources, each having their own measurement error. Yet, associations were similar between CPRD and HES cases in our sensitivity analysis and others have delivered evidence of the validity of using linked EHRs.[4,36]

Conclusions

In this large population based cohort study using linked EHRs in England we observed that diabetes, AF, COPD, age, social deprivation, modifiable lifestyle factors such as smoking, sedentary lifestyle, BMI and physiological measures such as haemoglobin, total white blood cell count and creatinine were associated with incident HF across age- and sex-specific groups. Mainly modifiable risk factors and comorbidities are of interest, considering a substantial PAR. This highlights the importance of preventive strategies targeting modifiable lifestyle risk factors for HF, besides BP management.

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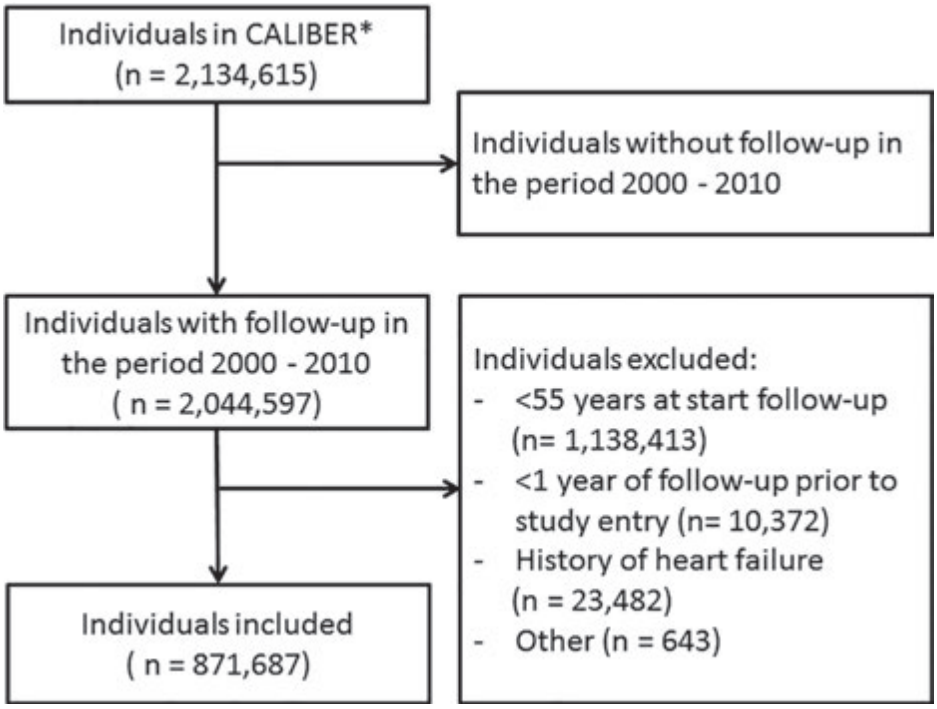
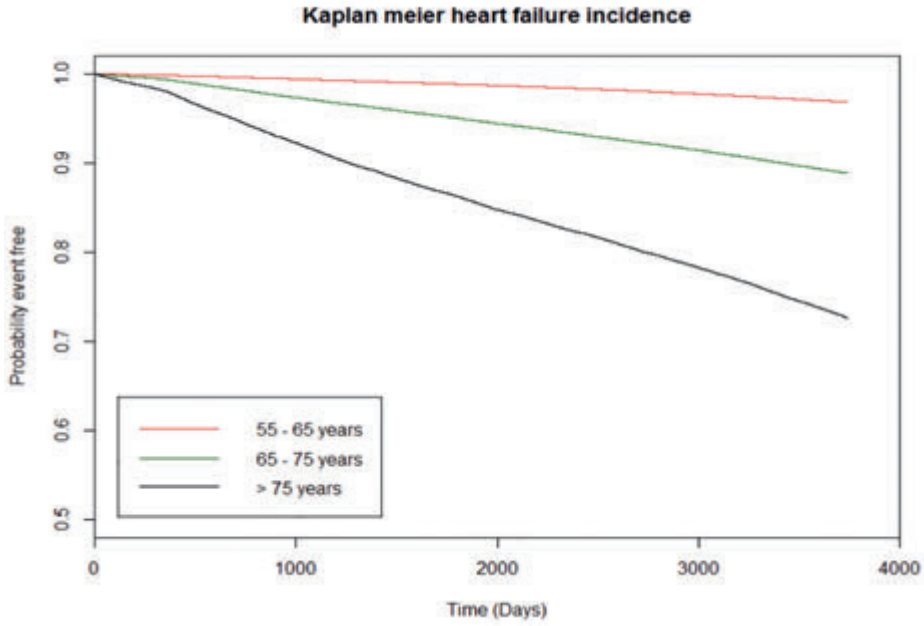
Supplemental material

Figure S1. Flowchart of study population



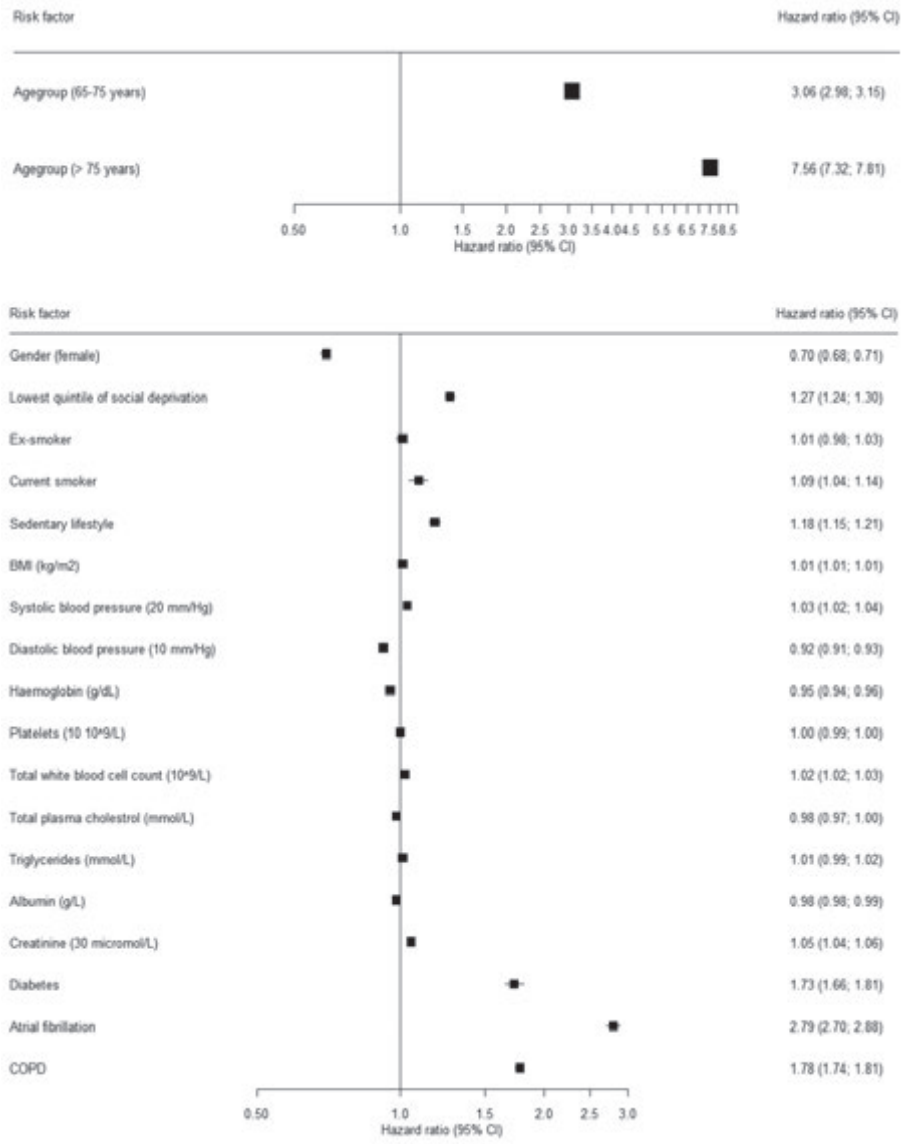
* CALIBER = Cardiovascular disease research using Linked Bespoke studies and Electronic health Records

Figure S2. Kaplan Meier time-to-event for incident HF



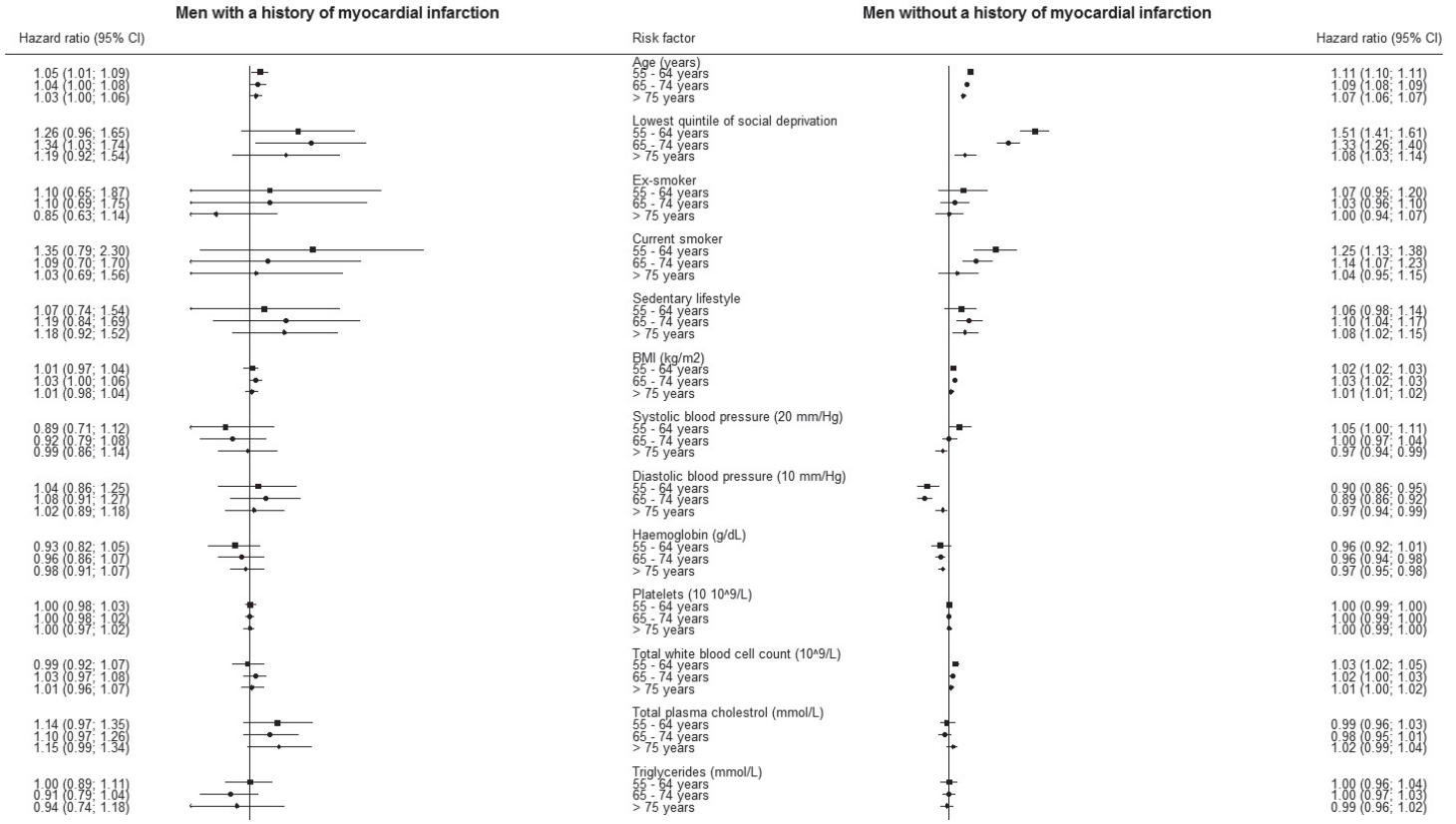
Kaplan Meier time-to-event curve stratified for age: 55 - 65 year, 65 - 75 years and > 75 years.

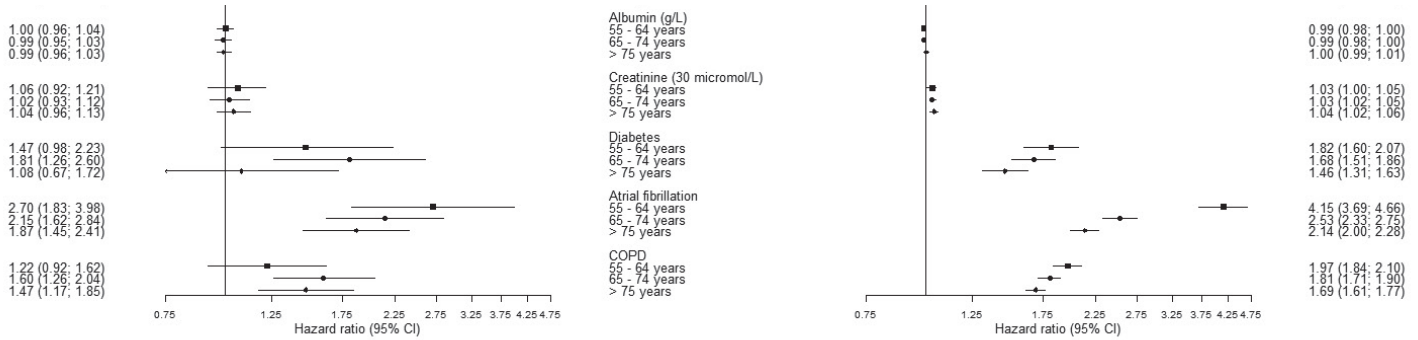
Figure S3. Risk factors associated with incident heart failure



Independent HRs for all individuals, further adjusted for ethnicity, blood pressure lowering medication and lipid regulating drugs. Lowest quintile of social deprivation assessed by index of multiple deprivation, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

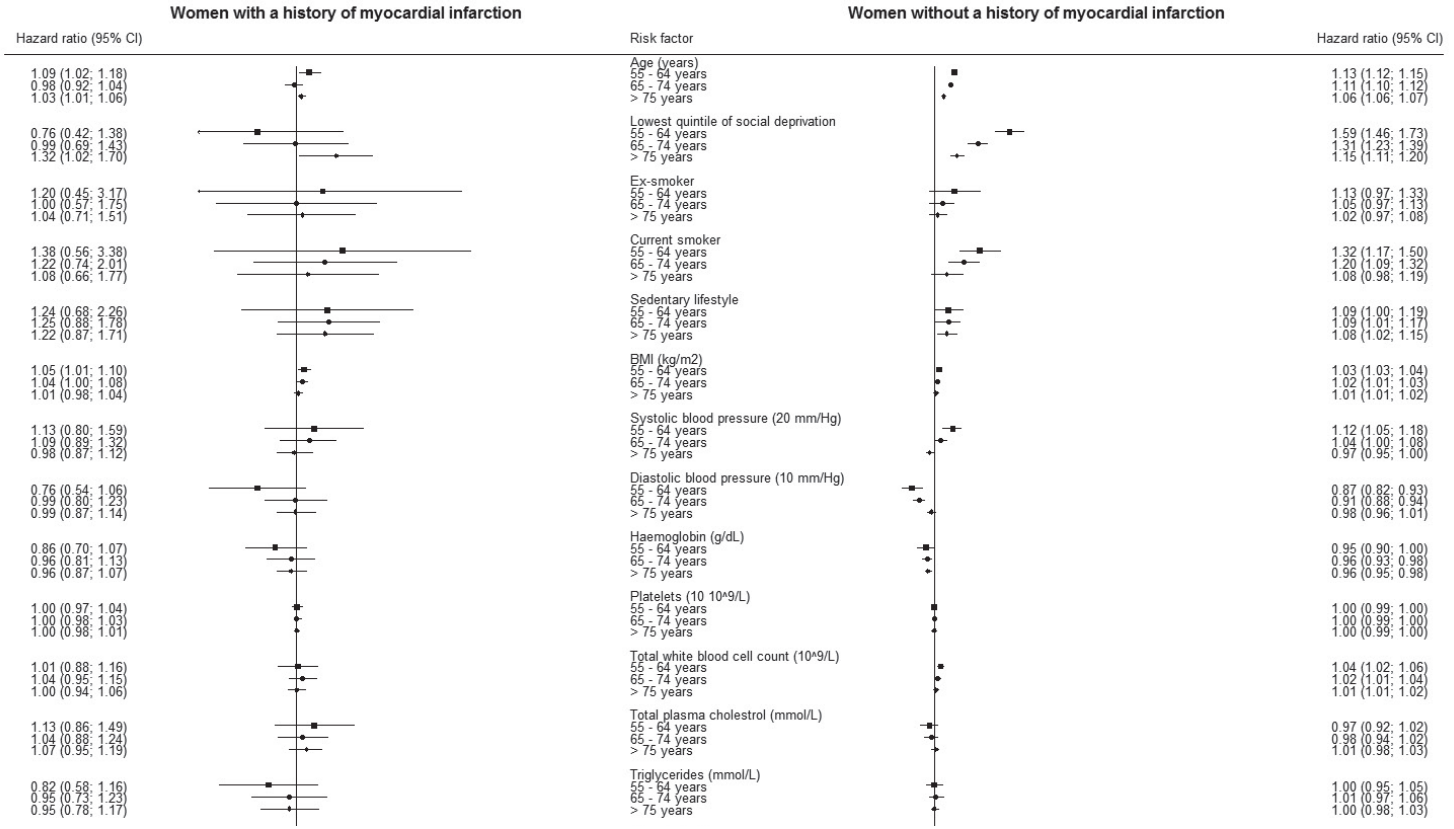
Figure S4. Risk factors associated with incident heart failure in men stratified by age and prior MI

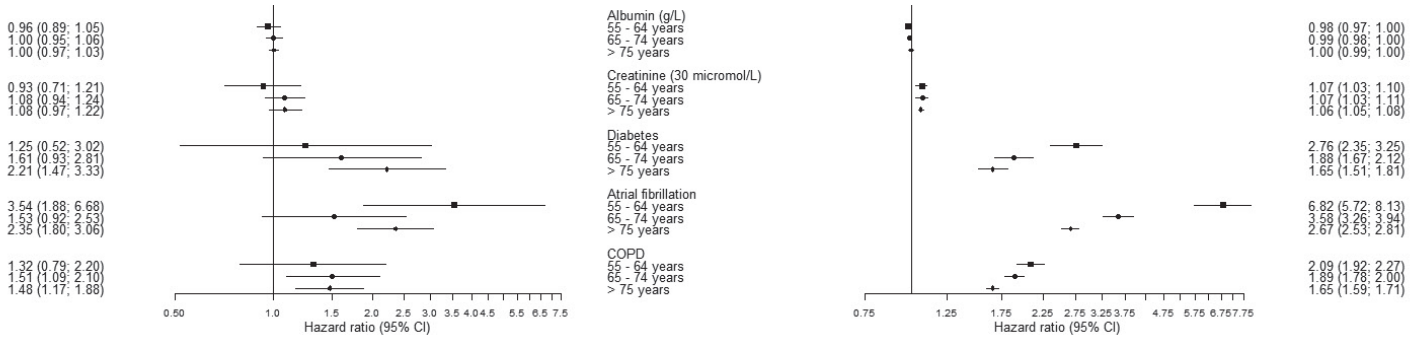




Independent HRs in a subset of individuals with and without prior MI, further adjusted for ethnicity, blood pressure lowering medication and lipid regulating drugs. Lowest quintile of social deprivation assessed by index of multiple deprivation, MI = Myocardial Infarction, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Patient events with prior MI: Age category 55-64 years n (events) = 2,426 (285) , age category 65-74 years n (events) = 1,362 (340), age category >75 years n (events) = 1,090 (372). Patient events without prior MI: Age category 55-64 years n (events) = 255,272 (5,123), age category 65-74 years n (events) = 87,054 (7,707), age category >75 years n (events) = 57,441 (9,487). Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

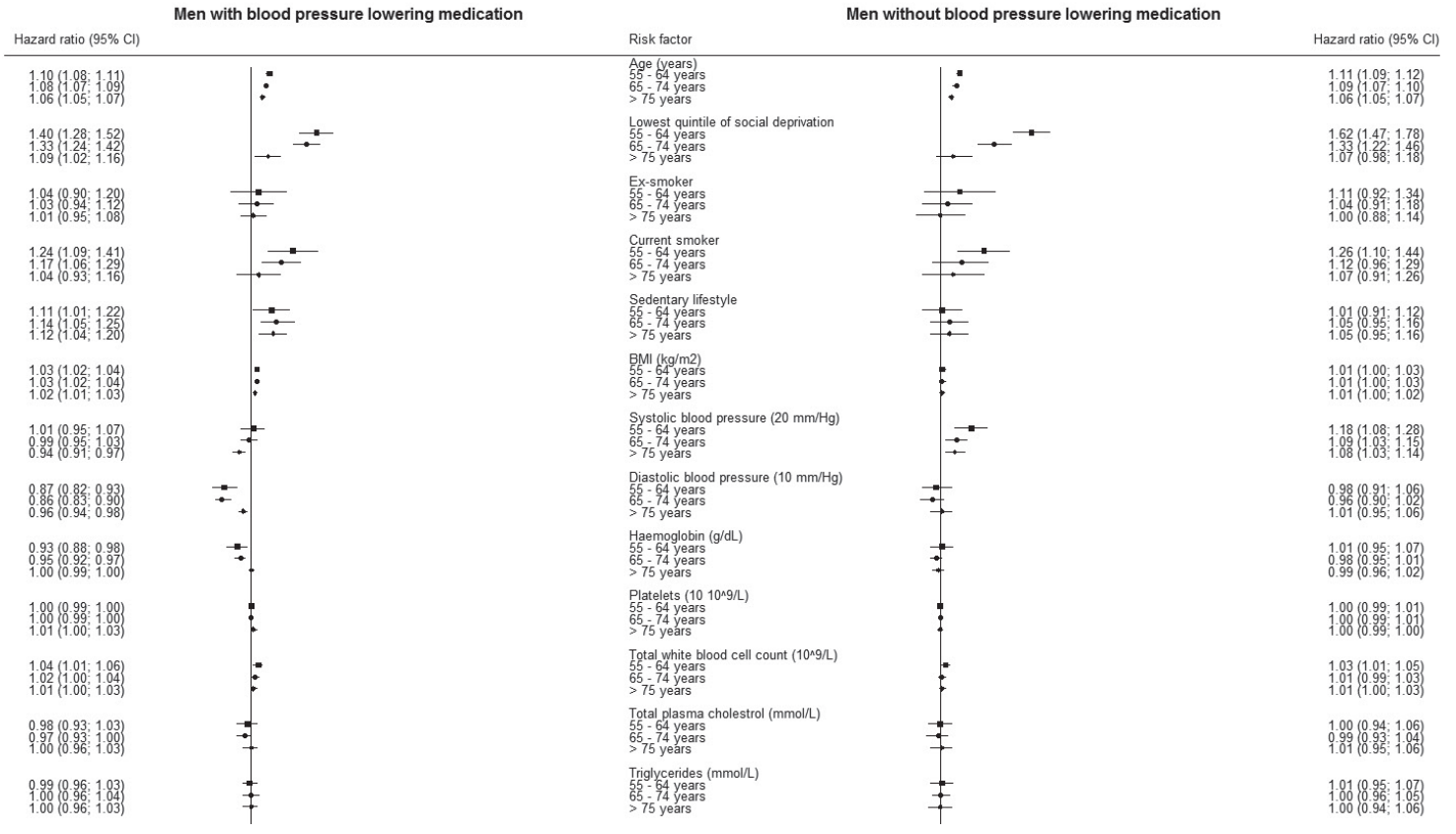
Figure S5. Risk factors associated with incident heart failure in women stratified by age and prior MI

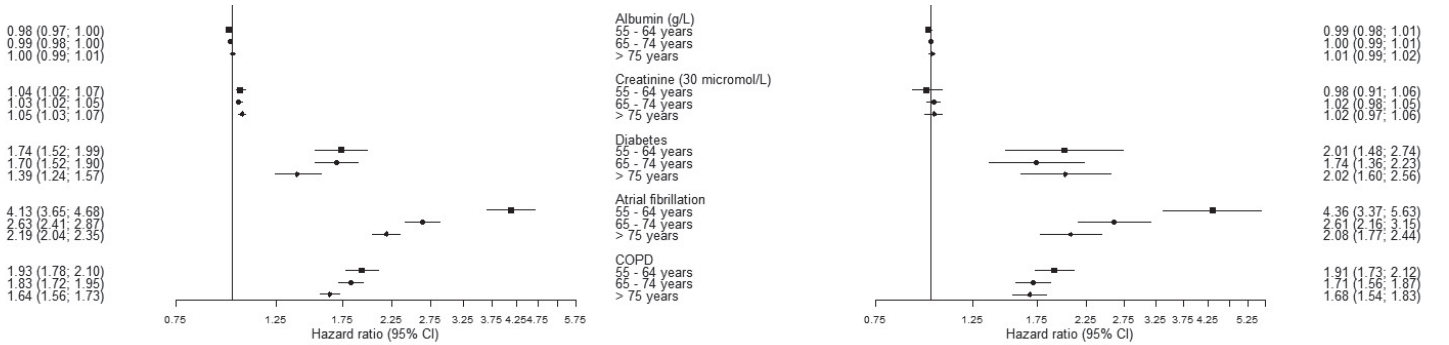




Independent HRs in subset of individuals with and without prior MI, further adjusted for ethnicity, blood pressure lowering medication and lipid regulating drugs. Lowest quintile of social deprivation assessed by index of multiple deprivation, MI = Myocardial Infarction, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Patient events with prior MI: Age category 55-64 years n (events) = 638 (76), age category 65-74 years n (events) = 688 (175), age category >75 years n (events) = 1,153 (349). Patient events without prior MI: Age category 55-64 years n (events) = 256,726 (2,808), age category 65-74 years n (events) = 100,504 (6,449), age category >75 years n (events) = 107,333 (14,822). Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

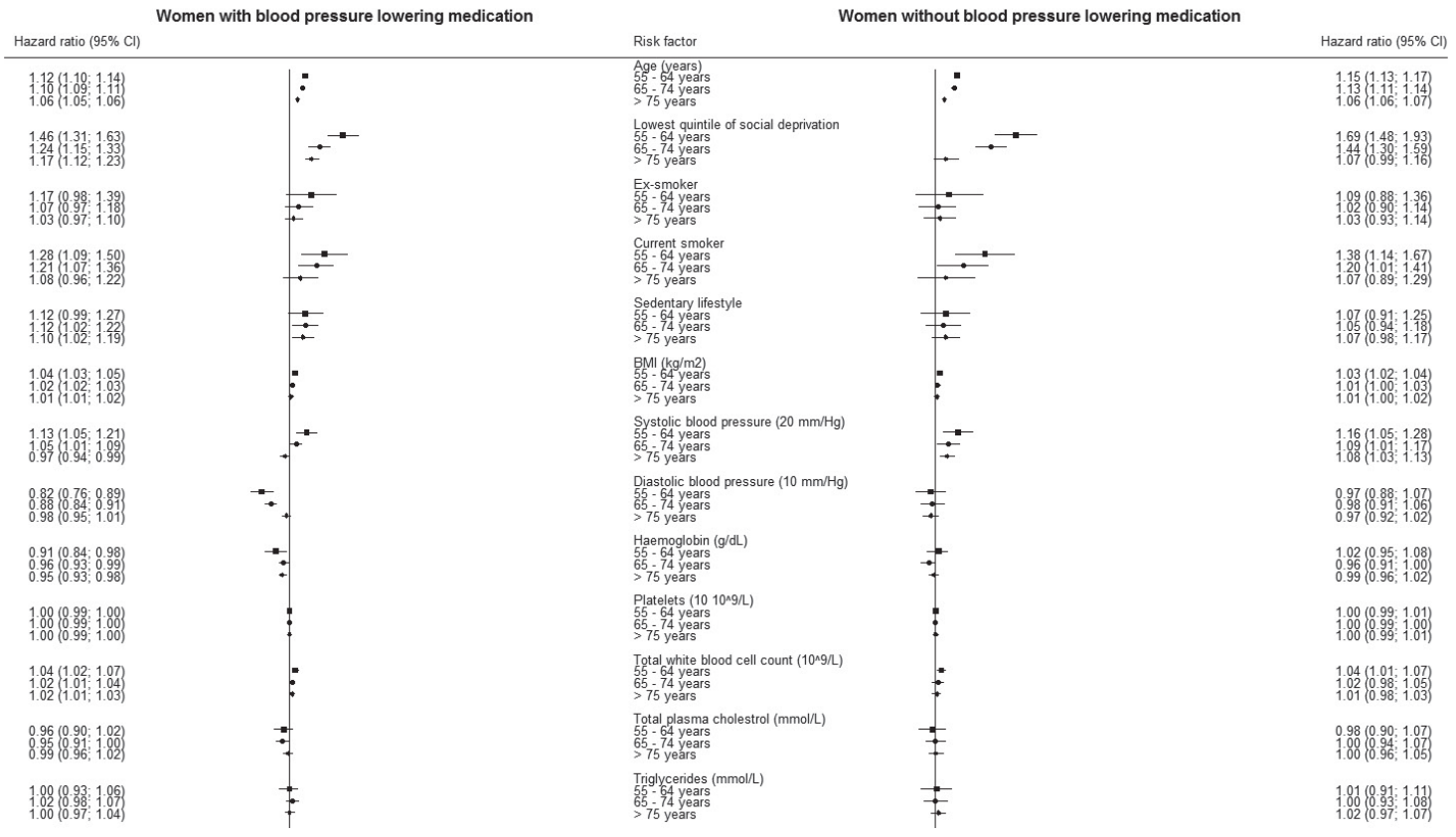
Figure S6. Risk factors associated with incident heart failure in men stratified by age and blood pressure lowering medication

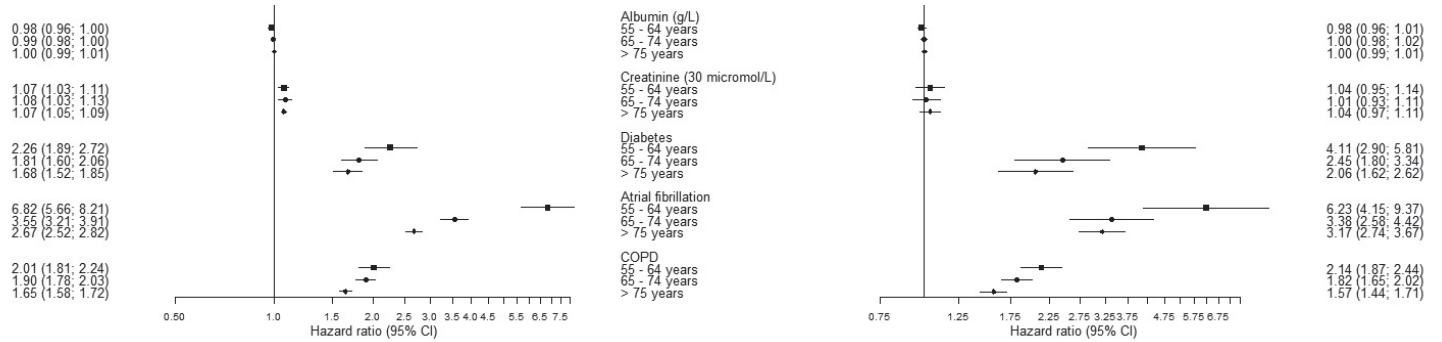




Independent HRs in subset of individuals with and without blood pressure lowering medication, further adjusted for ethnicity and lipid regulating drugs. Lowest quintile of social deprivation assessed by index of multiple deprivation, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Patient events with blood pressure lowering medication: Age category 55-64 years n (events) = 68,524 (2,921), age category 65-74 years n (events) = 36,768 (5,090), age category >75 years n (events) = 28,700 (6,725). Patient events without blood pressure lowering medication: Age category 55-64 years n (events) = 189,174 (2,487), age category 65-74 years n (events) = 51,648 (2,957), age category >75 years n (events) = 29,831 (3,134). Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

Figure S7. Risk factors associated with incident heart failure in women stratified by age and blood pressure lowering medication





Independent HRs in subset of individuals with and without blood pressure lowering medication, further adjusted for ethnicity and lipid regulating drugs. Lowest quintile of social deprivation assessed by index of multiple deprivation, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Patient events with blood pressure lowering medication: Age category 55-64 years n (events) = 69,912 (1659), age category 65-74 years n (events) = 43,712 (4490), age category >75 years n (events) = 60,311 (11,428). Patient events without blood pressure lowering medication: Age category 55-64 years n (events) = 187,452 (1,219), age category 65-74 years n (events) = 57,480 (2,134), age category >75 years n (events) = 48,175 (3,743). Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

Table S1. Overview of READ and ICD-10 codes used to identify heart failure and myocardial infarction in CPRD and HES data sources

	CPRD **READ codes**	**HES** **ICD 10**
Heart failure	G580400, G210.00, G210000, G210100, G211100, G21z100, G230.00, G232.00, G234.00, G1yz100, 1O1..00, 662W.00, 662p.00, 8B29.00, 8H2S.00, 9Or0.00, G400.00, G41z.11, G554000, G554011, G58..00, G58..11, G580.00, G580.11, G580.12, G580.13, G580.14, G580000, G580100, G580200, G580300, G581.00, G581.11, G581.13, G581000, G582.00, G58z.00, G58z.12, G5yy900, G5yyA00, R2y1000	I110, I130, I132, I260, I50
Non-fatal acute myocardial infarction	G30X000, G307100, 323..00, 3233.00, 3234.00, 3235.00, 3236.00, 323Z.00, 889A.00, G30..00, G30..12, G30..13, G30..15, G30..16, G300.00, G301.00, G301000, G301100, G301z00, G302.00, G303.00, G304.00, G305.00, G306.00, G307.00, G307000, G308.00, G309.00, G30B.00, G30X.00, G30y.00, G30y000, G30y100, G30y200, G30yz00, G30z.00, G31y100, G38..00, G380.00, G381.00, G384.00, G38z.00, Gyu3400	I21

Details of how these codes are defined can be found online at http://www.caliberresearch.org/portal/. CPRD = Clinical Practice Research Datalink; HES = Hospital Episode Statistics.

Table S2. Complete cases baseline characteristics stratified by age in men

	55 – 64 years		65–74 years		> 75 years		% missing HF subjects	% missing non HF subjects
	HF subjects	Non HF subjects	HF subjects	Non HF subjects	HF subjects	Non HF subjects		
Number of patients	5408	252290	8047	80369	9859	48672	23314	381331
Demographics								
Ethnicity (% Caucasian)	96.3	95.1	96.8	95.8	98.3	97.4	18.3	42.0
Most deprived fifth (%)*	26.1	17.1	22.8	18.0	19.4	19.2	0.24	0.35
Lifestyle (%) †								
Smoking							75.3	62.9
Current Smoking	41.7	27.9	23.0	18.0	12.3	12.2	n/a	n/a
Ex-smoker	31.6	29.9	40.4	38.1	40	40.7	n/a	n/a
Never smoked	26.7	42.3	36.6	43.9	47.7	47.2	n/a	n/a
Sedentary lifestyle	51.1	37.1	55.2	40.9	64.1	57.1	79.2	80.3
Clinical measures in mean (sd) or median [IQR] †								
Body Mass Index (kg/m^2)	29.5 (5.7)	27.9 (4.7)	28.0 (4.6)	26.8 (4.1)	26.2 (4.1)	25.4 (3.9)	55.7	58.6
Total cholesterol (mmol/L)	5.3 (1.4)	5.4 (1.1)	5.1 (1.0)	5.2 (1.0)	5.0 (1.1)	4.9 (1.1)	66.8	68.4
Triglycerides (mmol /L)	2.1 (1.4)	1.9 (1.3)	1.8 (1.1)	1.7 (1.0)	1.6 (1.0)	1.5 (0.9)	78.9	76.6
LDL cholesterol (mmol/L)	3.3 (1.0)	3.3 (1.0)	3.2 (1.0)	3.2 (1.0)	3.1 (1.1)	2.9 (1.0)	85.2	80.6
HDL cholesterol (mmol/L)	1.2 (0.4)	1.3 (0.4)	1.3 (0.6)	1.3 (0.4)	1.3 (0.5)	1.3 (0.4)	84.1	79.3
SBP (mmHg)	142.9 (19.9)	139.1 (17.2)	147.1 (19.4)	146.0 (18.4)	148.3 (19.9)	147.0 (19.5)	23.2	34.1
DBP (mmHg)	83.7 (10.5)	83.6 (9.6)	81.4 (9.6)	82.1 (9.5)	79.8 (9.8)	79.7 (9.7)	23.2	34.1
Heamoglobin (g/dL)	14.5 (1.6)	14.8 (1.2)	14.0 (1.7)	14.3 (1.5)	13.4 (1.7)	13.5 (1.7)	68.5	71.2
Platelets (10^9/L)	239.0 [87.0]	243.0 [76.5]	224.5 [83.0]	230.0 [80.0]	223.0 [85.3]	230.0 [88.0]	73.2	73.8

Table S2. Continued

	55 – 64 years		65–74 years		> 75 years		% missing HF subjects	% missing non HF subjects
	HF subjects	Non HF subjects	HF subjects	Non HF subjects	HF subjects	Non HF subjects		
Albumin (g/L)	41.2 (4.0)	42.6 (3.6)	40.6 (3.9)	41.2 (3.8)	39.4 (4.1)	39.3 (4.4)	75.8	74.1
Creatinine (micromol/L)	96.5 [25.5]	93.0 [19.0]	103.0 [28.0]	98.0 [22.5]	112.0 [38.8]	105.0 [31.0]	60.0	66.1
eGFR (mL/min/1.73 m^2)	70.2 (18.0)	74.0 (14.6)	62.5 (16.4)	66.1 (14.9)	55.0 (16.0)	59.4 (16.1)	61.4	75.5
Sodium (mmol/L)	139.0 (8.0)	139.7 (7.5)	139.0 (8.1)	139.5 (8.1)	138.8 (8.9)	138.9 (9.6)	64.5	68.0
Potassium (mmol/L)	4.4 (0.8)	4.4 (1.1)	4.6 (4.9)	4.4 (1.9)	4.5 (3.4)	4.4 (2.8)	64.5	68.0
Total WBC count (10^9/L)	8.0 (2.8)	7.1 (2.2)	7.7 (2.7)	7.2 (2.5)	7.7 (3.2)	7.4 (2.6)	72.9	73.9
Comorbidity (%) §								
Atrial fibrillation	6.5	0.9	8.8	2.4	11.1	4.6	n/a	n/a
COPD	22.4	10.2	25.4	13.8	27.7	18.1	n/a	n/a
Diabetes mellitus	5.5	1.6	5.3	2.3	3.7	2.4	n/a	n/a
Myocardial infarction	5.3	0.9	4.2	1.3	3.8	1.5	n/a	n/a
Hypertension	68.5	44.8	78.8	60.2	83.4	65.4	15.1	31.1
Obesity	19.5	11.4	13.6	7.9	6.8	4.3	55.7	58.6
Medication use (%) ¤								
Blood pressure lowering medication	37.3	15.9	48.7	26.4	59.0	34.9	n/a	n/a
Lipid regulating drugs	29.6	13.6	26.2	17.2	11.5	10.7	n/a	n/a

*assessed by index of multiple deprivation † measurement closest to and within 3 years before baseline. § denotes prior medical history of given comorbidity 3 years before baseline. SD = Standard Deviation; LDL = Low Density Lipoprotein; HDL = High Density Lipoprotein; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; total WBC count = total White Blood Cell count; eGFR = estimated Glomerular Filtration Rate; COPD = Chronic Obstructive Pulmonary Disease.

Table S3. Complete cases baseline characteristics stratified by age in women

	55 – 64 years		65 – 74 years		> 75 years		% missing HF subjects	% missing non HF subjects
	HF subjects	Non HF subjects	HF subjects	Non HF subjects	HF subjects	Non HF subjects		
Number of patients	2878	254486	6624	94568	15171	93315	24673	442369
Demographics								
Ethnicity (% Caucasian)	95.0	94.5	96.7	96.0	98.8	98.1	19.9	38.9
Most deprived fifth (%)*	29.4	16.3	25.3	18.5	22.1	19.0	0.24	0.36
Lifestyle (%) †								
Smoking							78.1	62.4
Current Smoking	34.8	22.0	22.3	13.9	8.2	7.1	n/a	n/a
Ex-smoker	25.7	21.2	26.1	22.9	23.1	21.4	n/a	n/a
Never smoked	39.6	56.8	51.7	63.2	68.7	71.6	n/a	n/a
Sedentary lifestyle	62.6	41.8	68.0	51.3	78.0	69.8	82.1	78.4
Clinical measures in mean (sd) or median [IQR] †								
Body Mass Index (kg/m^2)	31.3 (7.7)	27.8 (5.8)	29.0 (6.3)	27.0 (5.3)	26.2 (5.2)	25.1 (4.8)	61.0	54.6
Total cholesterol (mmol/L)	5.6 (1.2)	5.8 (1.1)	5.7 (1.2)	5.8 (1.2)	5.7 (1.3)	5.6 (1.2)	77.0	72.8
Triglycerides (mmol /L)	2.0 (1.1)	1.6 (1.0)	2.0 (1.2)	1.7 (0.9)	1.8 (1.1)	1.6 (0.9)	86.2	80.0
LDL cholesterol (mmol/L)	3.4 (1.1)	3.5 (1.0)	3.5 (1.1)	3.5 (1.1)	3.4 (1.2)	3.3 (1.2)	90.0	83.3
HDL cholesterol (mmol/L)	1.5 (0.5)	1.6 (0.5)	1.5 (0.5)	1.6 (0.5)	1.5 (0.5)	1.6 (0.5)	89.4	82.0
SBP (mmHg)	145.2 (19.8)	136.7 (17.7)	151.5 (20.1)	148.2 (18.9)	152.9 (21.0)	150.2 (20.8)	23.1	25.9
DBP (mmHg)	83.2 (9.9)	81.5 (9.3)	82.6 (9.9)	82.6 (9.3)	81.4 (9.9)	80.8 (10.0)	23.1	25.9
Heamoglobin (g/dL)	13.3 (1.6)	13.5 (1.1)	13.1 (1.5)	13.3 (1.3)	12.7 (1.5)	12.7 (1.5)	64.0	65.7
Platelets (10^9/L)	265.8 [94.0]	270.0 [82.0]	259.0 [93.0]	263.0 [87.5]	256.0 [95.8]	264.0 [96.5]	69.7	69.0

Table S3. Continued

	55 – 64 years		65 – 74 years		> 75 years		% missing HF subjects	% missing non HF subjects
	HF subjects	Non HF subjects	HF subjects	Non HF subjects	HF subjects	Non HF subjects		
Albumin (g/L)	40.4 (3.9)	42.0 (3.5)	40.2 (3.8)	40.9 (3.7)	39. (4.2)	39.0 (4.4)	75.8	73.1
Creatinine (micromol/L)	81.0 [23.0]	77.0 [16.5]	87.0 [25.5]	81.5 [20.0]	94.0 [32.5]	87.0 [27.0]	60.0	65.2
eGFR (mL/min/1.73 m^2)	64.2 (17.8)	68.9 (14.3)	56.5 (15.6)	61.1 (14.5)	50.5 (15.1)	55.0 (15.3)	61.7	74.1
Sodium (mmol/L)	139.3 (7.4)	139.9 (6.9)	138.9 (9.1)	139.4 (9.5)	138.2 (9.4)	138.3 (10.1)	63.9	66.7
Potassium (mmol/L)	4.3 (0.6)	4.3 (2.4)	4.5 (8.2)	4.4 (2.5)	4.3 (1.2)	4.3 (2.7)	63.9	66.7
Total WBC count (10^9 / L)	7.8 (2.5)	6.7 (2.1)	7.6 (2.4)	7.0 (2.3)	7.6 (2.7)	7.3 (2.5)	69.6	69.0
Comorbidity (%) §								
Atrial fibrillation	5.4	0.4	7.7	1.4	10.9	3.7	n/a	n/a
COPD	29.4	13.1	27.4	14.1	24.6	15.2	n/a	n/a
Diabetes mellitus	6.5	1.1	4.9	1.7	3.4	1.9	n/a	n/a
Myocardial infarction	2.6	0.2	2.6	0.5	2.3	0.9	n/a	n/a
Hypertension	72.6	46.6	81.5	63.3	86.8	70.4	11.5	21.9
Obesity	26.4	14.5	17.2	10.4	7.4	4.8	61.0	54.6
Medication use (%) ¤								
BP lowering medication	47.2	18.9	58.6	31.8	69.1	44.2	n/a	n/a
Lipid regulating drugs	22.9	9.4	21.6	14.3	8.8	8.7	n/a	n/a

*assessed by index of multiple deprivation † measurement closest to and within 3 years before baseline. § denotes prior medical history of given comorbidity 3 years before baseline. SD = Standard Deviation; LDL = Low Density Lipoprotein; HDL = High Density Lipoprotein; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; total WBC count = total White Blood Cell count; eGFR = estimated Glomerular Filtration Rate; COPD = Chronic Obstructive Pulmonary Disease.

Table S4. Complete case analysis for risk factors associated with incident heart failure stratified by age in men

	55 – 64 years	65 – 74 years	> 75 years	Total
n (events)	25,932 (478)	5,569 (498)	2,765 (346)	34,266 (1,322)
Risk Factors	**HR (95% CI)***	**HR (95% CI)***	**HR (95% CI)***	**HR (95% CI)***
Age (years)	1.05 (1.06; 1.15)	1.09 (1.03; 1.16)	1.08 (1.03; 1.12)	1.08 (1.05; 1.11)
Most deprived fifth †	1.09 (1.21; 2.12)	1.65 (1.13; 2.42)	1.40 (0.91; 2.15)	1.34 (1.07; 1.67)
Ex-smokers	1.27 (0.77: 1.67)	0.77 (0.53; 1.13)	0.95 (0.64; 1.41)	0.98 (0.78; 1.23)
Current-smokers	1.67 (0.71; 1.67)	1.17 (0.69; 2.01)	1.50 (0.75; 2.98)	1.45 (1.09; 1.94)
Sedentary lifestyle	1.11 (1.13; 2.53)	1.31 (0.92; 1.87)	1.78 (1.15; 2.74)	1.34 (1.09; 1.64)
Body Mass Index (kg/m^2)	1.06 (1.01; 1.05)	1.01 (0.97; 1.05)	1.04 (0.99; 1.09)	1.05 (1.02; 1.07)
SBP (per 20 mm/hg)	0.85 (0.85; 1.26)	1.06 (0.85; 1.32)	0.82 (0.64; 1.06)	0.90 (0.79; 1.04)
DBP (per 10 mm/hg)	0.86 (0.76; 1.02)	0.82 (0.66; 1.01)	0.97 (0.75; 1.24)	0.87 (0.76; 0.99)
Haemoglobin (g/dL)	0.86 (0.91; 1.01)	0.92 (0.82; 1.04)	0.91 (0.79; 1.04)	0.90 (0.84; 0.97)
Platelets (per 10 10^9/L)	0.98 (0.96; 1.00)	0.98 (0.95; 1.01)	0.97 (0.94; 1.00)	0.98 (0.96; 0.99)
Total WBC count (10^9/L)	1.14 (1.06; 1.16)	1.01 (0.92; 1.10)	1.03 (0.94; 1.14)	1.07 (1.03; 1.12)
Total cholesterol (mmol/L)	0.99 (0.87; 1.12)	0.94 (0.78; 1.13)	0.96 (0.78; 1.19)	0.97 (0.87; 1.08)
Triglycerides (mmol /L)	0.87 (0.90; 1.13)	1.17 (0.97; 1.42)	0.91 (0.69; 1.19)	0.95 (0.86; 1.05)
Albumin (g/L)	0.95 (0.92; 0.99)	0.92 (0.88; 0.97)	0.99 (0.94; 1.05)	0.95 (0.93; 0.98)
Creatinine (per 30 µmol/L)	1.13 (1.03; 1.17)	1.04 (0.99; 1.09)	1.23 (1.06; 1.43)	1.05 (1.02; 1.08)
Diabetes	0.72 (0.37; 1.38)	1.27 (0.70; 2.32)	1.31 (0.67; 2.56)	1.01 (0.70; 1.44)
Atrial fibrillation	2.47 (1.32; 4.60)	2.59 (1.54; 4.36)	1.93 (1.13; 3.29)	2.34 (1.90; 4.24)
COPD	1.87 (1.32; 2.65)	1.23 (0.80;1.90)	1.20 (0.76; 1.88)	1.43 (1.14; 1.79)

* Further adjusted for ethnicity, blood pressure lowering medication and lipid regulating drugs. † Assessed by index of multiple deprivation, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

Table S5. Complete case analysis for risk factors associated with incident heart failure stratified by age in women

	55 – 64 years	65 – 74 years	> 75 years	Total
n (events)	26,036 (227)	5,846 (325)	4078 (423)	35,960 (984)
Risk Factors	**HR (95% CI)***	**HR (95% CI)***	**HR (95% CI)***	**HR (95% CI)***
Age (years)	1.09 (1.02; 1.16)	1.08 (1.00; 1.18)	1.08 (1.04; 1.13)	1.09 (1.06; 1.12)
Most deprived fifth †	1.17 (0.70; 1.95)	1.60 (0.96; 2.64)	1.26 (0.84; 1.90)	1.34 (1.04; 1.76)
Ex-smokers	0.79 (0.44: 1.43)	1.76 (1.00; 3.09)	1.38 (0.95; 2.02)	1.25 (0.95; 1.64)
Current-smokers	0.99 (0.54; 1.82)	2.28 (1.13; 4.60)	1.48 (0.71; 3.11)	1.50 (1.03; 2.19)
Sedentary lifestyle	1.63 (1.00; 2.68)	1.35 (0.79; 2.30)	1.39 (0.90; 2.15)	1.42 (1.08; 1.87)
Body Mass Index (kg/m^2)	1.02 (0.98; 1.05)	1.04 (0.99; 1.09)	1.00 (0.97; 1.04)	1.02 (1.00; 1.04)
SBP (per 20 mm/hg)	0.88 (0.63; 1.24)	0.82 (0.61; 1.12)	1.00 (0.81; 1.24)	0.93 (0.80; 1.09)
DBP (per 10 mm/hg)	0.96 (0.71; 1.29)	0.85 (0.63; 1.14)	0.98 (0.79; 1.20)	0.92 (0.80; 1.06)
Haemoglobin (g/dL)	0.94 (0.77; 1.14)	0.98 (0.79; 1.22)	0.94 (0.82; 1.09)	0.93 (0.84; 1.03)
Platelets (per 10 10^9/L)	1.00 (0.96; 1.03)	0.96 (0.93; 1.00)	0.98 (0.96; 1.01)	0.98 (0.96; 1.00)
Total WBC count (10^9 / L)	1.08 (1.00; 1.16)	0.97 (0.85; 1.12)	1.05 (0.99; 1.11)	1.04 (1.00; 1.09)
Total cholesterol (mmol/L)	1.10 (0.88; 1.38)	0.91 (0.72; 1.15)	0.96 (0.81; 1.14)	0.99 (0.89; 1.11)
Triglycerides (mmol /L)	1.02 (0.84; 1.25)	1.16 (0.90; 1.50)	0.90 (0.68; 1.19)	1.01 (0.88; 1.15)
Albumin (g/L)	0.90 (0.84; 0.97)	0.96 (0.90; 1.02)	0.97 (0.92; 1.03)	0.95 (0.94; 0.99)
Creatinine (per 30 µmol/L)	1.06 (0.93; 1.21)	0.99 (0.72; 1.36)	1.07 (0.92; 1.24)	1.04 (0.94; 1.16)
Diabetes	2.76 (1.46; 5.24)	2.59 (1.17; 5.75)	1.43 (0.66; 3.11)	2.28 (1.52; 3.41)
Atrial fibrillation	6.09 (2.52; 14.73)	5.94 (2.85; 12.33)	1.34 (0.71; 2.54)	2.50 (1.66; 3.78)
COPD	2.31 (1.43; 3.75)	4.15 (2.55; 6.75)	1.85 (1.21; 2.81)	2.39 (1.84; 3.09)

* Further adjusted for ethnicity, blood pressure lowering medication and lipid regulating drugs. † Assessed by index of multiple deprivation, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

Table S6. Heterogeneity at practice level for the association of risk factors with HF stratified by age in men

	55 – 64 years	65 – 74 years	> 75 years
n (events)	257,698 (5,408)	88,416 (8,047)	58,531 (9,859)
Risk Factors	**HR (95% CI)***	**HR (95% CI)***	**HR (95% CI)***
Age (years)	1.10 (1.09; 1.11)	1.08 (1.08; 1.09)	1.07 (1.06; 1.07)
Most deprived fifth †	1.41 (1.31; 1.51)	1.27 (1.19; 1.35)	1.08 (1.02; 1.15)
Ex-smokers	1.08 (0.96; 1.21)	1.03 (0.97; 1.10)	1.00 (0.94; 1.06)
Current-smokers	1.27 (1.15; 1.41)	1.15 (1.07; 1.23)	1.06 (0.96; 1.16)
Sedentary lifestyle	1.06 (0.99; 1.14)	1.10 (1.04; 1.17)	1.08 (1.01; 1.15)
Body Mass Index (kg/m^2)	1.02 (1.01; 1.03)	1.02 (1.02; 1.03)	1.01 (1.01; 1.02)
SBP (per 20 mm/hg)	1.03 (0.98; 1.08)	0.99 (0.96; 1.02)	0.96 (0.93; 0.99)
DBP (per 10 mm/hg)	0.91 (0.87; 0.95)	0.90 (0.87; 0.92)	0.97 (0.94; 0.99)
Haemoglobin (g/dL)	0.96 (0.92; 1.01)	0.96 (0.95; 0.98)	0.97 (0.95; 0.99)
Platelets (per 10 10^9/L)	1.00 (0.99; 1.00)	1.00 (0.99; 1.00)	1.00 (0.99; 1.00)
Total WBC count (10^9 / L)	1.03 (1.02; 1.05)	1.02 (1.00; 1.03)	1.01 (1.00; 1.02)
Total cholesterol (mmol/L)	0.99 (0.95; 1.03)	0.98 (0.95; 1.01)	1.02 (0.99; 1.05)
Triglycerides (mmol /L)	1.00 (0.96; 1.03)	0.99 (0.96; 1.02)	0.99 (0.96; 1.02)
Albumin (g/L)	0.99 (0.97; 1.00)	0.99 (0.98; 1.00)	1.00 (0.99; 1.01)
Creatinine (per 30 µmol/L)	1.03 (1.01; 1.05)	1.03; 1.01; 1.05)	1.04 (1.02; 1.06)
Diabetes	1.80 (1.59; 2.04)	1.69 (1.53; 1.87)	1.44 (1.30; 1.60)
Atrial fibrillation	4.09 (3.66; 4.58)	2.52 (2.33; 2.73)	2.16 (2.02; 2.30)
COPD	1.94 (1.81; 2.07)	1.82; 1.73; 1.92)	1.69 (1.62; 1.77)

*Estimates of random effects accounting for practice level heterogeneity, further adjusted for ethnicity, blood pressure lowering medication and lipid regulating drugs. † Assessed by index of multiple deprivation, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

Table S7. Heterogeneity at practice level for the association of risk factors with HF stratified by age in women

	55 – 64 years	65 – 74 years	> 75 years
n (events)	257,364 (2,878)	101,192 (6,624)	108,486 (15,171)
Risk Factors	**HR (95% CI)***	**HR (95% CI)***	**HR (95% CI)***
Age (years)	1.14 (1.12; 1.15)	1.11 (1.10; 1.12)	1.06 (1.06; 1.07)
Most deprived fifth †	1.46 (1.33; 1.60)	1.27 (1.19; 1.36)	1.12 (1.07; 1.18)
Ex-smokers	1.14 (0.97; 1.34)	1.05 (0.97; 1.14)	1.03 (0.98; 1.09)
Current-smokers	1.34 (1.19; 1.51)	1.21 (1.10; 1.32)	1.09 (0.99; 1.20)
Sedentary lifestyle	1.09 (1.00; 1.19)	1.08 (1.01; 1.16)	1.08 (1.01; 1.14)
Body Mass Index (kg/m^2)	1.03 (1.03; 1.04)	1.02 (1.02; 1.03)	1.01 (1.01; 1.01)
SBP (per 20 mm/hg)	1.11 (1.04; 1.17)	1.03 (1.00; 1.07)	0.97 (0.95; 0.99)
DBP (per 10 mm/hg)	0.87 (0.82; 0.92)	0.91 (0.88; 0.94)	0.98 (0.96; 1.01)
Haemoglobin (g/dL)	0.95 (0.90; 1.01)	0.96 (0.93; 0.98)	0.97 (0.95; 0.98)
Platelets (per 10 10^9/L)	1.00 (0.99; 1.00)	1.00 (0.99; 1.00)	1.00 (0.99; 1.00)
Total WBC count (10^9/L)	1.04 (1.02; 1.06)	1.02 (1.01; 1.04)	1.01 (1.01; 1.02)
Total cholesterol (mmol/L)	0.97 (0.92; 1.02)	0.98 (0.94; 1.01)	1.01 (0.98; 1.03)
Triglycerides (mmol /L)	1.00 (0.95; 1.05)	1.01 (0.96; 1.05)	1.00 (0.97; 1.02)
Albumin (g/L)	0.98 (0.97; 1.00)	0.99 (0.98; 1.00)	1.00 (0.99; 1.00)
Creatinine (per 30 µmol/L)	1.06 (1.03; 1.10)	1.06 (1.02; 1.11)	1.06 (1.04; 1.08)
Diabetes	2.71 (2.31; 3.18)	1.89 (1.68; 2.13)	1.66 (1.52; 1.82)
Atrial fibrillation	6.90 (5.82; 8.19)	3.51 (3.20; 3.85)	2.70 (2.56; 2.84)
COPD	2.11 (1.94; 2.29)	1.94 (1.83; 2.05)	1.65 (1.59; 1.72)

* Estimates of random effects accounting for practice level heterogeneity, further adjusted for ethnicity, blood pressure lowering medication and lipid regulating drugs. † Assessed by index of multiple deprivation, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

Table S8. Associations of risk factors with incident HF stratified by age and end points from different sources of EHR in men

	55 – 64 years		65 – 74 years		> 75 years	
	CPRD	**HES**	**CPRD**	**HES**	**CPRD**	**HES**
n (events)	254,731 (2,441)	255,257 (2,967)	84,150 (3,781)	84,635 (4,266)	53,146 (4,474)	54,057 (5,385)
Risk Factors	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age (years)	1.12 (1.11; 1.13)	1.09 (1.08; 1.11)	1.09 (1.08; 1.11)	1.08 (1.07; 1.09)	1.05 (1.04; 1.06)	1.08 (1.07; 1.09)
Most deprived fifth †	1.41 (1.28; 1.56)	1.58 (1.45; 1.72)	1.24 (1.14; 1.34)	1.44 (1.33; 1.54)	1.00 (0.93; 1.08)	1.15 (1.08; 1.23)
Ex-smokers	1.08 (0.92; 1.27)	1.07 (0.93; 1.24)	1.02 (0.92; 1.13)	1.04 (0.96; 1.14)	0.99 (0.90; 1.08)	1.00 (0.93; 1.08)
Current-smokers	1.23 (1.07; 1.42)	1.31 (1.14; 1.51)	1.10 (0.97; 1.25)	1.21 (1.09; 1.34)	1.05 (0.91; 1.21)	1.06 (0.94; 1.20)
Sedentary lifestyle	1.09 (0.98; 1.22)	1.03 (0.93; 1.14)	1.10 (1.00; 1.22)	1.12 (1.03; 1.22)	1.07 (0.97; 1.19)	1.10 (1.02; 1.19)
Body Mass Index (kg/m^2)	1.03 (1.02; 1.04)	1.02 (1.01; 1.03)	1.03 (1.02; 1.04)	1.02 (1.01; 1.03)	1.01 (1.01; 1.02)	1.01 (1.01; 1.02)
SBP (per 20 mm/hg)	1.01 (0.94; 1.08)	1.06 (0.99; 1.12)	0.95 (0.91; 1.00)	1.04 (1.00; 1.09)	0.99 (0.95; 1.03)	0.94 (0.91; 0.98)
DBP (per 10 mm/hg)	0.91 (0.85; 0.97)	0.90 (0.85; 0.96)	0.90 (0.86; 0.94)	0.89 (0.85; 0.93)	0.97 (0.93; 1.02)	0.96 (0.92; 0.99)
Haemoglobin (g/dL)	0.97 (0.93; 1.02)	0.95 (0.89; 1.02)	0.96 (0.94; 0.99)	0.96 (0.93; 0.99)	0.97 (0.94; 1.00)	0.96 (0.94; 0.98)
Platelets (per 10 10^9/L)	1.00 (0.99; 1.01)	1.00 (0.99; 1.00)	1.00 (0.99; 1.00)	1.00 (0.99; 1.00)	0.99 (0.99; 1.00)	1.00 (0.99; 1.00)
Total WBC count (10^9 / L)	1.03 (1.01; 1.06)	1.03 (1.01; 1.05)	1.02 (1.00; 1.04)	1.02 (1.00; 1.03)	1.02 (1.00; 1.03)	1.01 (0.99; 1.02)
Total cholesterol (mmol/L)	0.98 (0.92; 1.04)	1.00 (0.95; 1.06)	0.99 (0.94; 1.03)	0.98 (0.94; 1.02)	1.03 (1.00; 1.07)	1.01 (0.98; 1.05)
Triglycerides (mmol /L)	1.01 (0.96; 1.05)	1.00 (0.95; 1.04)	0.98 (0.93; 1.04)	1.00 (0.97; 1.04)	0.99 (0.95; 1.04)	0.99 (0.95; 1.03)
Albumin (g/L)	0.99 (0.98; 1.00)	0.99 (0.97; 1.01)	0.99 (0.97; 1.00)	0.99 (0.98; 1.00)	0.99 (0.98; 1.01)	1.00 (0.99; 1.01)
Creatinine (per 30 µmol/L)	1.03 (0.99; 1.06)	1.04 (1.01; 1.06)	1.02; 1.00; 1.05)	1.03; 1.02; 1.05)	1.04 (1.01; 1.07)	1.05 (1.02; 1.08)
Diabetes	1.75 (1.45; 2.10)	1.88 (1.60; 2.22)	1.49 (1.27; 1.73)	1.97 (1.72; 2.24)	1.27 (1.07; 1.50)	1.63 (1.42; 1.87)
Atrial fibrillation	4.61 (3.93; 5.39)	3.83 (3.28; 4.48)	2.82 (2.52; 3.15)	2.45 (2.19; 2.75)	2.22 (2.02; 2.44)	2.25 (2.07; 2.46)
COPD	2.00 (1.82; 2.20)	1.90 (1.74; 2.08)	2.02 (1.88; 2.17)	1.68 (1.56; 1.80)	1.91 (1.79; 2.03)	1.59 (1.50; 1.69)

* Further adjusted for ethnicity, blood pressure lowering medication and lipid regulating drugs. † Assessed by index of multiple deprivation, EHR = Electronic Health Records, CPRD = Clinical Practice Research Datalink, HES = Hospital Episode Statistics, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

Table S9. Associations of risk factors with incident HF stratified by age and end points from different sources of EHR in women

	55 – 64 years		65 – 74 years		> 75 years	
	CPRD	**HES**	**CPRD**	**HES**	**CPRD**	**HES**
n (events)	255,703 (1,216)	256,148 (1,662)	97,522 (2,954)	98,238 (3,670)	100,096 (6,781)	101,705 (8,390)
Risk Factors	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Age (years)	1.16 (1.14; 1.18)	1.12 (1.10; 1.13)	1.11 (1.10; 1.13)	1.11 (1.11; 1.13)	1.05 (1.05; 1.06)	1.07 (1.07; 1.08)
Most deprived fifth †	1.53 (1.34; 1.75)	1.61 (1.44; 1.80)	1.25 (1.15; 1.37)	1.36 (1.26; 1.47)	1.07 (1.01; 1.14)	1.24 (1.17; 1.30)
Ex-smokers	1.13 (0.88; 1.43)	1.16 (0.98; 1.36)	1.02 (0.90; 1.16)	1.08 (0.98; 1.18)	1.02 (0.94; 1.11)	1.03 (0.97; 1.09)
Current-smokers	1.30 (1.04; 1.64)	1.39 (1.20; 1.61)	1.17 (1.02; 1.36)	1.26 (1.11; 1.42)	1.02 (0.89; 1.18)	1.15 (1.02; 1.30)
Sedentary lifestyle	1.14 (0.97; 1.32)	1.07 (0.95; 1.20)	1.06 (0.94; 1.18)	1.12 (1.03; 1.21)	1.08 (1.00; 1.17)	1.09 (1.01; 1.18)
Body Mass Index (kg/m^2)	1.03 (1.02; 1.05)	1.04 (1.03; 1.05)	1.02 (1.01; 1.03)	1.02 (1.01; 1.03)	1.01 (1.00; 1.02)	1.01 (1.01; 1.02)
SBP (per 20 mm/hg)	1.09 (1.00; 1.19)	1.13 (1.05; 1.22)	1.04 (0.99; 1.10)	1.04 (0.99; 1.09)	0.98 (0.95; 1.01)	0.97 (0.94; 1.00)
DBP (per 10 mm/hg)	0.88 (0.80; 0.97)	0.86 (0.80; 0.93)	0.92 (0.88; 0.97)	0.89 (0.85; 0.93)	1.01 (0.97; 1.04)	0.96 (0.93; 0.99)
Haemoglobin (g/dL)	0.97 (0.89; 1.05)	0.93 (0.88; 0.99)	0.97 (0.93; 1.01)	0.94 (0.91; 0.97)	0.97 (0.95; 0.99)	0.96 (0.93; 0.98)
Platelets (per 10 10^9/L)	1.00 (0.99; 1.01)	1.00 (0.99; 1.01)	1.00 (0.99; 1.00)	1.00 (0.99; 1.01)	1.00 (0.99; 1.00)	1.00 (0.99; 1.00)
Total WBC count (10^9 / L)	1.04 (1.01; 1.08)	1.04 (1.01; 1.07)	1.03 (1.01; 1.05)	1.02 (1.00; 1.04)	1.01 (1.00; 1.03)	1.02 (1.00; 1.03)
Total cholesterol (mmol/L)	0.94 (0.88; 1.01)	0.99 (0.92; 1.06)	0.97 (0.92; 1.03)	0.98 (0.93; 1.03)	1.02 (0.99; 1.06)	1.00 (0.97; 1.03)
Triglycerides (mmol /L)	1.00 (0.92; 1.09)	1.00 (0.94; 1.06)	1.01 (0.95; 1.07)	1.01 (0.96; 1.06)	0.99 (0.96; 1.03)	1.00 (0.97; 1.04)
Albumin (g/L)	0.98 (0.97; 1.00)	0.98 (0.96; 1.00)	0.99 (0.98; 1.01)	1.00 (0.98; 1.01)	0.99 (0.99; 1.00)	1.00 (0.99; 1.01)
Creatinine (per 30 µmol/L)	1.07 (1.02; 1.12)	1.06 (1.02; 1.11)	1.05 (1.00; 1.09)	1.08 (1.03; 1.14)	1.06 (1.03; 1.09)	1.08 (1.05; 1.10)
Diabetes	2.49 (1.94; 3.18)	2.90 (2.36; 3.57)	1.60 (1.33; 1.93)	2.21 (1.90; 2.57)	1.54 (1.34; 1.77)	1.90 (1.69; 2.13)
Atrial fibrillation	7.38 (5.76; 9.46)	7.03 (5.60; 8.82)	3.83 (3.35; 4.39)	3.55 (3.13; 4.03)	2.76 (2.55; 2.98)	2.95 (2.75; 3.16)
COPD	2.21 (1.95; 2.51)	2.01 (1.80; 2.24)	2.08 (1.92; 2.26)	1.80 (1.67; 1.94)	1.98 (1.87; 2.09)	1.47 (1.40; 1.55)

* Further adjusted for ethnicity, blood pressure lowering medication and lipid regulating drugs. † Assessed by index of multiple deprivation, EHR = Electronic Health Records, CPRD = Clinical Practice Research Datalink, HES = Hospital Episode Statistics, HR (95% CI) = Hazard Ratio (95% Confidence Interval), SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, total WBC count = total White Blood Cell count. Hazard ratios were considered statistically significant if p-value < 0.001 (Bonferroni corrected threshold).

CHAPTER 3

RISK OF HEART FAILURE: THE OPPORTUNITY FOR PREVENTION WITH AMERICAN HEART ASSOCIATION'S LIFE'S SIMPLE 7

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Abstract

Background. The American Heart Association recommends the concept of Life's Simple 7 (LS7); healthy behaviours that have shown to reduce cardiovascular disease.

Objectives. We examined whether combinations of specific LS7 components are associated with a reduced risk of heart failure (HF).

Methods. We included 37,803 participants from the European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) cohort with a mean age of 49.4 (SD 11.9) years and 74.7% women. The LS7 score ranged from 0–14 and was calculated based on 0, 1, or 2 points for smoking, physical activity, body mass index (BMI), diet, blood pressure, total cholesterol, and blood glucose. 23.2% of participants had an overall ideal score (11-14 points), 35.3% an intermediate (9-10 point) and 41.5% an inadequate score (0-8 points).

Results. Over a median follow-up of 15.2 years [IQR 14.1;16.5] 690 participants (1.8%) developed HF. In Cox proportional hazard models, ideal and intermediate LS7 scores were associated with a reduced risk of HF compared to the inadequate category (hazard ratio (HR) 0.45, 95% confidence interval (95%CI) 0.34;0.60 and HR 0.53, 95%CI 0.44;0.64, respectively). Our analyses show that combinations with specific LS7 components, notably glucose, BMI, smoking or blood pressure, are associated with a lower incidence of HF.

Conclusions. A healthy lifestyle, as reflected in an ideal LS7 score, was associated with a 55% lower risk of HF compared to an inadequate LS7 score. Preventive strategies that target combinations of specific LS7 components could have a significant impact on decreasing incident HF in the population at large.

Introduction

Heart failure (HF) is one of the leading causes of morbidity and mortality and one of the main presentations of cardiovascular disease (CVD).[1] Similar to other types of CVD, the incidence of HF could be reduced by modifying lifestyle factors such as smoking, physical activity and diet. Previous research indeed suggests that adherence to a healthy lifestyle reduces the risk of HF.[2–5]

The American Heart Association recommends the concept of Life's Simple 7 (LS7); health behaviours that could reduce the burden of CVD.[6] LS7 consists of known CVD risk factors: smoking, physical activity, body mass index, diet, blood pressure, total cholesterol, and glucose. To date, several studies have established the relationship between LS7 and HF which showed that a reduced risk of HF was achieved with a more favourable LS7 score. [7–10] Thus, behavioural changes could improve cardiovascular health, but resources to achieve an "ideal" lifestyle are often lacking and it is known that it can be challenging to change one's lifestyle.[11] Therefore, questions as whether even modest improvements, such as reducing one or two specific LS7 components, could decrease the risk of HF are of interest. The European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) cohort has gathered data on individual components that could be responsible for reduced CVD risk.[12]

Hence, we sought to address the detailed relationship between health behaviours and the risk of HF. We studied American Heart Association LS7 and the risk of HF in a general Dutch population and aimed to provide insight in combinations of specific LS7 components that could reduce the risk of HF.

Methods

Study population

The EPIC-NL cohort consists of the MORGEN (Monitoring Project on Risk Factors for Chronic Diseases) and the Prospect cohorts. Details of the design and rationale of EPIC-NL have been described elsewhere.[12] Both cohorts were set up between 1993 and 1997. The MORGEN cohort included 10,260 men and 12,394 women aged 20–64 years and the Prospect cohort included 17,357 women aged 49–70 years. All participants gave written informed consent.
In total, we included n = 37,803 participants. Participants were ineligible if they had a HF diagnosis at baseline (n = 47). Participants were excluded if they did

not give permission for linkage with disease or mortality registries (n = 1,630), had an implausible basal metabolic rate, defined as the top and bottom 0.5% of the ratio of reported energy intake over estimated energy requirement (n = 367) or had a missing outcome (n = 81). Participants were followed over time until HF diagnosis, censor date, death or end of follow-up (01-01-2011).

Baseline measurements

At cohort inclusion a general questionnaire and a food frequency questionnaire (FFQ) were filled out and a non-fasting blood sample was taken. The general questionnaire included demographic characteristics (sex, education), risk factors (smoking, physical activity, diet) and presence of chronic diseases (hypertension, hyperlipidaemia, diabetes). Education level was categorised into high (higher vocational education and university) and other. Physical activity was assessed by combining activities of occupational and recreational nature during the past year in the Cambridge Physical Activity Index (CPAI).[13] During physical examination, height and weight were measured and Body Mass Index (BMI) was calculated as weight (kg)/height squared (m^2). At baseline, mean systolic (SBP) and diastolic blood pressure (DBP) were measured in 2 repeated measurements after at least 5 minutes of resting. Hypertension and hyperlipidaemia were either self-reported, based on measurements from physical examination or registered use of medication.[14] The validated EPIC FFQ was used to assess food intake based on the usual consumption frequency of 79 main food categories during the year preceding enrolment.[15] Food groups incorporated in the LS7 diet component were fruit and vegetables (>400 grams/day), fish (>200 grams/week), whole grains (>50 grams/day), sodium (<1500 mg/day) and sugar sweetened beverages (<450 kcal/week).[6, 16] The diet score was adjusted for total energy intake (kcal/day) using the regression residual method.[17]

Biochemical measurements

Serum total cholesterol, high density lipoprotein (HDL) cholesterol and glucose were measured in samples collected at baseline. In the MORGEN cohort, the biochemical measurements were performed in all participants at baseline. In the Prospect cohort 90% of participants had either serum cholesterol, citrate plasma values of cholesterol or both measured in a later stage. These measurements were standardised into one serum cholesterol value. Single imputation with non-Bayesian linear regression was used to impute missing serum values for both total cholesterol and HDL cholesterol.

In the Prospect cohort, glucose was determined in a subpopulation of 1700 participants. For all participants with glucose measurements, we determined whether blood glucose was measured fasting (>=480 min since last meal or since last drink) or non-fasting (<480 min since last meal or since last drink). This was taken into account in calculating points for the glucose component in the LS7 score (**Table S1**). For those participants who did not have a glucose measurement at baseline we used information on self-reported diabetes, diabetes diagnosis abstracted from the Hospital Discharge Register or registered diabetes medication.

LS7 components

An overall healthy lifestyle score was calculated based on 7 known CVD risk factors (smoking, physical activity, body mass index, diet, blood pressure, total cholesterol, and blood glucose). All risk factors were scored as ideal: 2 points, intermediate: 1 point or inadequate: 0 points. **Table S1** shows the definitions of the LS7 components, the associated score and the distribution among the EPIC-NL participants. The healthy lifestyle score was summed and ranged from 0 to 14. The overall LS7 score was categorised approximating tertiles; a score from 0–8 = inadequate, 9–10 = intermediate, 11–14 = ideal.

Outcome measure

Hospitalisation for and death from HF were used to define HF incidence. Primary and secondary hospital discharge diagnoses were obtained from the Hospital Discharge Register. The database was linked to the EPIC-NL cohort on the basis of birth date, sex, postal code, and general practitioner by a validated probabilistic method.[18] Information on vital status was obtained through the municipal registry and causes of death were obtained from the Cause of Death Register at Statistics Netherlands. Causes of death were coded according to ICD-9 codes until 1996, and after that, according to ICD-10 codes. (**Table S2**). A primary diagnosis was defined as the underlying disease for hospitalisation or the underlying cause of death. A secondary diagnosis was defined as a comorbidity of the primary hospital admission, a complication of the primary cause of death, or another disease which might have contributed to death.

Statistical analysis

All statistical analyses were performed in R software version 3.4.1. A Kaplan-Meier curve was created to visualise time to HF event, stratified by healthy lifestyle score. Missing data in the baseline risk factors, except glucose,

comorbidities and medication data, were imputed using multiple imputation from the *mice* algorithm in the statistical software package R. **Table S3** shows the percentage missing per baseline variable. Analyses were performed on 10 imputed datasets separately and results were pooled using Rubin's rules. Patient characteristics were summarised as mean (SD) or median [IQR] for continuous variables and percentages for categorical variables.

A Cox proportional hazard model was used to estimate the hazard ratios (HR) with 95% confidence interval (95% CI) for the association of the healthy lifestyle score with the outcome. The reference was the lowest category of the LS7 score (inadequate). We also estimated the HR and 95% CI for each individual component of the healthy lifestyle score in a multivariable Cox proportional hazard model. The proportional hazards assumption was verified by assessment of the Schoenfeld residuals. All analyses were adjusted for the potential confounders sex, age and educational level. Analyses for the separate LS7 components were additionally adjusted for the other components in the score. Due to the nature of the EPIC-NL cohort, the merging of two existing cohorts, we added cohort as a random effects variable in the model to adjust for cohort variability. Finally, we separately compared clusters of one, two or three specific LS7 ideal components to a combined cluster of five, six and seven inadequate LS7 components in a Cox proportional hazard model to investigate whether combinations of specific LS7 components reduce the risk of HF. We selected clusters with a sample size of > 300 individuals for our analyses.

In sensitivity analyses we compared the healthy lifestyle score in a subset of participants in whom glucose had been measured at baseline (n = 20,694). Furthermore, we excluded sodium from the diet score in a sensitivity analysis, since no information was available on added salt via the FFQ which could have biased our LS7 diet component.

Results

Baseline characteristics

Baseline characteristics of the overall cohort as well as stratified by healthy lifestyle score are presented in **Table 1**. Overall, the population consisted of 74.7% females with a mean age of 49.4 years (11.9 SD). The individuals with an ideal healthy lifestyle score were generally younger, more often female and

had higher education levels compared to individuals with an intermediate or inadequate score (all p-value <0.001).

Life's Simple 7 components and incidence of heart failure

Over a median follow-up of 15.2 years [IQR 14.1; 16.5] a total of 690 patients (1.8%) developed HF. A Kaplan-Meier curve for HF-free survival by healthy lifestyle score is shown in **Figure 1**. HF-free survival rate significantly differed between healthy lifestyle score groups (log rank, p-value < 0.001). The association between the healthy lifestyle score and incident HF is shown in **Table 2**. With inadequate healthy lifestyle score as a reference, we found a significantly decreased risk of HF incidence for individuals with an intermediate (HR 0.53, 95% CI 0.44; 0.64) and ideal healthy lifestyle score (HR 0.45, 95% CI 0.34; 0.60) after adjusting for age, sex and education level. Furthermore, we investigated the association of number of ideal LS7 components and incident HF (**Table 2**). Two or more ideal LS7 components showed a significant decreased risk of incident HF (HR 0.48, 95% CI 0.29; 0.80), with 0 ideal LS7 components as a reference and adjusted for age, sex and education level.

Individual components of LS7 and heart failure risk

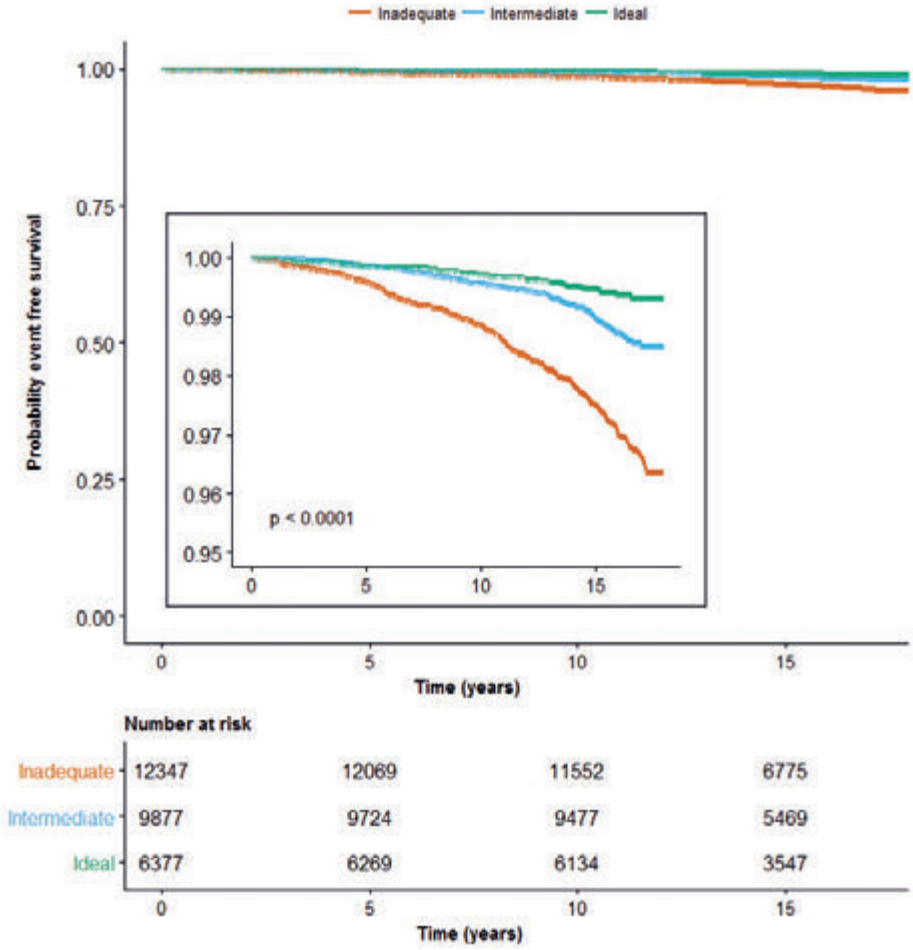
The associations between individual components of the LS7 and incident HF are shown in **Figure 2**. Intermediate and ideal scores of glucose, smoking, BMI and blood pressure were all significantly associated with a decreased HF incidence, compared to inadequate levels. Intermediate scores of diet and both intermediate and ideal scores of physical activity were associated with reduced incidence of HF, compared to inadequate scores in the model adjusted for age, sex and education level, but were not statistically significantly associated with incident HF in the fully adjusted model. No statistically significant association of cholesterol scores with incidence of HF was observed.

Table 1. Baseline characteristics EPIC-NL cohort

	Overall EPIC-NL* cohort	**LS7 score ideal (11 – 14)**	**LS7 score intermediate (9 – 10)**	**LS7 score inadequate (0 – 8)**
		23.2%	35.3%	41.5 %
	(n = 37,803)	(n = 8,770)	(n = 13,345)	(n = 15,688)
Demographics				
Age (years)	49.4 (11.9)	43.8 (12.5)	48.9 (12.1)	52.6 (10.1)
Female sex (%)	74.7	77.2	76.2	71.9
High education (%)	20.2	30.7	21.2	13.5
Lifestyle factors (%)				
Smoking				
Current	30.3	6.1	25.9	49.0
Ex-smoker	31.5	39.5	32.6	23.1
Physical activity				
Active	41.6	64.9	45.1	25.5
Sedentary	7.6	0.9	3.5	14.8
Diet score				
0 – 1	29.1	12.7	25.2	41.7
2 – 3	68.4	82.5	72.3	57.1
4 – 5	2.5	4.8	2.5	1.1
Clinical measurements (mean (SD))				
SBP (mmHg)	126.4 (19)	114 (11.7)	123.8 (16.5)	135.4 (19.7)
DBP (mmHg)	77.9 (10.6)	61.6 (7.9)	76.5 (9.5)	82.5 (10.7)
BMI (kg/m^2, median [IQR])	25.2 [4.9]	23.1 [2.9]	24.7 [4.2]	27.1 [5.1]
WHR	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.9 (0.1)
Total cholesterol (mg/dL)	214.6 (42.0)	185.3 (30.9)	207.7 (38.7)	233.3 (40.2)
HDL cholesterol (mg/dL)	56.6 (16.1)	59.4 (15.2)	57.9 (16.2)	53.3 (15.6)
Glucose (mg/dL, median IQR])	90.1 [18.0]	84.7 [14.4]	88.3 [16.2]	95.5 [21.6]
Comorbidities (%)				
Hypertension	37.5	13.8	30.1	56.6
Diabetes mellitus	1.5	0.1	0.3	3.3
Myocardial infarction	1.3	0.6	1.1	1.9

* EPIC-NL = European Prospective Investigation into Cancer and Nutrition-Netherlands, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, BMI = Body Mass Index, WHR = Waist-Hip Ratio, HDL = High Density Lipoprotein, IQR = Inter Quartile Range.

Figure 1. Kaplan Meier for the probability of HF free survival



Stratified by healthy lifestyle score: ideal (score 11–14), intermediate (score 9–10) and inadequate (score 0–8). Log-rank test for differences in event free survival based on healthy lifestyle score: p < 0.0001. Insert: zoomed in survival curves.

Table 2. Associations between LS7 and incident HF

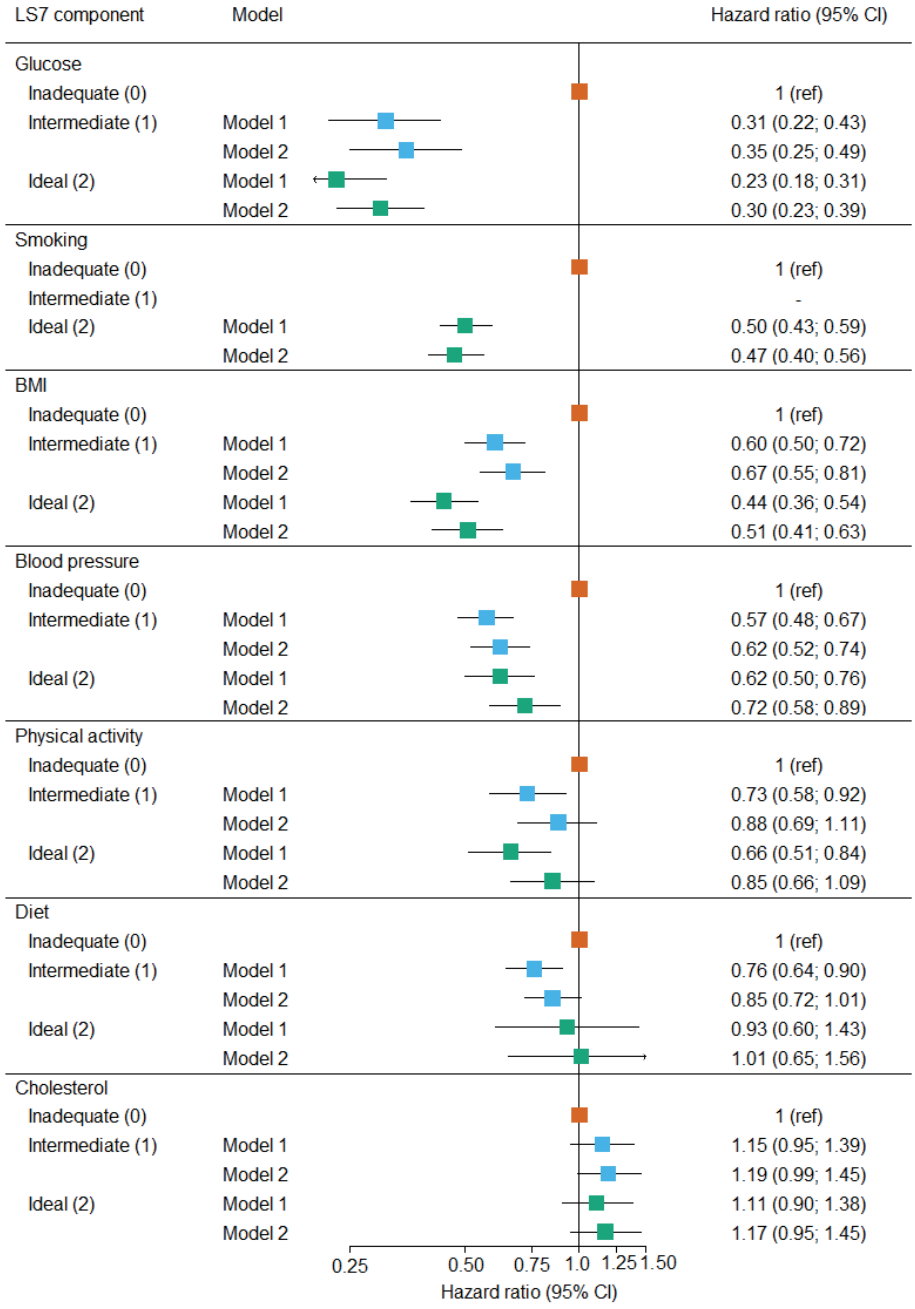
Associations of healthy lifestyle score with incident HF		
	Model 1	**Model 2**
	HR (95% CI)	HR (95% CI)
Inadequate (0 - 8)	1 (ref)	1 (ref)
Intermediate (9 - 10)	0.41 (0.34; 0.50)	0.53 (0.44; 0.64)
Ideal (11 - 14)	0.22 (0.17; 0.30)	0.45 (0.34; 0.60)
Associations of LS7 ideal components with incident HF		
	Model 1	**Model 2**
	HR (95% CI)	HR (95% CI)
0 ideal components	1 (ref)	1 (ref)
1 ideal components	1.03 (0.61; 1.72)	0.93 (0.56; 1.57)
2 ideal components	0.58 (0.35; 0.95)	0.48 (0.29; 0.80)
3 ideal components	0.40 (0.24; 0.66)	0.39 (0.23; 0.64)
4 ideal components	0.26 (0.16; 0.45)	0.35 (0.20; 0.59)
5 ideal components	0.11 (0.06; 0.22)	0.23 (0.12; 0.43)
6 - 7 ideal components	0.07 (0.02; 0.21)	0.20 (0.07; 0.59)

Model 1 = crude model, model 2 = adjusted for age, sex and education level. HR (95% CI) = Hazard ratio (95% Confidence interval). N = 37,803, number of events = 690.

LS7 clusters and heart failure risk

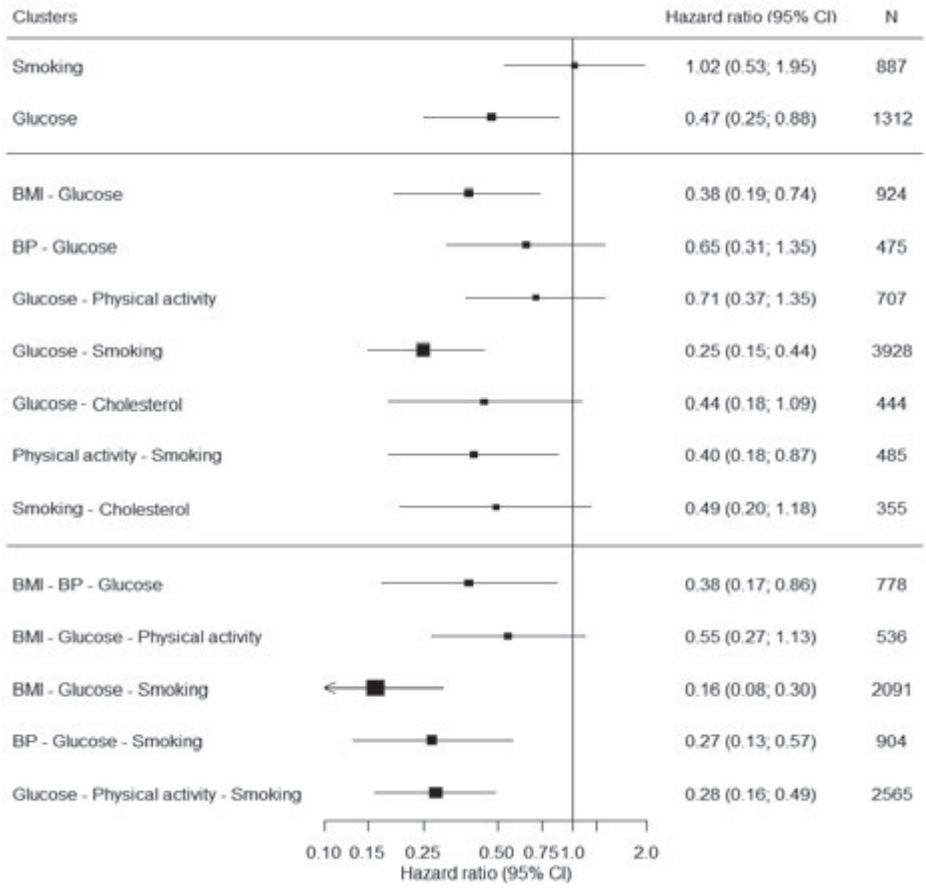
Associations between clusters of LS7 ideal scores with incident HF are shown in **Figure 3**. The group with a score of five, six or seven inadequate LS7 components (N = 238) was used as reference. Individuals with two ideal components from the clusters of BMI – glucose, smoking – glucose and physical activity – smoking had a lower risk of HF incidence compared to the reference group. In individuals with three ideal components, the clusters with BMI – blood pressure – glucose, BMI – glucose – smoking, blood pressure – glucose – smoking and lastly glucose – physical activity – smoking showed a statistically significant lower incidence of HF. No statistical significant associations were observed between other clusters and incident HF.

Figure 2. Associations between individual components of the LS7 and incident HF



Model 1 = adjusted for age, sex and education level, model 2 = adjusted for age, sex, education level and all LS7 components. N = 37,803, number of events = 690. Red boxes = Inadequate level of LS7 component, Blue boxes = intermediate level of LS7 component, Green boxes = Ideal level of LS7 component. BMI = Body Mass Index.

Figure 3. Associations between clusters of ideal LS7 components with incident HF



Analyses are adjusted for age, sex and education level. Individuals with five, six and seven inadequate LS7 components were the reference group (N = 238). Hazard ratio (95% CI) = Hazard ratio (95% confidence interval). N = size of cluster, BMI = Body Mass Index, BP = Blood Pressure. Number of events displayed in **Online Table 6**.

Sensitivity analyses

Table S4 shows that associations of intermediate and ideal healthy lifestyle scores with incident HF were even stronger in the subset of patients with baseline glucose measurements available compared to the main analysis. In addition, removing salt from the LS7 diet component did not affect our results (**Table S5**).

Discussion

In this large cohort study with almost 20 years of follow-up we found that a healthy lifestyle score was associated with a reduced risk of HF. Individuals with intermediate and ideal healthy lifestyle scores had a 47% and 55% lower risk of incident HF compared to an inadequate healthy lifestyle score, respectively. In this cohort 41.5% individuals scored inadequately on the LS7 score, showing there is ample room for improvements in healthy lifestyle behavior that may reduce HF in the general population.

Life's Simple 7 and incident HF

Findings in this study are consistent with previous studies reporting on the association between LS7 and HF (**Table 3**).[7–10] All previous studies were conducted in cohorts from the United States (U.S.), and this study is the first examining LS7 in a European cohort. Nearly all studies categorized a healthy lifestyle in ideal, intermediate and inadequate, but definitions of these categories varied markedly. Even though different definitions were used, all studies found a reduced risk of incident heart failure in those with an ideal healthy lifestyle.[7–10] Of note, only 690 patients (1.8%) developed HF in our study. Compared to other cohorts, the incidence of HF is quite low. [7–10] This could be attributed to only having access to HF diagnoses in secondary care as outcome, while many HF patients are primarily known in primary care. Other reasons could be the relative young age of the participants (mean 49.4 years (11.9 SD) and almost 75% females in the study. It has been shown that the incidence of HF is considerably lower in females and younger individuals.[19] Still, we found strong associations between LS7 and incident HF. Associations could be even stronger in a balanced age and sex cohort.

Table 3. EPIC-NL main findings in context of previous studies

	Studies				
	EPIC-NL	**MESA study** (7)	**Jackson Heart Study** (8)	**Framingham Offspring Study** (9)	**ARIC study** (10)
Definition LS7 categories	Ideal (>= 11 points), intermediate (9 - 10 points), inadequate (<= 8 points)	Ideal (>= 11 points), intermediate (9 - 10 points), inadequate (<= 8 points)	Ideal >= 4 ideal components (>= 8 points), intermediate (5 - 7 points), inadequate = 0 - 2 ideal components (0 - 4 points)	Linear scale 0 - 14 points	Ideal (>= 10 points), intermediate (5 - 10 points), inadequate (<= 4 points)
Cohort size	37,803	6,506	4,195	3,201	13,462, for cardiac remodeling 6,538 participants
Adjustments	1) Adjusted for age, sex and education, 2) Adjusted for age, sex, education and all other LS7 components	Adjusted for age, sex, race/ethnicity, education, income and health insurance.	1) Adjusted for age and sex, 2) adjusted for age, sex and all other LS7 components	Adjusted for age and sex	Adjusted for inverse probability weights: 1) age, sex, race, and education at Visit 1, 2) age, sex, race, study center, education, prevalent HF and CAD, all other LS7 variables measured at Visit 1; systolic and diastolic blood pressure, heart rate, BMI, smoking and drinking status, diabetes, hypertension medication at Visit 4; and incident HF through 2011.

Table 3. Continued

	Studies				
	EPIC-NL	**MESA study** (7)	**Jackson Heart Study** (8)	**Framingham Offspring Study** (9)	**ARIC study** (10)
Outcome	Ideal score was associated with a 55% risk reduction compared to inadequate score. Strongest independent predictors for risk reduction in HF were glucose, smoking and BMI.	Ideal score was associated with 69% risk reduction compared to inadequate score.	Ideal score was associated with a 61% risk reduction compared to inadequate score. Achieving ideal blood pressure, BMI, glucose and smoking was associated with lower risk of adverse cardiac remodeling.	Each 1 point higher LS7 score was associated with a 23% risk reduction for incident HF, consistent across ejection fraction.	Ideal score associated with 14.4% lower lifetime risk of HF among middle-aged participants (45 - 64 years) compared to inadequate score.
Novelty	1) relationship between clusters of risk factors and incident HF: clusters including glucose, BMI, smoking or blood pressure are associated with a risk reduction of HF, 2) First time LS7 evaluated in a European cohort.	Across racial/ethnic groups a similar trend was observed for the association of LS7 and HF risk, Black participants had the highest incidence of HF and the poorest LS7 status followed by Hispanic, white and Chinese American participants.	Blood pressure, physical activity, smoking and glucose were independently associated with a risk reduction in HF. The combined population attributable risk for these components was 37.1%.	Higher LS7 scores were associated with a lower prevalence of adverse cardiac remodeling and echocardiographic measures including left ventricular wall thickness.	Ideal score associated with lower left ventricular hypertrophy and diastolic dysfunction.

Independent associations of Life's simple 7 components and incident HF

We extended the earlier findings with several new observations. Most studies did not investigate independent associations of individual components of LS7.[7, 9, 10] However, our multivariable models showed that lower glucose levels, higher BMI , non-smoking and blood pressure <140/90 mmHg were all independently associated with a lower risk of incident HF. These associations are consistent with existing literature on these CVD risk factors.[19–23] Interestingly, our study also showed that not only an ideal healthy lifestyle was associated with a lower incidence of HF, also an intermediate healthy lifestyle yielded a considerable risk reduction of 47%. This shows that potentially modest improvements, i.e. from an inadequate healthy lifestyle to an intermediate healthy lifestyle would be beneficial in lowering HF incidence.

Our analyses showed that, after adjustments for age, sex and education level, physical activity (both ideal and intermediate) and an intermediate diet score were associated with reduced HF risk, which complements previous literature. Several studies reported that there is a dose-response relationship between physical activity and HF risk.[24–26] Conflicting results have been previously reported for the association between diet and HF.[2, 7, 27, 28] Despite the observed associations of physical activity and diet in our adjusted model, these components were not independently associated from the other LS7 components with a reduced risk of HF. Physical activity and diet are closely related to BMI, blood pressure and glucose and could influence these biological risk factors. Therefore, it could be hypothesised that the association of these factors with incident HF is mediated through the other LS7 components.[29–32] Lastly, it is known that total cholesterol is a strong predictor for coronary artery disease, which is one of the most common causes of HF.[33] Interestingly, previous studies observed no association between LS7 total cholesterol and HF, a finding that is confirmed in our study.[7, 8] A potential explanation could be that total cholesterol is only associated with HF with reduced ejection fraction. Further research is needed to confirm this hypothesis. Another explanation could be that cholesterol might not play a substantial role in HF. Results from the Controlled Rosuvastatin in Multinational Trial in Heart Failure (CORONA) study did not show any beneficial effect of rosuvastatin in HF on the composite outcome of cardiovascular death, nonfatal myocardial infarction or stroke, while it did reduce LDL cholesterol.[34]

The current study is the first to examine the relationship between clusters of risk factors and incident HF. As it could be challenging to change one's

lifestyle, we investigated whether specific combinations of LS7 components could reduce the risk of HF. Our analyses suggest that clusters with specific LS7 components, notably clusters including glucose, BMI, smoking or blood pressure, are associated with a lower incidence of HF. Therefore, it stands to reason that preventive strategies that target combinations of these specific LS7 components could have a large impact on decreasing incident HF in the general population. Yet, this should be further confirmed by intervention studies. Several clusters did not often occur in the population, which prevented us from studying all clusters of LS7 components thoroughly. We did observe a stepwise trend of the associations; clusters with two or three ideal LS7 components show a larger reduction in incident HF than one ideal component.

Strengths and limitations

Strengths of this study are the large sample size of the cohort, with rich data collection, including in depth information on risk factors. Another strength of this study was the long follow-up, which allowed for the assessment of incident HF. Our results are generalizable to other Western European populations; however, caution should be used comparing our results to U.S. populations due to more diversity in race distribution in U.S. cohorts. Several other limitations should be addressed. First, only baseline measurements of LS7 components were available, which might not reflect the risk factor status over time. In a subset of the EPIC-NL cohort repeated measurements were available and in an earlier study it was observed that in those who improve their baseline risk profile, compared to those with a stable profile over time, CVD incidence is up to two times lower.[35] Furthermore, the FFQ might not be an ideal instrument to measure dietary intake, especially for sodium intake, which may have affected the association of diet with HF. Our sensitivity analysis showed, however, that excluding sodium from our diet score does not affect the results. Glucose measurements were available in the MORGEN cohort, while only in subset of participants of the PROSPECT cohort. Therefore, we used other information to determine glucose status, such as diabetes diagnosis and medication use. Patients with (yet) unrecognised diabetes from the PROSPECT cohort were not taken into account in these analyses, which is a limitation of our study. However, the results were robust in the sensitivity analysis. HF diagnoses were based on the Hospital Discharge Register and Cause of Death Register, however many HF patients are only known in primary care and not secondary care. Using these registries could have led to an underestimation of HF cases. Furthermore, we were unable to differentiate between HF phenotypes, since we had no access to

detailed echocardiography estimates to assess systolic function. Lastly, due to the observational design of the study, residual confounding cannot be excluded.

Conclusions

A healthy lifestyle, as reflected in an ideal LS7 score, was associated with a 55% lower risk of HF. Given the robust associations between a healthy lifestyle and reduced incidence of HF, this study provides evidence that prevention of incident HF could be accomplished by implementing healthy lifestyle patterns. The American Heart Association LS7 could be seen as a way to improve cardiovascular health and to reduce morbidity and mortality from CVDs, and in particular HF.

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Supplemental material

Table S1. Definition and distribution of LS7 components in the EPIC-NL cohort

LS7 Components	Score	Definition	% EPIC-NL participants*
Smoking	0	Current smoker	30.9
	1	Former smoker, quit < 12 months ago	-
	2	Never smoker or quit > 12 months ago	69.1
BMI	0	≥ 30 kg/m^2	13.1
	1	25 - 30 kg/m^2	38.6
	2	≤ 25 kg/m^2	48.2
Physical activity[¶]	0	Inactive: Sedentary job and no recreational activity	7.6
	1	Moderately inactive or moderately active: Sedentary job with 0.5 h to 1 h recreational activity per day *or* standing job with no recreational activity *or* standing job with 0.5 h recreational activity per day *or* physical job with no recreational activity	50.8
	2	Active: sedentary job with 1 h recreational activity per day *or* standing job with 0.5 h recreational activity per day *or* physical job with at least some recreational activity *or* heavy manual job	41.6
Diet	0	0 – 1 components healthy diet	29.1
	1	2 – 3 components healthy diet	68.4
	2	4 – 5 components healthy diet	2.5
Total cholesterol	0	≥ 240 mg/dL	26.4
	1	200 – 240 mg/dL	35.9
	2	≤ 200 mg/dL	37.7
Blood pressure	0	≥ SBP 140 mmHg or ≥ DBP 90 mmHg	24.4
	1	SBP 120 – 140 mmHg or DBP 80 – 90 mmHg or treated < 120/80 mmHg	39.2
	2	≤ SBP 120 mmHg and ≤ DBP 80 mmHg, not treated	36.4

Table S1. Continued

LS7 Components	Score	Definition	% EPIC-NL participants*
Blood glucose	0	≥ 126 mg/dL (fasting), ≥ 200 mg/dL (non-fasting), diabetes diagnosis untreated	1.5
	1	100 – 126 mg/dL (fasting), 140 – 200 mg/dL (non-fasting), diabetes diagnosis treated	13.8
	2	≤ 100 mg/dL mmol/L (fasting), ≤ 140 mmol/L (non-fasting), no diabetes diagnosis	84.7

* EPIC-NL = European Prospective Investigation into Cancer and Nutrition-Netherlands. BMI = Body Mass Index.
¶ Physical activity was defined according to the Cambridge Physical Activity index (Wareham NJ, Jakes RW, Rennie KL, et al. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Public Health Nutr. 2003;6:407–413)

Table S2. ICD-9 codes and ICD-10 codes to define heart failure

ICD codes	
ICD-9	428, 402.0-402.9, with fifth-digit 1, 404.0-404.9 with fifth-digit 1 or 3
ICD-10	I50, I11.0, I13.0, I13.2

Table S3. Numbers and percentages of missing measurements in the EPIC-NL cohort

	N missing in EPIC-NL*	% missing in EPIC-NL*
Demographics		
Age	0	0
Sex	0	0
Education level	234	0.6
Lifestyle factors		
Smoking	150	0.4
Physical activity	5347	14.1
Diet score	179	0.5
Clinical measures		
Systolic blood pressure	88	0.2
Diastolic blood pressure	68	0.2
BMI	24	0.1
WHR	72	0.2
Total cholesterol	1516	4.0
HDL cholesterol	1567	4.2
Glucose	17109	45.3

* EPIC-NL = European Prospective Investigation into Cancer and Nutrition-Netherlands, BMI = Body Mass Index, WHR = Waist-Hip Ratio, HDL = High Density Lipoprotein.

Table S4. Associations between LS7 and incident HF in a subset with glucose measurements (n = 20,694)

	Model 1	Model 2
	HR (95% CI)	HR (95% CI)
Inadequate (0 - 8)	1 (ref)	1 (ref)
Intermediate (9 - 10)	0.24 (0.17; 0.33)	0.36 (0.25; 0.50)
Ideal (11 - 14)	0.14 (0.09; 0.23)	0.34 (0.21; 0.56)

Model 1 = crude model, model 2 = adjusted for age, sex and education level. HR (95% CI) = Hazard ratio (95% Confidence interval)

Table S5. Associations between the LS7 diet component without sodium and incident heart failure

	Model 1	Model 2
	HR (95% CI)	HR (95% CI)
Inadequate (0 - 8)	1 (ref)	1 (ref)
Intermediate (9 - 10)	0.76 (0.64; 0.89)	0.85 (0.66; 1.09)
Ideal (11 - 14)	0.88 (0.54; 1.43)	0.95 (0.58; 1.54)

Model 1 = adjusted for age, sex and education level, model 2 = adjusted for model 2 + glucose, BMI, blood pressure, physical activity, smoking and cholesterol. HR (95% CI) = Hazard ratio (95% Confidence interval)

Table S6. Number of events table for figure 3: associations between clusters and incident heart failure

Cluster	N	Events
Reference (5 – 6 – 7 inadequate LS7 components)	238	17
Smoking	887	52
Glucose	1312	47
BMI – Glucose	924	20
BP – Glucose	475	17
Glucose – Physical activity	707	27
Glucose – Smoking	3928	95
Glucose – Cholesterol	444	11
Physical activity – Smoking	485	13
Smoking – Cholesterol	355	10
BMI – BP – Glucose	778	12
BMI – Glucose – Physical activity	536	15
BMI – Glucose - Smoking	2091	30
BP – Glucose – Smoking	904	14
Glucose – Physical activity - Smoking	2565	54

BMI = Body Mass Index, BP = Blood Pressure

PART II – TREATMENT OF HEART FAILURE

CHAPTER 4

TEMPORAL TRENDS IN HEART FAILURE MEDICATION USE: A POPULATION-BASED COHORT STUDY USING LINKED ELECTRONIC HEALTH RECORDS

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Abstract

Background. We examined temporal heart failure (HF) prescription patterns in a large representative sample of real-world patients in the UK, using electronic health records (EHR).

Methods and results. From the CALIBER resource, we identified 85,732 patients with a HF diagnosis between 2002-2015. Almost 50% of HF patients were women and the median age was 79.1 [70.2-85.7] years, with age at diagnosis increasing over time. We found several trends in pharmacological HF management, including increased beta-blocker prescriptions over time (29% in 2002-2005 and 54% in 2013-2015), which was not observed for mineralocorticoid receptor-antagonists (MR-antagonists) (18% in 2002-2005 and 18% in 2013-2015); higher prescription rates of loop diuretics in women and elderly patients together with lower prescription rates of RAS-inhibitors, beta-blockers, or MR-antagonists in these patients; little change in medication prescription rates after 6 months of HF diagnosis; and lastly, patients hospitalised for HF who had no follow-up in primary care had considerably lower prescription rates compared to patients with a HF diagnosis in primary care with or without HF hospitalisation.

Conclusions. In the general population, the use of MR-antagonists for HF remained low and did not change throughout 13 years of follow up. With large differences between HF patients, with lowest prescription rates observed in women, elderly patients, and those not followed-up in primary care, these findings suggest HF management can be improved by focusing effort and healthcare resources on improving communication between primary and secondary care.

Introduction

Heart failure (HF) is a common public health burden, with the prevalence of HF estimated at approximately 500.000 patients in the UK.[1,2] Once diagnosed, initiation and up titration of guideline recommended therapies can reduce morbidity and mortality, however 5-year survival still remains 20% to 50%.[3,4]

Several observational studies have assessed treatment uptake in HF patients following their diagnosis. These studies suggest that many patients did not receive guideline recommended therapies, or at low doses with sparse attempts for up titration.[5–8] Optimal treatment for effective disease management seems to be particularly challenging in elderly patients, women or patients with multiple comorbidities and contraindications for treatments.[7,8] At present, few data are available for prescription trends in HF patients in the general population and even fewer data are available that shed light on medication use in HF patients in the years prior to their HF diagnosis.

The CALIBER resource curates primary and secondary care EHR of 5 million individuals in the UK, including HF diagnosis and medication prescriptions.[9] Given the amount of information available, medication use of all HF patients in the community may be investigated – including those which are underrepresented in heart failure disease registries of randomised clinical trials.

Therefore, we sought to examine HF treatment prescription patterns following a HF diagnosis for the overall population as well as specific subgroups based on gender (e.g. women), age (e.g. elderly), social economic status and healthcare setting (e.g. primary care or secondary care), in a large representative sample of real-world patients in the UK, using electronic health records (EHR).[10]

Methods

Data source

Patients were selected from the CALIBER resource, which consists of three linked databases: The Clinical Practice Research Datalink (CPRD) with primary care EHR, Hospital Episodes Statistics (HES) containing coded diagnoses and surgical procedures from inpatient hospital admissions, and the Office for National Statistics (ONS) registry containing cause-specific mortality data.[10]

Previous work has shown that these patients are representative of the general population in the UK.[11–13]

Study population

Patients were included at their first record of HF from CPRD or HES between January 1st 2002 and December 31st 2015. In CPRD, events were defined by a diagnosis of HF based on READ clinical codes and in HES by a diagnosis of HF based on ICD-10 codes. The same HF diagnosis codes were used as in previous papers, with in addition several newer READ codes listed in **Table S1**.[14,15] All patients were eligible for inclusion if they were aged 18 years or older, were registered with a GP for at least one year prior to diagnosis of HF, in a practice that had at least one year of up-to-standard data recording in CPRD. The first record of HF from CPRD or HES was considered the index date. Individuals were censored at the earliest date from the date of de-registration, the last data collection date, the date of death or at the study end date (31st December 2015). Data from HF patients up to 3 years prior to index date was included in this study.

EHR phenotyping variables

Baseline patient characteristics were based on records from CPRD and/or HES prior to index date, including demographics (age, sex, ethnicity, social deprivation) cardiovascular risk factors (smoking, BMI, diastolic blood pressure and systolic blood pressure and estimated glomerular filtration rate, comorbidities (a medical history of atrial fibrillation, chronic obstructive pulmonary disease (COPD), diabetes, hypertension, ischaemic heart disease, valvular disease and history of cancer) and medication prescription, classified as: RAS-inhibitors (Angiotensin converting enzyme-inhibitors and/or angiotensin II receptor blockers), beta-blockers, mineralocorticoid receptor-antagonists (MR-antagonists) and loop diuretics. Definitions of these variables could be found online at http://www.caliberresearch.org/portal/.

Medication prescription for RAS-inhibitors, beta-blockers, MR-antagonists and loop diuretics was identified between three years prior to HF diagnosis up to three years after HF diagnosis per the following increments: -36 months to -24 months, -24 months to -18 months, -18 months to -12 months, -12 months to -6 months, -6 months to -3 months, -3 months to HF diagnosis, HF diagnosis to +3 months, +3 months to +6 months, +6 months to +12 months, +12 months to +18 months, +18 months to +24 months and +24 to +36 months.

Healthcare setting was characterised as primary care only (no HF hospitalisation), secondary care only (no HF diagnosis recorded in primary care) or HF diagnosis in both primary and secondary care. Ethnicity records from CPRD and HES were combined and categorised as Caucasian, Asian, Black or Other. Social deprivation was measured as quintiles of the index of multiple deprivation of the geographical area of the primary care practice, a score calculated based on seven indices of deprivation: income, employment, health and disability, education, barrier to housing and services, crime and living environment.[16] Smoking status was classified as never, ex- or current smokers.

Statistical analysis

Patient characteristics were summarized as mean (SD) or median [IQR] for continuous variables and percentages for categorical variables. The percentage of HF patients prescribed pharmacological treatments was calculated per increment and per time period as defined by publication year of previous ESC guidelines (2001, 2005, 2008 and 2012)[1,17–20]: 2002-2005, 2006-2008, 2009-2012 and 2013-2015. In addition to the overall cohort, we investigated several subgroups: age (< vs. ≥ 75 years old), sex (men vs. women), social economic status (lowest quintile of social deprivation vs. the rest) and setting (only follow-up in primary care vs. only in secondary care vs. follow-up in primary care after HF hospitalisation). All analyses were performed using R version 3.6.1.

Table 1. Baseline characteristics of heart failure patients between 2002 and 2015

	Overall	2002 - 2005	2006 - 2008	2009 - 2012	2013 - 2015	% missing
n	85732	25366	17715	26114	16537	
Demographics						
Age (Years, median [IQR])	79.1 [70.2, 85.7]	78.7 [70.7, 84.9]	78.7 [69.9, 85.4]	79.5 [70.1, 86.3]	79.7 [70.0, 86.4]	0
Sex (% Women)	48.6	49.3	48.4	48.4	48.0	0
Ethnicity (% Caucasian)	96.5	97.5	96.9	96.1	95.1	3.5
Social deprivation (% lowest quintile)	24.3	25.1	25.0	24.0	22.9	0
Clinical and lifestyle measurements						
SBP (mmHg, mean (sd))	136.2 (20.7)	140.6 (22.3)	135.9 (20.7)	134.6 (20.0)	132.9 (18.7)	13.0
DBP (mmHg, mean (sd))	76.2 (12.0)	78.4 (12.0)	76.2 (12.0)	75.4 (12.0)	74.4 (11.6)	13.0
BMI (kg/m^2, mean (sd))	28.6 (6.6)	28.2 (6.4)	28.4 (6.6)	28.7 (6.8)	28.8 (6.8)	54.0
eGFR (min/m^2/1.73mL, median [IQR])	58.4 [45.3, 72.1]	54.7 [43.4, 66.1]	56.5 [44.3, 68.8]	60.5 [46.3, 75.3]	62.9 [47.5, 78.2]	24.0
Smoking status (% Current)	20.8	22.3	20.0	20.4	20.5	38.7
Medical history (%)¶						
Atrial Fibrillation	36.6	28.4	36.3	40.6	43.0	-
COPD	17.9	14.8	17.3	19.5	21.0	-
Diabetes	22.3	18.1	22.2	23.7	26.7	-
Hypertension	60.7	46.0	60.7	67.9	72.0	-
Ischaemic heart disease	44.2	39.0	46.0	46.4	46.8	-
Valvular disease	16.5	9.5	14.9	19.9	23.8	-
Medication prescription up to 3 months after HF diagnosis (%)¶						
RAS-inhibitors	60.8	59.6	63.5	62.0	57.6	-
Beta-blockers	42.5	28.9	41.0	49.3	54.1	-
MR-antagonists	18.0	18.4	17.9	17.6	18.2	-
Loop diuretics	63.0	68.4	63.5	61.1	57.0	-

* Assessed by index of multiple deprivation, § denotes prior medical history of given comorbidity, ¤ Medication 12 months prior to index date, Mean (SD) = Mean (Standard deviation), Median [IQR] = Median [Interquartile range], CPRD = Clinical Practice Research Datalink, SBP = systolic blood pressure, DBP = Diastolic blood pressure, BMI = Body Mass Index, eGFR = estimated glomerular filtration rate, COPD = Chronic Obstructive Pulmonary Disease, RAS-inhibitors = ACE-inhibitors and/or angiotensin II receptor blockers, MR-antagonists = mineralocorticoid receptor antagonist. ¶Medical conditions and prescriptions were considered absent if not recorded.

Results

Baseline characteristics

We identified 85,732 patients with a HF diagnosis. The study flow diagram could be found in **Figure S1**. Median follow-up after HF diagnosis (index date) was 2.1 years [0.6 – 4.5] years. **Table 1** shows the overall baseline patient characteristics and per time period 2002-2005, 2006-2008, 2009-2012 and 2013-2015. Almost 50% of patients were women and the median age was 79.1 [70.2 - 85.7] years, with age at HF diagnosis increasing over time. Overall, many HF patients had comorbidities, most common were hypertension (61%), ischaemic heart disease (44%) and atrial fibrillation (37%), with increasing numbers of patients with comorbidities over time. Approximately 40% (n= 34,489) of patients were followed-up in primary care after a HF hospitalisation, 20% (n= 15,330) of patients were only known in primary care and never hospitalised for HF and the remaining 40% (n = 35,913) of patients had no follow-up in primary care after HF hospitalisation.

Overall prescription patterns

Overall prescription patterns are shown in **Figure 1**. Many patients were prescribed medication before HF diagnosis, especially RAS-inhibitors (20% in 2002-2005 to 46% in 2013-2015). Over time, beta-blocker prescription after HF diagnosis increased from 30% in 2002-2005 to 55% in 2013-2015. Throughout the follow up of 13 years, there were little observed changes for MR-antagonist uptake, this remained at 20% throughout time after HF diagnosis. The largest observed changes in prescription patterns occurred between 6 months before and after HF diagnosis (**Figure 1**). Approximately 20% of HF patients were prescribed a loop diuretic up to three years prior to HF diagnosis.

Setting-specific prescription patterns

Setting-specific prescription patterns are shown in **Figure 2**. Patients followed-up in primary care after HF hospitalisation had the highest prescription rates for all types of medication. Over time, the prescription for loop-diuretics, RAS-inhibitors and beta-blockers converged together. In these patients the prescription for MR-antagonists increased over time after HF diagnosis from 20% in 2002-2005 to 30% in 2013-2015.

Patients known in primary care but never hospitalised for HF had lower prescription rates for all types of treatment compared to patients with primary care follow-up and at least one HF hospitalisation. Mainly loop diuretics were

less prescribed in these patients and the prescription of loop diuretics decreased over time with 65% of patients receiving loop diuretics after HF diagnosis in 2002-2005 compared to just over 40% in 2013-2015. Patients hospitalised for HF but without a HF diagnosis in primary care, had the lowest prescriptions rates for loop diuretics, RAS-inhibitors and beta-blockers, which remained stable over time (50%, 45%, and 45% in 2013-2015 respectively). MR-antagonists were only prescribed in 13% of patients after HF diagnosis, this was similar for each time period.

Age-specific prescription patterns

Differences in prescription according to age categories are shown in **Figure 3**. The observed increase in prescriptions for RAS-inhibitors, beta-blockers, and MR-antagonists between 6 months before HF diagnosis to 6 months after HF diagnosis was less pronounced in elderly patients. The average increase in elderly patients was 12%, 7%, 8% for RAS-inhibitors, beta-blockers and MR-antagonists respectively, while younger patients had an average increase of 23%, 19% and 13% for RAS-inhibitors, beta-blockers and MR-antagonists respectively. On the other hand, a higher proportion of elderly patients were treated with loop-diuretics compared to younger patients, both before and after HF diagnosis (45% before and 63% after HF diagnosis in elderly compared to 27% before and 47% after HF diagnosis for younger patients in 2013-2015). After HF diagnosis, a higher percentage of younger patients were prescribed with RAS-inhibitors and beta-blockers compared to older patients.

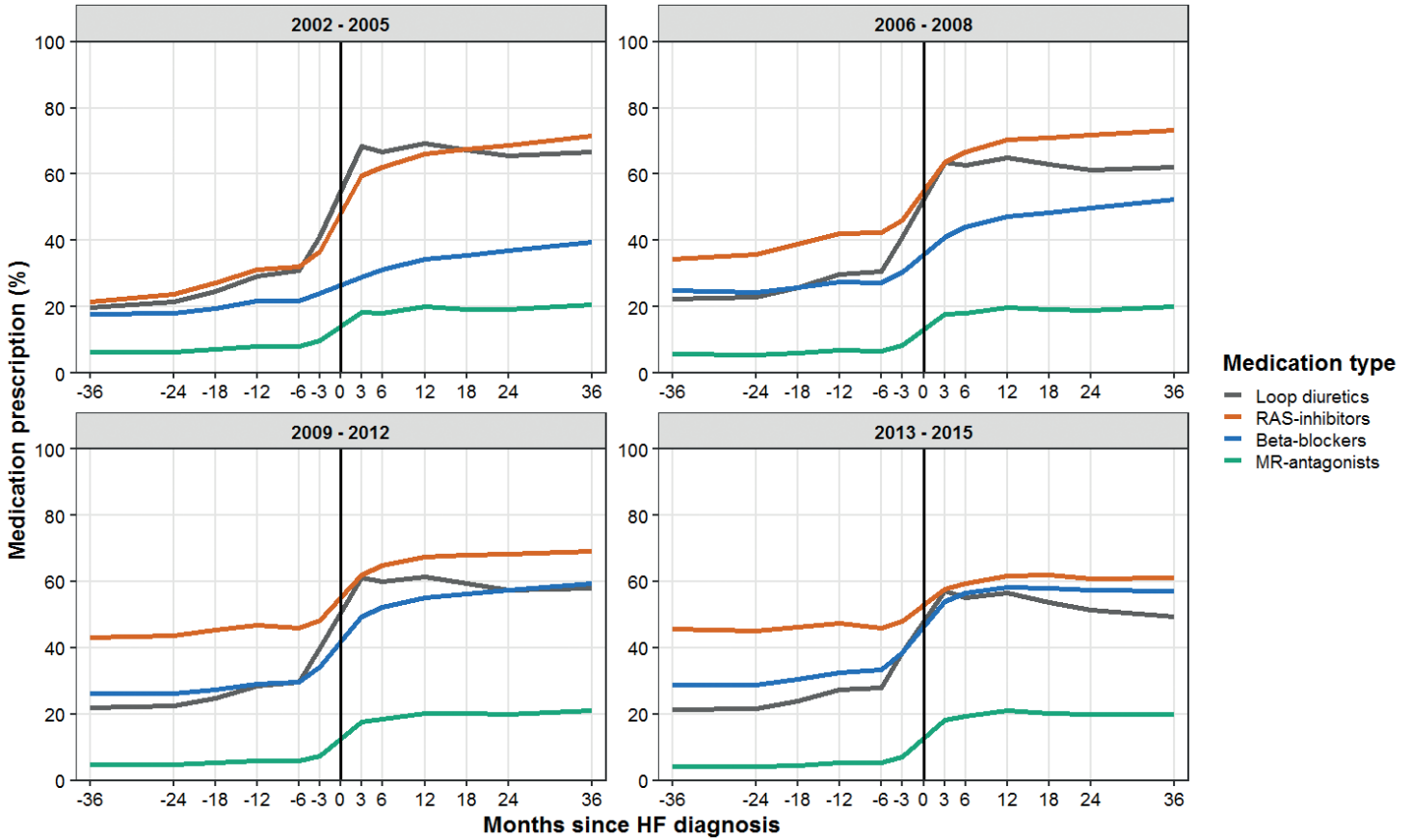
Sex-specific prescription patterns

Differences in prescription between men and women are shown in **Figure 4**. Loop diuretics were prescribed in a higher proportion of women compared to men, this difference was already present prior to HF diagnosis where 6 months before diagnosis 30% of women and 20% of men were prescribed a loop diuretic. After HF diagnosis, the most prescribed medication for women was a loop diuretic, while a higher proportion of men were prescribed a RAS-inhibitor. Men were also more often prescribed RAS-inhibitors, beta-blockers and MR-antagonists after HF diagnosis compared to women.

Social economic status-specific prescription patterns

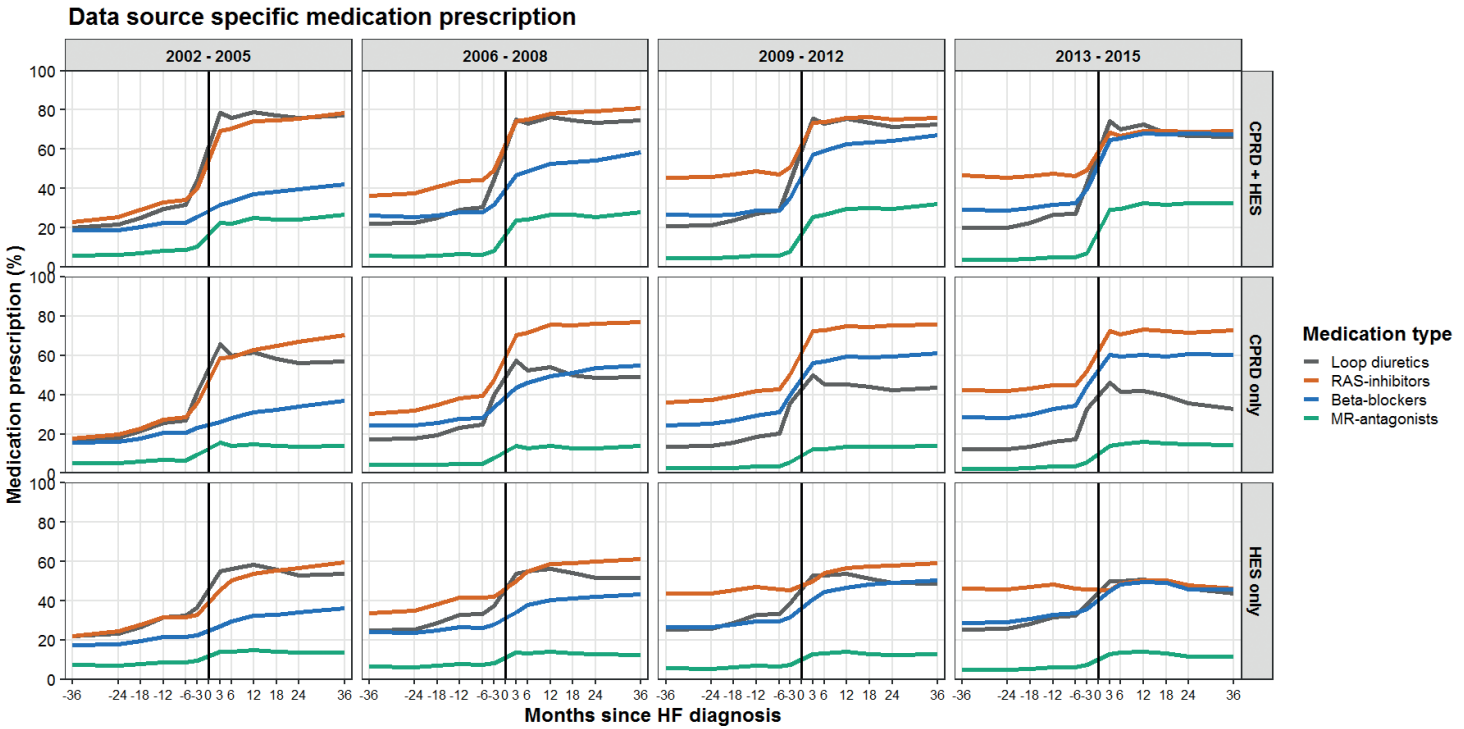
Social economic status-specific prescription patterns are shown in **Figure 5**. We did not observe any discernible differences between patients in low vs. high social-economic areas (highest quintile of social economic deprivation).

Figure 1. The percentage of HF patients receiving prescriptions of RAS-inhibitors, beta-blockers, MR-antagonists, loop diuretics per months since HF diagnosis.



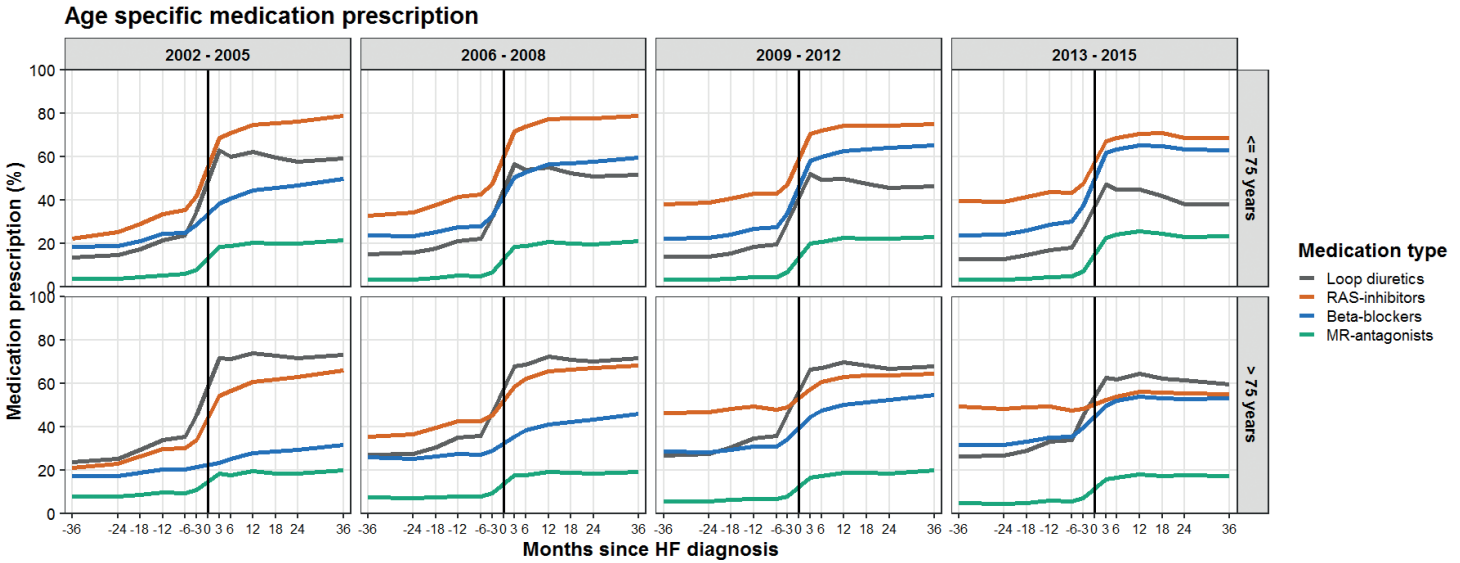
RAS-inhibitors = ACE-inhibitors and/or ARB; MR-antagonists = mineralocorticoid receptor antagonists.

Figure 2. The percentage of HF patients receiving prescriptions of RAS-inhibitors, beta-blockers and MRAs per months since HF diagnosis, stratified by setting (primary care only, secondary care only, both primary and secondary care).



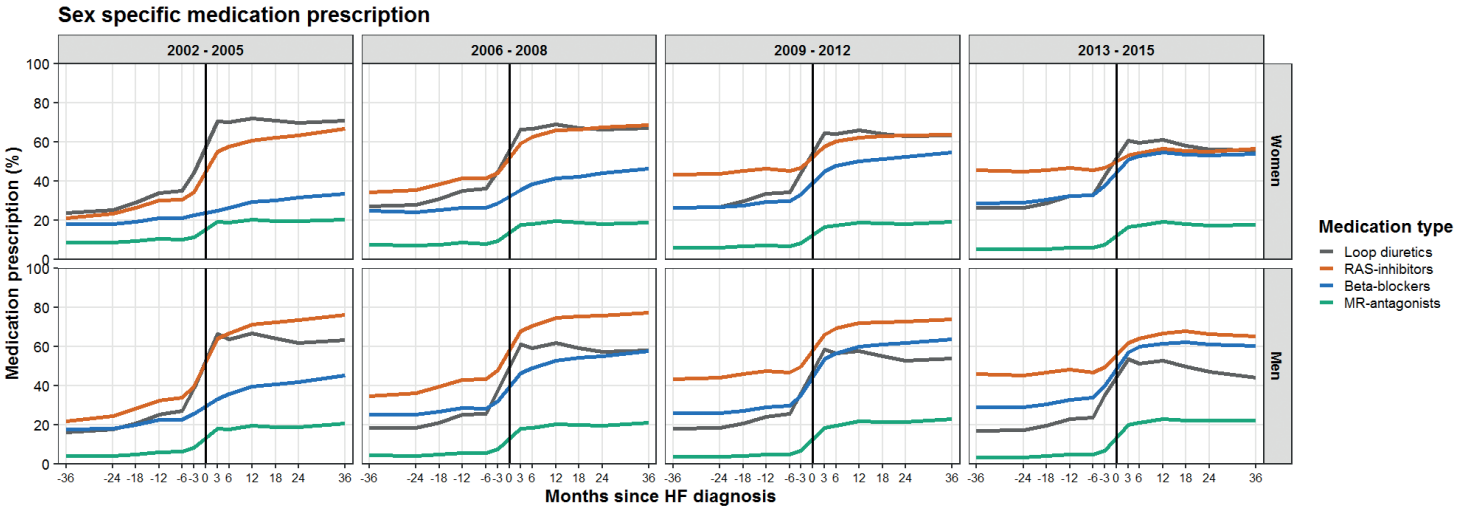
RAS-inhibitors = ACE-inhibitors and/or ARB; MR-antagonists = mineralocorticoid receptor antagonists

Figure 3. The percentage of HF patients receiving prescriptions of RAS-inhibitors, beta-blockers and MRAs per months since HF diagnosis, stratified by age.



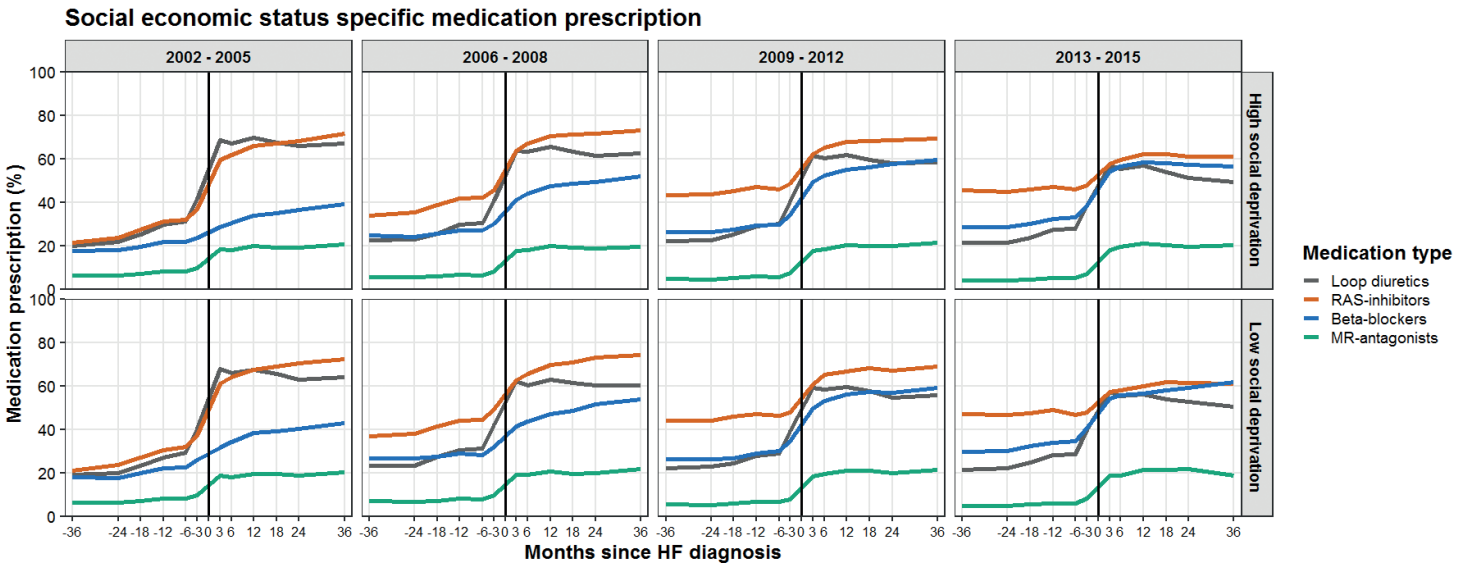
RAS-inhibitors = ACE-inhibitors and/or ARB; MR-antagonists = mineralocorticoid receptor antagonists.

Figure 4. The percentage of HF patients receiving prescriptions of RAS-inhibitors, beta-blockers and MRAs per months since HF diagnosis, stratified by sex.



RAS-inhibitors = ACE-inhibitors and/or ARB; MR-antagonists = mineralocorticoid receptor antagonists.

Figure 5. The percentage of HF patients receiving prescriptions of RAS-inhibitors, beta-blockers and MRAs per months since HF diagnosis, stratified by social status (highest quintile of social deprivation vs. the rest).



RAS-inhibitors = ACE-inhibitors and/or ARB; MR-antagonists = mineralocorticoid receptor antagonists.

Discussion

In this large-scale study of 85,732 HF patients we investigated treatment prescription patterns in a representative sample of real-world patients with HF in the UK between 2002 and 2015. We found three important trends in pharmacological HF management: a) increased use of beta-blockers, whereas there was no increased uptake of MR-antagonists over 13 years follow up; b) prescription rates remained almost unchanged after the first 6 months following a HF diagnosis; and lastly, c) higher rates of loop diuretics in women and elderly patients together with lower prescription rates for RAS-inhibitors, beta-blockers, or MR-antagonists.

Temporal trends in heart failure medication

Even though prescription rates increased over time from 2002 to 2015, overall prescription rates remained low. This is in line with previously published studies.[5–8,21] Low prescription rates could be attributed to the mixed HF cases found in EHR. We were unable to distinguish HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) based on medical records, thereby including known differences in treatment recommendations for these HF phenotypes.[1]

We found no major differences in prescription behaviour after the publication of ESC guidelines, however we did observe the gradual increase of beta-blockers as one of the cornerstones of HF treatment. RAS-inhibitors were prescribed in a high proportion of patients throughout the years of the study, presumably because the first clinical trials in HFrEF showing a beneficial effect were from the late 1980s and early 1990s.[22] Surprisingly, we found lower than expected prescription rates for MR-antagonists, which persisted over the years included in this study. This is in spite of multiple clinical trials which have shown benefit in HFrEF patients.[23] Besides HFrEF trials, a post-hoc analysis of the TOPCAT trial in 2015 (Spironolactone, a MR-antagonist, for HFpEF) reported regional differences between Americas and Russia/Georgia, where the American patients showed clinical benefits.[24] The American College of Cardiology/American Heart Association focused update on HF management in 2017 gave spironolactone a grade IIb recommendation, thereby stimulating that selected HFpEF patients could be treated with spironolactone to decrease re-hospitalisations.[25]

Heart failure medication initiation following diagnosis

Most activity in treatment prescription behaviour was observed between 6 months before to 6 months after HF diagnosis. After the 6 month mark we did not observe many patients starting any of the medication investigated. This is in line with previous studies showing that there are few changes in medication use and little up titration of medication after treatment initiation.[5,26] This leaves room for improvement in starting treatment longer after HF diagnosis, especially as patients hospitalised with acute HF may not immediately tolerate negative inotropic medication such as beta-blockers.

Impact of heart failure hospitalisation on medication prescription

We found differences in prescription patterns between patients if with HF diagnosis recorded in different settings. Patients with a primary care HF diagnosis without HF hospitalisation had much lower prescription rates of loop diuretics compared to patients with a HF diagnosis recorded in both primary and secondary care. It could be that these patients have less severe fluid overload that requires alleviation by loop diuretics.

Previously it was shown that there are differences in overall five-year survival of patients with HF diagnosis recorded in primary care only, secondary care only and in both, with the worst survival seen in HF patients identified only in secondary care and the best survival for HF patients identified in primary care with or without hospitalisation for HF.[14] Here, we advance current knowledge by showing that there are longitudinal differences in HF care of patients with diagnosis recorded in different settings. Importantly, HF patients with HF hospitalisation and no diagnosis of HF recorded in primary care had the lowest prescription rates, signifying a potential quality of care gap between secondary and primary care, where patients are not treated optimally. Primary care is the basis of many healthcare systems, including the UK. If there is no HF diagnosis recorded in primary care after HF hospitalisation, which is indicative for worse survival, rehospitalisation and severity of disease, this could be detrimental for patients.

Heart failure treatment in women and elderly

Over time, we observed that HF was diagnosed at a later age, with the median almost 80 years old between 2013-2015. This is also seen in many other developed countries where the mean age of HF diagnosis is over 70 years old.[27,28] We observed lower prescription rates in elderly patients compared to younger

patients for RAS-inhibitors, beta-blockers and MR-antagonists, although the difference in MR-antagonists was less pronounced. Many elderly patients were already using RAS-inhibitors prior to HF diagnosis, therefore the increase in prescription rate is not as steep as compared to younger HF patients who are prescribed less medication prior to HF diagnosis. This could be explained by the presence of comorbidities, such as atrial fibrillation or hypertension, which are much more prevalent among elderly compared to younger patients, and for which these elderly patients could be prescribed RAS-inhibitors.

Remarkably, the difference between prescription of RAS-inhibitors and beta-blockers prior to HF diagnosis was less than 5% for men and women, and only after the diagnosis of HF was a higher proportion of men prescribed a RAS-inhibitor or beta-blocker. This could potentially be related to the fact that elderly women are more likely to develop HFpEF and therefore tend to be treated symptomatically with loop diuretics, rather than with RAS-inhibitors and beta-blockers. However, the literature also shows that there are differences in treatment prescription in men and women with HFrEF, for which there is no obvious explanation.[29]

Both elderly patients and women received more loop diuretics. However, this could potentially be harmful, especially for elderly, since loop diuretics could lead to electrolyte disturbances and acute kidney injury.[30] Elderly patients are often excluded or underrepresented in clinical trials, therefore current recommendations lack convincing evidence in the elderly population. However, recently a large meta-analysis reported a significant effect of beta-blockers on overall mortality regardless of age.[31] These studies indicate that elderly patients also benefit from HF-specific medication and should be a choice of treatment for these patients, besides loop diuretics for symptom alleviation.

Strengths and limitations

Strengths of this study are the large cohort of HF patients and a long follow-up period. Patient records available are representative of the general UK population, which provides evidence for the validity of using these EHR for research.[11–13] However, we were limited by the inability to differentiate between HF phenotypes based on medical records, since there was no access to detailed echocardiography estimates to assess systolic function. We were also unable to assess patients' symptom class (which would affect their eligibility for

treatments such as MRA-antagonists), and contraindications or intolerances that may affect the choice of medication.

Conclusions

The results of this population-based study of over 80,000 patients with heart failure in England shows variable increases in uptake of evidence-based treatments, with no change in prescription of MR-antagonists over 13 years, but an increase in beta-blocker use. Large differences were observed between HF patient groups, with lowest prescription rates in women, elderly patients, and those without a primary care diagnosis. These findings suggest HF management can be improved by focusing effort and healthcare resources on improving communication between primary and secondary care. There is still a need for effective implementation of guideline-recommended therapies in real-world HF care.

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Supplemental material

Figure S1. Study flow diagram

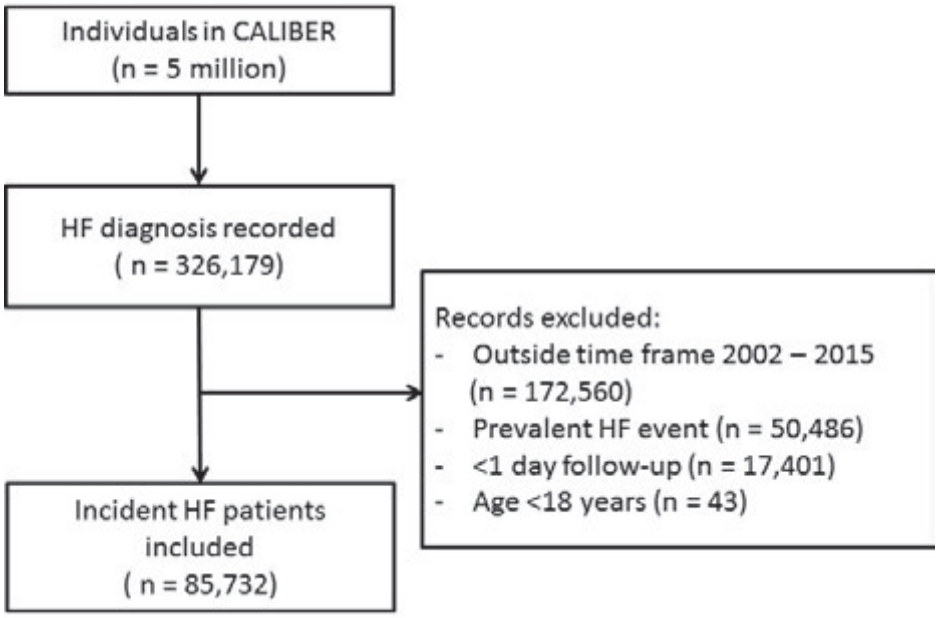

Table S1. Additional READ codes used to identify heart failure in the Clinical Practice Research Datalink

Heart Failure codes
585g.00, G5yyC00, G5yyA00, G583.12, G583.11, G583.00, G5yy900, 585f.00

CHAPTER 5

ASSOCIATION BETWEEN BETA-BLOCKER USE AND MORTALITY/MORBIDITY IN OLDER PATIENTS WITH HEART FAILURE WITH REDUCED EJECTION FRACTION

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Abstract

Background. Beta-blockers reduce mortality and morbidity in heart failure with reduced ejection fraction (HFrEF). However, patients older than 80 years are poorly represented in randomised controlled trials (RCTs). We assessed the association between beta-blocker use and outcomes in HFrEF patients ≥80 years.

Methods and results. We included patients with EF<40%, age ≥80 years from the Swedish HF Registry. The association between beta-blocker use, all-cause mortality and cardiovascular (CV) mortality/HF hospitalisation was assessed by Cox proportional hazard models in a 1:1 propensity score (PS)-matched cohort. To assess consistency, the same analyses were performed in a positive control cohort, age <80 years. A negative control outcome analysis was run using hospitalisation for cancer as endpoint.

Of 6,562 patients age ≥80 years, 5640 (86%) received beta-blockers. In the matched cohort including 1,732 patients, beta-blocker use was associated with a significant reduction in risk of all-cause mortality (HR: 0.89; 95%CI: 0.79–0.99). Reduction in CV mortality/HF hospitalisation was not significant (HR: 0.94; 95%CI: 0.85–1.05) due to the lack of association with HF hospitalisation, whereas CV death was significantly reduced. After adjustment rather than matching for the PS in the overall cohort, beta-blocker use was associated with reduced risk of all outcomes. In patients aged <80 years, use of beta-blockers was associated with reduced risk of all-cause death (HR: 0.79, 95%CI: 0.68-0.92) and of the composite outcome (HR: 0.88, 95%CI: 0.77-0.99).

Conclusions. In HFrEF patients ≥80 years of age, use of beta-blockers was high and was associated with improved all-cause and CV survival.

Introduction

The aging of the general population has increased the prevalence of heart failure (HF) and the mean age of HF patients, which now exceeds 70 years in most developed countries.[1, 2] Although octogenarians represent up to one-third of the general HF population in Europe, they have been excluded from or are underrepresented in randomised controlled trials (RCTs), leading to uncertainty about the effect of therapies and optimal management of older patients with HF with reduced left ventricular ejection fraction (HFrEF).[2, 3] They are more frail, have more comorbidities and a higher risk of cardiovascular (CV) and non-CV events than younger HF patients.[4] Further issues concern lower tolerance to medications, altered pharmacokinetics and drug interactions due to polypharmacy that lead to undertreatment and high rates of discontinuation.[2, 4]

Beta-blockers reduce mortality/morbidity in patients with HFrEF,[5-8] and thus represent one of the cornerstones of HFrEF therapy. However, limited data on their efficacy/tolerability in older HFrEF patients is currently available.[9] The SENIORS trial, tested the efficacy/safety of nebivolol in patients >70 years and the findings supports the use of beta-blockers in elderly.[10] However, no significant impact on mortality was observed and the trial included very few patients >80 years.[10] A large meta-analysis of RCTs recently reported a significant effect of beta-blockers on overall mortality regardless of age, but with a minor attenuation of treatment effect for CV mortality in older age and almost no enrolled patient >80 years of age.[11]

We sought to assess the use of beta-blockers in HFrEF patients aged ≥80 years, and test their association with all-cause mortality and CV mortality/HF hospitalisation in a large, contemporary, real-world HFrEF cohort.

Methods

Study population

The Swedish Heart Failure Registry (SwedeHF) has been previously described.[12] Briefly, patients with clinician-judged HF have been included in the registry since 11 May 2000. Approximately 80 variables are recorded at hospital discharge or after out-patient clinic visit in a web-based case report form and entered into a database managed by the Uppsala Clinical Research Center.

For the current analysis, SwedeHF was linked to the National Patient Registry which provided the outcomes hospital admission for HF, syncope, cancer and additional baseline comorbidities, and the Causes of Death registry which provided date and cause of death. Variable definitions are reported in **Table S1**. Linkage with Statistics Sweden provided socioeconomic characteristics. This study with linking of the above registries was approved by a multisite ethics committee and complies with the Declaration of Helsinki.

Patients *(Figure S1)*

Patients registered between 11 May 2000 and 31 December 2015, with age ≥80 years, EF <40%, HF duration ≥3 months (similar to the inclusion criterion for HF trials testing beta-blockers), follow-up ≥1 day (i.e. patients who died during the hospitalisation/visit linked with the registration in SwedeHF were excluded), and no missing data for beta-blocker use were considered for this analysis. We excluded patients receiving beta-blockers other than those recommended by HF guidelines (i.e. bisoprolol, carvedilol or metoprolol, **Table S2**).[13] If the same patient was registered more than once, we considered the first registration. End of follow-up was 31 December 2015.

Statistical analysis

Multiple imputation (R-package *mice;*[14] 10 imputed datasets generated) was used to handle missing values in variables which were required for multivariable models. Variables included in multiple imputation model are reported in **Table 1**, whereas **Table S3** shows the number of missing records per baseline variable. Variables with more than 40% missing were not imputed and excluded in further analyses. The propensity score (PS) for beta-blocker use was separately calculated in each imputed dataset by a logistic regression model including the clinically relevant variables reported in **Table 1** as covariates, and then averaged across the 10 imputed datasets.[15] Beta-blocker users and non-users were then matched 1:1 using the nearest neighbor method with caliper <0.01 and no replacement. The ability of the matching to balance baseline characteristics in beta-blocker users vs. non-users was assessed by absolute standard differences, with a value <10% considered as not significant. Non-linearity was assessed and variables were transformed accordingly if non-linearity was present.

The primary outcomes of this study were 5-year all-cause mortality and a 5-year composite of CV mortality and first HF hospitalisation (with censoring for

non-CV death). Secondary outcomes were 5-year CV mortality (with censoring for non-CV death), first HF hospitalisation and hospitalisation for syncope (with censoring for death). We used a Cox proportional hazard model to estimate the association between beta-blocker use and outcomes. Results are presented as hazard ratio (HR) with 95% confidence interval (CI) and survival estimates are visualised by the Kaplan-Meier method. The proportional hazards assumption was verified by assessment of the Schoenfeld residuals.

Matching reduced the sample size and may limit generalisability, therefore, a Cox proportional hazard models was fitted in the overall cohort adjusting, rather than matching, for the PS. A positive and negative control analysis was also performed. The positive control analysis consisted of a PS matched and adjusted Cox proportional hazard model in patients aged <80 years, while the negative control analysis consisted of a model fitted in patients aged ≥80 years with hospitalisation for cancer as outcome, since this is not expected to be associated with beta-blocker use. All statistical analyses were performed in R software version 3.5.1.

Results

A total of 6,562 patients were ≥80 years of age and fulfilled the inclusion criteria. Among the overall cohort, 5,640 (86%) treated with beta-blockers and 922 (14%) were untreated. After PS matching, the analysis was restricted to 1,732 patients, 866 (50%) treated and 866 (50%) untreated.

Baseline characteristics

Median age of the overall cohort was 84 [interquartile range (IQR): 82-87] years, 34.7% were women. Of patients treated with beta-blockers, 21.1% received target dose, 36.4% received 50–99% of target dose and the remaining 42.5% received <50% of the target dose (definition of target dose reported in **Table S2**).

Treated and untreated patients differed for most of the baseline characteristics (**Table 1**). Those receiving beta-blockers were younger, more likely female and following up in specialist care, had less severe HF, higher body mass index, different pattern of comorbidities (less likely anaemic and with peripheral artery disease, more likely diabetic, with hypertension and ischaemic heart disease) and higher use of pharmacological and device based therapies except for mineralocorticoid receptor antagonists. Consequently, in the overall cohort PS

were differently distributed across the study arms (**Figure 1**). After matching, there were no statistically significant differences in baseline characteristics between beta-blocker users and non-users (**Figure 1, Table 1**). Standardised differences were <10% for all variables, with the exception of NT-proBNP (14.6%). Among the matched beta-blocker users, 19.0% received guideline recommended target dose, 33.4% received 50–99% of target dose, 33.4% between 25–49% of target dose and 14.2% received <25% of target dose.

Figure 1. Kernel density plot reporting the propensity score distribution in the overall (n = 6,562) and matched (n = 1,720) cohort of patients ≥80 years of age by treatment arm.

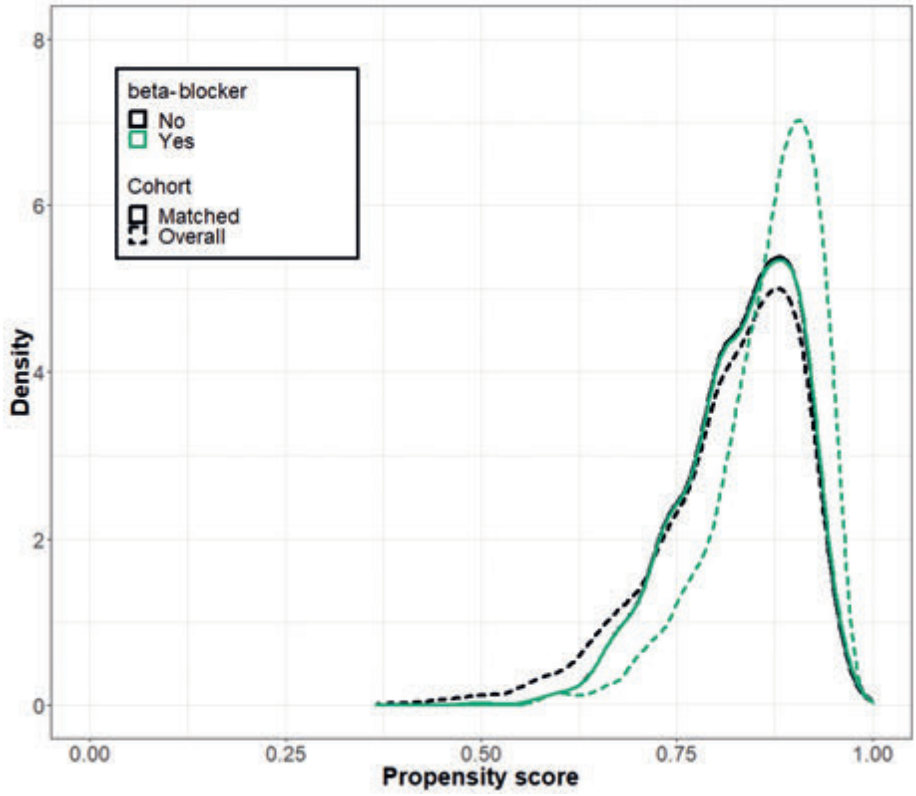


Table 1. Baseline characteristics of patients ≥80 years old in the overall and matched cohort

	Overall cohort			Matched cohort		
	Beta-blocker non-users	**Beta-blocker users**	**p-value**	**Beta-blocker non-users**	**Beta-blocker users**	**Absolute standardised difference***
n	922 (14%)	5640 (86%)		866 (50%)	866 (50%)	
Age (years, mean (SD))[a, b]	85.4 (4.2)	84.6 (3.6)	<0.001	85.2 (4.0)	85.3 (3.8)	1.1%
Sex = Female (%)[a, b]	30.5	35.4	0.004	30.9	31.5	1.2%
Location = Out-patient (%)[a, b]	36.7	40.2	0.052	37.5	34.9	5.5%
Follow-up location = Specialty (%)[a, b]	36.6	47.0	<0.001	38.5	39.2	1.5%
NYHA class (%)[a, b]			<0.001			3.8%
NYHA-I	5.7	3.5		4.8	4.0	
NYHA-II	31.9	37.6		33.3	33.4	
NYHA-III	51.7	51.8		52.0	52.6	
NYHA-IV	10.7	7.1		9.9	10.0	
EF = 30 - 39% (%)[a, b]	55.3	53.8	0.385	55.5	54.0	3.8%
Clinical measures						
BMI (kg/m^2, mean (SD))	24.3 (4.2)	25.1 (4.3)	0.001	24.4 (4.2)	24.5 (4.0)	2.9%
SBP (mmHg, mean (SD))	124.8 (19.8)	124.7 (20.1)	0.862	124.9 (19.7)	123.9 (20.5)	4.9%
DBP (mmHg, mean (SD))	69.3 (11.5)	70.4 (11.3)	0.008	69.3 (11.6)	70.0 (11.3)	6.0%
MAP (mmHg, mean (SD))[a, b]	87.8 (12.5)	88.5 (12.5)	0.122	87.8 (12.6)	87.9 (12.6)	1.0%
Heart Rate (bpm, median [IQR])[a, b]	72.0 [63.0, 82.0]	72.0 [64.0, 82.0]	0.611	72.0 [63.0, 82.0]	71.0 [63.0, 82.0]	4.7%
<60 bmp	14.4%	12.2%		14.6%	11.6%	
eGFR (mL/min/1.73m^2, median [IQR])[a, b]	45.3 [34.2, 59.6]	44.5 [33.5, 58.0]	0.222	44.9 [34.1, 59.4]	45.1 [33.6, 59.0]	1.4%
>60	24.9%	22.3%		24.4	23.4	
30-60	57.3%	59.2%		57.8	57.8	
<30	17.9%	18.5%		17.9	18.8	
NT-proBNP (pg/L, median [IQR])	4773.5 [2106.3, 10454.8]	5228.5 [2410.0, 11805.3]	0.195	4761.0 [2143.5, 9926.0]	5711.0 [2456.5, 13234.5]	14.6%

Table 1. Continued

	Overall cohort			Matched cohort		
	Beta-blocker non-users	**Beta-blocker users**	**p-value**	**Beta-blocker non-users**	**Beta-blocker users**	**Absolute standardised difference***
Smoking (%)[a, b]			0.966			7.6%
never	51.6	52.0%		50.6	52.5	
former	44.2	43.7%		45.0	44.5	
current	4.2	4.3%		4.4	3.0	
Medical history (%)						
Atrial fibrillation [a, b]	65.5	68.4	0.088	65.9	67.1	2.4%
Anaemia [a, b]	50.0	44.7	0.003	48.7	49.8	2.1%
COPD [a, b]	15.2	15.9	0.641	15.7	13.3	6.9%
Dilated Cardiomyopathy [a, b]	10.1	9.8	0.797	9.6	11.3	5.7%
Diabetes [a, b]	21.9	28.9	<0.001	22.6	22.5	0.3%
Hypertension [a, b]	58.8	69.2	<0.001	60.9	62.1	2.6%
Ischaemic heart disease [a, b]	66.8	74.4	<0.001	68.4	70.2	4.0%
Peripheral artery disease [a, b]	16.3	13.3	0.016	16.3	16.2	0.3%
Stroke and/or TIA [a, b]	19.3	20.1	0.604	19.7	19.4	0.9%
Valvular disease [a, b]	40.9	38.5	0.178	41.2	40.9	0.7%
Cancer in the previous 3 years [a, b]	14.1	12.9	0.346	14.0	14.8	2.3%
Dementia	2.4	2.6	0.828	2.4	2.4	0.1%
Procedures (%)						
Coronary revascularisation [a, b]	32.8	37.1	0.012	33.6	34.2	1.2%
Devices (CRT or ICD) [a, b]	3.3	5.5	0.008	3.5	2.5	5.4%
Pacemaker (CRT-D, CRT-P or pacemaker)	19.2	19.5	0.137	19.2	20.6	3.7%

Table 1. Continued

	Overall cohort			Matched cohort		
	Beta-blocker non-users	Beta-blocker users	p-value	Beta-blocker non-users	Beta-blocker users	Absolute standardised difference*
Medication use (%)						
RAS-inhibitors [a, b]	72.4	81.7	<0.001	75.5	73.7	4.1%
MRA [a, b]	32.3	32.5	0.958	32.8	34.9	4.4%
Digoxin [a, b]	15.6	17.1	0.281	15.8	17.6	2.1%
Diuretics [a, b]	89.9	91.0	0.321	90.6	90.0	2.1%
Statins [a, b]	31.4	44.4	<0.001	33.4	35.0	3.4%
Anticoagulants [a, b]	34.5	42.3	<0.001	36.0	36.6	1.3%
Anti-platelets [a, b]	50.9	53.0	0.256	52.4	50.6	3.6%
Nitrates [a, b]	24.2	28.0	0.018	24.9	26.5	3.5%
Social economic characteristics (%)						
Marital status [a, b]			0.723			2.3%
Married	45.7	47.0		46.9	45.7	
Single	15.8	15.2		15.1	15.5	
Widowed	38.5	37.8		38.0	38.8	
Education level [a, b]			0.867			3.3%
Compulsory school	57.9	57.4		57.3	58.9	
Secondary school	30.5	31.3		31.2	30.0	
University	11.6	11.3		11.5	11.1	
Income > median [a, b]	42.2	42.8	0.763	42.7	41.6	2.3%

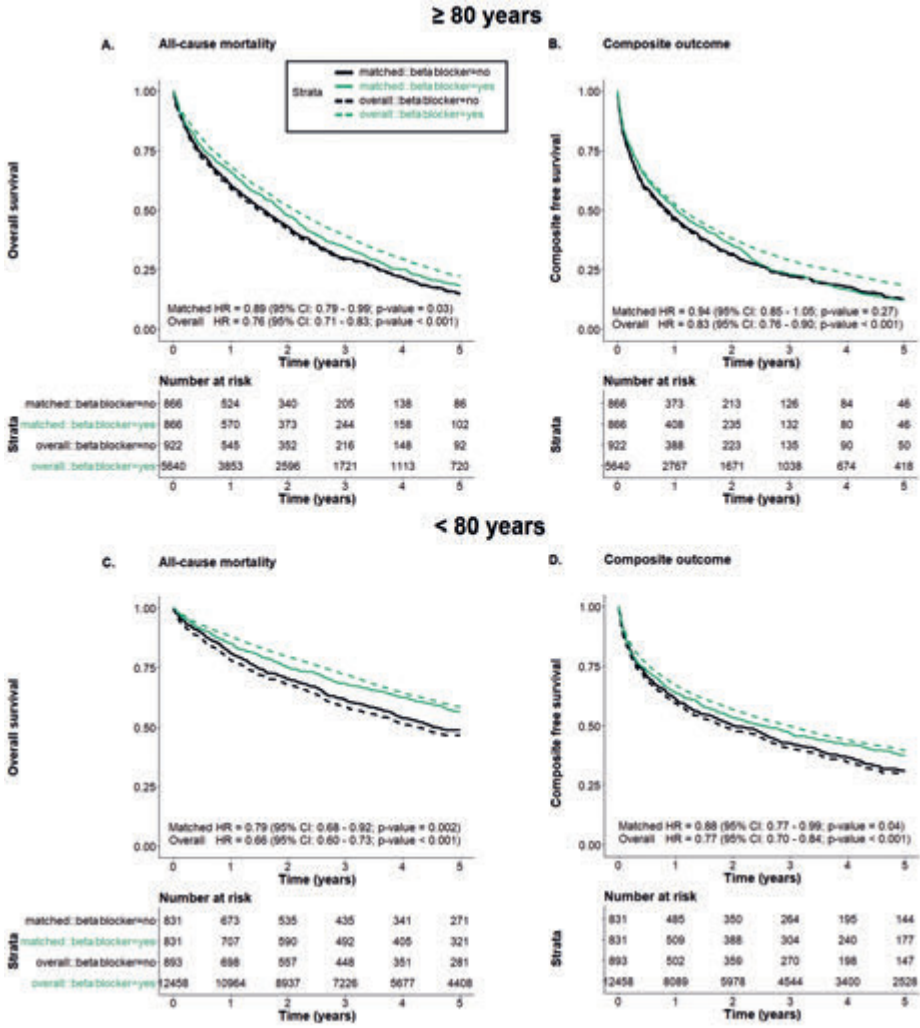
NYHA: New York heart association; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; eGFR: Estimated glomerular filtration rate (calculated by CKD-epi formula); COPD: Chronic obstructive pulmonary disease; TIA: Transient ischaemic attack; CRT: Cardiac resynchronisation therapy; ICD: Implantable cardioverter defibrillator; RAS-inhibitor: Renin-angiotensin-system inhibitor; MRA: Mineralocorticoid receptor antagonist; SD: Standard deviation; IQR: Interquartile range.

[a] = variables included in multiple imputation together with index year, duration of HF, the composite outcome, and beta-blocker use (yes/no);

[b] = variables included to estimate the propensity score together with index year and duration of HF.

* = Absolute standardised differences are defined as the difference in means, proportions or ranks divided by the mutual standard deviation

Figure 2. Kaplan-Meier curves of association between beta-blocker use and all-cause mortality and the composite outcome (cardiovascular mortality or heart failure hospitalisation).



(A) and (B) patients aged ≥80 years. (C) and (D) patients aged <80 years (positive control analysis).

Primary outcomes

All-cause mortality (**Figure 2A**)

In the overall cohort, over a median follow-up of 1.76 [IQR: 0.64-3.39] years, 4,658 (71%) patients died from any cause. The 5-year event rate was 32.2 per 100 patient-years for beta-blocker users vs. 42.8 per 100 patient-years for non-users, with a HR of 0.76 (95%CI: 0.71-0.83).

In the matched cohort the 5-year event rate for beta-blocker users was 36.7 vs. 41.8 per 100 patient-years for non-users, with a HR of 0.89 (95%CI: 0.79-0.99).

In the unmatched overall cohort a statistically significant association between beta-blocker use and 5-year all-cause mortality was confirmed adjusting rather than matching for PS, yielding a HR of 0.89 (95%CI: 0.82-0.97).

Composite outcome (CV mortality or HF hospitalisation) (Figure 2B)
In the overall cohort, 4,701 (71.6%) patients experienced CV mortality or HF hospitalisation. The 5-year event rate for beta-blocker users was 46.7 vs. 58.8 per 100 patient-years for non-users, with a HR of 0.83 (95%CI: 0.76-0.90).

In the matched cohort the 5-year event rate for beta-blocker users was 54.4 vs. 58.2 per 100 patient-years in non-users, with a HR of 0.94 (95%CI: 0.85-1.05).

Conversely, the PS adjusted Cox regression model fitted in the overall cohort yielded to a statistically significant association between beta-blocker use and reduced risk of the composite outcome, with a HR of 0.90 (95%CI: 0.83-0.97).

Secondary outcomes
CV mortality (Figure S2A)
In the overall cohort the event rates for 5-year CV mortality in beta-blocker users vs. non-users were 23.2 vs. 32.0 per 100 patient-years, respectively. The crude HR was 0.74 (95%CI: 0.67-0.81).

In the matched cohort the 5-year event rates were 26.2 vs. 31.1 per 100 patient-years for beta-blocker users vs. non-users, yielding a HR of 0.86 (95%CI: 0.75-0.97).

In the overall cohort, adjusting rather than PS matching, beta-blocker use was consistently associated with a statistically significant reduction in CV mortality, with a HR of 0.87 (95%CI 0.79-0.95).

HF hospitalisation (Figure S2B)
In the overall cohort the event rates for 5-year risk of HF hospitalisation were 33.8 vs. 40.4 per 100 patient-years for beta-blocker users vs. non-users, respectively. The crude HR was 0.87 (95%CI: 0.79-0.96).

In the matched cohort the 5-year event rates were 38.5 vs. 41.0 per 100 patient-years for beta-blocker users vs. non-users, with a HR of 0.94 (95%CI: 0.83-1.07).

Conversely, the PS-adjusted association between beta-blocker use and HF hospitalisation in the overall cohort showed a statistically significant HR of 0.90 (95%CI: 0.82-0.99).

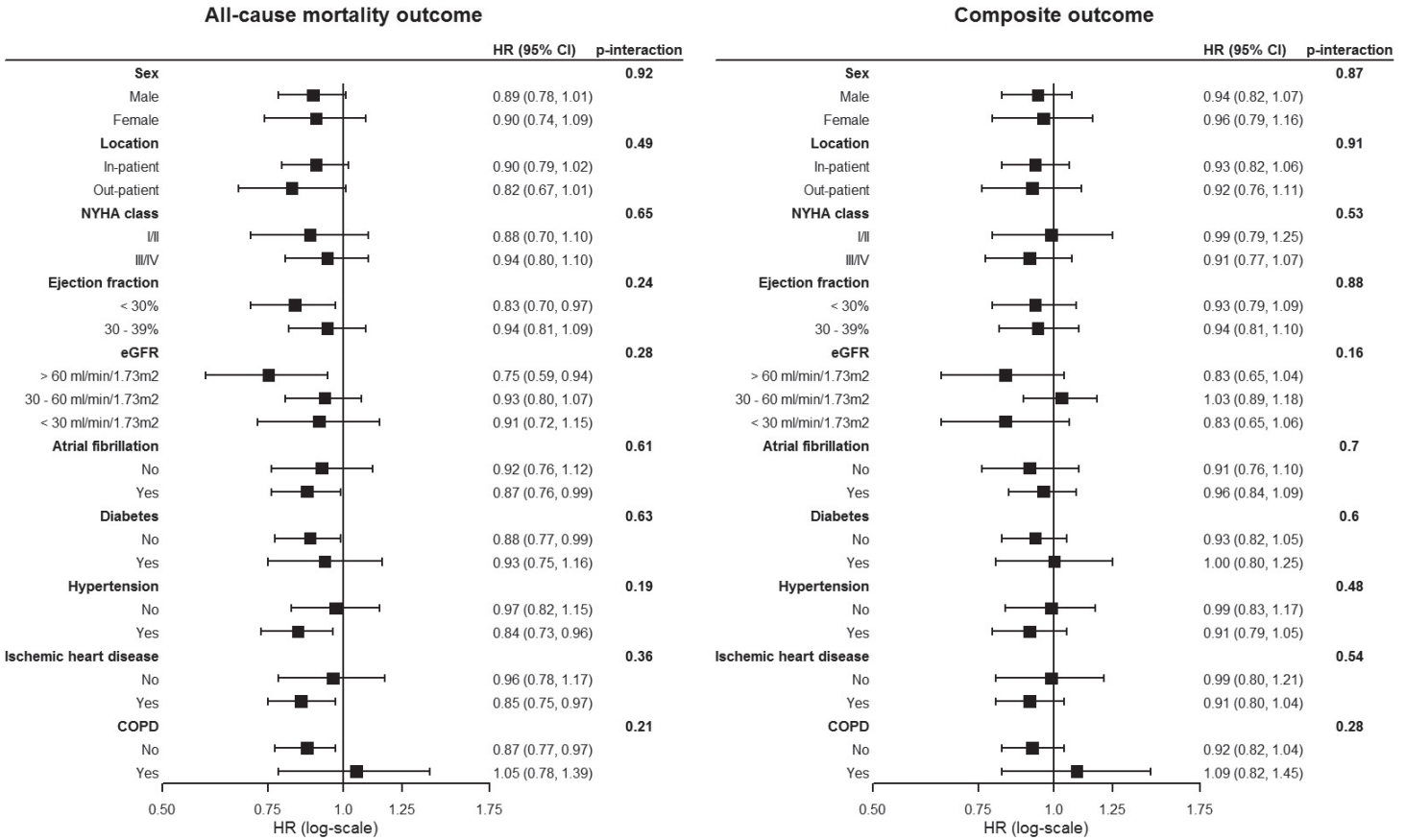
Safety outcome (Figure S2C)
In the overall cohort the 5-year event rates for hospitalisation for syncope in beta-blocker users vs. non-users were 1.3 vs. 1.2 per 100 patient-years, respectively. The crude HR was 1.09 (95%CI: 0.69-1.71).

In the matched cohort the 5-year event rates were 1.7 vs. 1.2 per 100 patient-years for beta-blocker users vs. non-users, respectively, with a HR of 1.04 (95%CI: 0.69-1.58).

Consistently with the PS-matched analysis, in the PS-adjusted analysis the HR for the association between beta-blocker use and risk of hospitalisation for syncope was 1.03 (95%CI: 0.65–1.64).

Subgroup analysis (Figure 3)
The association between beta-blocker use, all-cause mortality and the composite outcome was further investigated in clinically relevant subgroups (**Figure 3**). There were no significant interactions between beta-blocker use and any variable defining the subgroups of interest (including atrial fibrillation).

Figure 3. The association between beta-blocker use, all-cause mortality and the composite of CV mortality and HF hospitalisation in pre-specified subgroups in the matched cohort ≥80 years of age



NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate (calculated by MDRD formula); COPD: Chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval.

Positive control analysis

Primary outcomes (Figure 2C-2D)

In the positive control analysis, we tested the association between beta-blocker use and outcomes in patients <80 years of age (n=13,351). Of them, 12,458 (93.3%) were treated with beta-blockers. Baseline characteristics of the overall and the matched cohorts aged <80 years are summarised in **Table S4**.

In beta-blocker users vs. non-users, 5-year event rates were 11.0 vs. 16.8 per 100 patient-years for all-cause mortality, and 23.5 vs. 31.9 per 100 patient-years for the composite outcome, respectively. The crude HR for all-cause mortality was 0.66 (95%CI: 0.60-0.73), whereas the HR for the composite outcome was 0.77 (95%CI: 0.70-0.84).

After PS matching, the positive control analysis was restricted to 1,662 patients, including 831 (50%) beta-blocker users. The 5-year event rate for all-cause mortality was 12.1 per 100 patient-years for beta-blocker users vs. 15.5 per 100 patient-years for non-users, while the 5-year event rate for the composite outcome was 25.2 vs. 30.0 per 100 patient-years, respectively. The HR for all-cause mortality was 0.79 (95%CI: 0.68-0.92), and 0.88 (95%CI: 0.77-0.99) for the composite outcome. There was no statistically significant interaction between beta-blocker use and atrial fibrillation for both outcomes.

Similar results were reported when we adjusted rather than PS-matched in the overall cohort. The HR for all-cause mortality was 0.89 (95%CI: 0.80–0.99) and 0.86 (95%CI: 0.78–0.94) for the composite outcome.

Secondary outcomes

In the overall cohort the 5-year event rates for CV mortality in beta-blocker users vs. non-users were 7.2 vs. 11.3 per 100 patient-years, respectively. The crude HR was 0.65 (95%CI: 0.57–0.73).

In the matched cohort the 5-year event rates were 8.0 vs. 10.3 per 100 patient-years for beta-blocker users vs. non-users, yielding a HR of 0.79 (95%CI: 0.66–0.94). The PS-adjusted analysis resulted in a HR of 0.84 (95%CI: 0.75–0.96).

For HF hospitalisation the event rates for beta-blocker users vs. non-users were 20.2 vs. 26.2 per 100 patient-years. The crude HR was 0.80 (95%CI: 0.73–0.88).

In the matched cohort the 5-year event rates were 21.6 vs. 25.0 per 100 patient-years for beta-blocker users vs. non-users, yielding a HR of 0.90 (95%CI: 0.79–1.03). Conversely, when we adjusted rather than PS-matched in the overall cohort, beta-blocker use was associated with reduced risk of HF hospitalisation, with an HR of 0.84 (95%CI: 0.75–0.96).

Negative control analysis

In the matched cohort aged ≥80 years, 5-year event rates for hospitalisation for cancer were 2.7 vs. 2.6 per 100 patient-years for beta-blocker users vs. non-users, respectively, yielding an HR of 1.04 (95%CI: 0.69-1.58). The PS-adjusted model in the overall cohort yielded an HR of 0.97 (95%CI: 0.70–1.36). Corresponding HRs in the cohort aged <80 years were 1.21 (95%CI: 0.81–1.79), and 1.26 (95%CI: 0.92–1.72), respectively.

Discussion

Among HFrEF patients aged ≥80 years included in SwedeHF, 86% were treated with a beta-blocker as compared to 93% of those aged <80 years. Beta-blocker use was associated with reduced risk of all-cause mortality and CV death regardless of age, suggesting that the survival benefit from this treatment is not impaired by older age. In patients ≥80 years, use of beta-blockers was not significantly associated with the composite outcome of CV mortality and HF hospitalisation. This was mainly due to the lack of a significant association with HF hospitalisation in the elderly population, whereas it was associated with this outcome in younger patients. PS matching limited the sample size and thus the statistical power of our analysis. When we adjusted rather than matched for PS in the overall cohort, beta-blocker use was also associated with a statistically significant reduction in risk of the composite outcome and of HF hospitalisation alone. In both PS-matched and adjusted analyses, beta-blocker use was not associated with an increased risk of the safety outcome (i.e. hospital admission for syncope) and the negative control outcome (i.e. hospitalisation for cancer), regardless of age.

Beta-blocker use in HFrEF patients aged ≥80 years

In our real-world population, 86% of patients ≥80 years of age received a beta-blocker as compared to 93% in the younger subgroup, confirming the feasibility of beta-blocker treatment in older age. More underuse has been observed in the Euro Heart Survey II (56%), in the West Tokyo HF registry (66%),[16, 17] and, although

to a lower degree, in the Get With the Guidelines-HF programme (83%).[18] The inpatient setting of these studies may explain the lower use of beta-blockers as compared with our cohort.

According to the current HF guidelines, beta-blockers are indicated in HFrEF regardless of age.[19] However, beta-blocker use has been reported to be less and discontinuation rates higher in older HF patients due to concerns regarding tolerance and efficacy,[2, 20-24] although dedicated studies showed good tolerability supporting the use of beta-blockers in the elderly.[25, 26] In a meta-analysis of 11 RCTs, older age has not been shown to be associated with higher likelihood of beta-blocker therapy discontinuation, but the lower median age (64 years) compared to real-world populations may contribute to explain this finding.[11] Indeed, in the CHAMP-HF registry, beta-blockers were less likely uptitrated in older patients.[27]. Consistently with previous studies showing underdosing of beta-blockers in the overall HF population,[23, 28, 29] we observed that only 19% of patients ≥80 years received target doses and 47.6% received <50% of the target dose. Potential reasons for beta-blocker underuse in the older population may be related to safety concerns and in particular potential hypotensive or bradyarrhythmic events.[30] However, in our study the risk of hospitalisation for syncope, which may be a consequence of hypotension or bradiarrhythmia, was similar regardless of the use of beta-blockers. Further potential reasons for underuse in older patients may be related to misconceptions regarding risk in patients with respiratory disorders, as well as comorbidities, frailty, polypharmacy, less specialist care, and social circumstances (e.g. living alone).[2] Finally, age per se may explain the observed underuse of beta-blockers and other HF drugs in elderly. Indeed, RCTs lacked representative samples of older patients which may have lead clinicians to limit the use of beta-blockers in octogenerians.[9]

Association between beta-blocker use and outcomes in HFrEF patients aged ≥80 years

The advances in medical management of HF and the aging of the general population has drastically modified the shape of the HF population worldwide. Now most patients with HF in developed countries are ≥70 years of age, which underlines the significance of our analysis given the prevailing uncertainty of beta-blocker safety and efficacy in the elderly.[1, 2]

In an analysis from SwedeHF, 33% of the HFrEF cohort was ≥80 years old, which is higher than the Euro Heart Survey II population where 21% were octogenarians.[16] Nevertheless, patients aged ≥80 years have been excluded or largely underrepresented in RCTs due to several reasons, such as less use of specialist care or comorbidities more likely affecting older patients which represent exclusion criteria in RCTs.[31] Potential efficacy/tolerability of beta-blockers in the elderly can only be extrapolated from the results of RCTs enrolling younger populations with a mean age ranged 58-64 years.[5-8] The only study designed to assess the efficacy of beta-blockers in older HF patients was the SENIORS trial (inclusion criteria≥70 years, mean age=76 years), which showed a significant reduction in the risk of death or CV rehospitalisation, but non significant effect on survival, in patients receiving beta-blockers vs. not.[10] Notably, most of the patients enrolled were <80 years old and 36% had left ventricular EF >35%.[10] It is unclear whether older age of patients enrolled in the SENIORS vs. other RCTs may explain the lower efficacy of nebivolol in terms of mortality compared to other beta-blockers. A recent meta-analysis of RCTs testing beta-blockers in patients with HFrEF and sinus rhythm showed a significant benefit in terms of all-cause mortality that was consistent across age groups.[11] Similar results were observed for HF hospitalisation, albeit with a minor attenuation of beta-blocker effect in older patients.[11]

The present analysis of SwedeHF, one of the largest octogenarian cohorts worldwide, showed that beta-blocker use was significantly associated with improved survival in both patients aged ≥80 years and in the positive control cohort of patients aged <80 years, but with slightly less favorable HR in older vs. younger patients. We observed that the HR reported in our elderly cohort was the same as in the SENIORS trial, although in our analysis, but not in the trial, the association between beta-blocker use and mortality was statistically significant.[10] This may be explained by the two-fold higher mortality rates in our real-world cohort as compared with the SENIORS trial and thus higher statistical power. Neverthless, the SENIORS trial was not powered for all-cause mortality but for the composite of all-cause mortality and CV hospitalisation. The less favorable HR for mortality in older vs. younger patients observed in our study may also be explained by death from a natural cause competing with the benefits of the treatment. The HR for mortality in our positive control was higher than in RCTs, which may be due to the enrollment of a contemporary cohort of HFrEF patients, more likely to receive other guideline recommended HFrEF treatments as compared to more than 10 years ago when RCTs were run. Moreover, although

including patients aged <80 years, our positive-control cohort was older and probably more likely affected by comorbidities and concomitant diseases than patients enrolled in RCTs. Finally, in our matched cohort aged ≥80 years we could not observe a significant reduction in risk of the composite of CV death and HF hospitalisation associated with beta-blockers. Indeed, although the risk of CV death was significantly reduced in treated vs. untreated patients, the risk of HF hospitalisation was not. In the matched positive control cohort of patients aged <80 years, beta-blocker use was associated with reduced risk of the composite of CV death and HF hospitalisation, of CV death alone but again not of HF hospitalisation. A potential explanation for the lack of a significant association between beta-blocker use and risk of HF hospitalisation in the matched cohort might be that the PS matching reduced the sample size and the power of our analysis, masking any significant association between beta-blocker use and risk of HF hospitalisation. Indeed in the analyses fitted in the overall cohort where we adjusted, rather than PS-matched, we observed a significant reduction in risk of the composite outcome and of HF hospitalisation alone in treated vs. untreated patients. Finally, the low proportion of patients at target dose might have further underestimated the strenght of the association between beta-blocker use and outcomes.

Limitations

Although SwedeHF collects many variables allowing for an extensive adjustment using PS matching, that was further strengthened by a negative control outcome analysis, we cannot rule out potential unmeasured confounders. Additionally, in SwedeHF, most of the patients received beta-blockers, which led to a great reduction of sample size and statistical power after matching. Beta-blocker use was defined at baseline and potential cross-over throughout the follow-up may have diluted the association with outcomes. Additionally, whether patients received beta-blockers before the enrolment in SwedeHF but then interrupted because of tolerance/adherence issues or worsening health/harms related to comorbid conditions was unknown. In our cohort the prevalence of indexes of frailty and the rate of comorbidities were lower compared to other real-world studies.[3, 32] A potential explanation may be that patients more compromised and with higher burden of comorbidities were less likely included in the SwedeHF, since they are generally managed by general practitioners and hospitalised in first-level medicine or geriatric departments. Finally, as registrations in the SwedeHF include patients from different hospitals and primary care clinics in

Sweden, we cannot exclude some heterogeneity in medical care and outcomes between different centres and areas.

Conclusions

In HFrEF patients aged ≥80 years, the use of beta-blockers was high, although lower than in those aged <80 years, and was associated with reduced risk of all-cause and CV mortality but not with increased risk of hospitalisation for syncope. Our analysis supports current guidelines recommendation on beta-blocker therapy in HFrEF patients regardless of age.

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Supplemental material

Table S1. Variable definitions

Variable	Definition
Medical history	
Atrial fibrillation	Diagnosis in SwedeHF (history of atrial fibrillation or ECG showing atrial fibrillation) or in NPR (ICD-10 code: I48).
Anaemia	Haemoglobin <120 g/l in females and <130 g/l in males
COPD	Diagnosis in NPR (ICD-10 codes: J40-J44)
Diabetes mellitus	Diagnosis in SwedeHF or in NPR (ICD-10 codes: E10-E14)
Dilated cardiomyopathy	Diagnosis in SwedeHF or in NPR (ICD-10 code: I420)
Hypertension	Diagnosis in SwedeHF or in NPR (ICD-10 codes:I10-I15)
Peripheral artery disease	Diagnosis in NPR (ICD-10 codes: I70-I73)
Ischaemic heart disease	Diagnosis in SwedeHF or in NPR (ICD-10 codes: I20-I25; procedure codes: FNG, FNA, FNB, FNC, FND, FNE, FNF, FNH, Z951, Z955).
Cancer in previous 3 years	Diagnosis in NPR within 3 years prior to the registrations in SwedeHF (ICD-10 codes: C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C81-C85, C88, C90-C97)
Stroke/TIA	Diagnosis in NPR (I61-I64, G458, G459, I639)
Valvular disease	Diagnosis in SwedeHF or in NPR (ICD-10 codes: A520, I05-I08, I091, I098, I34-I39, Q230-Q233, Z952, Z954)
Dementia	Diagnosis in NPR (ICD-10 codes: F00, F01, F02, F03, F04)
Outcomes	
CV mortality	Main diagnosis in Causes of Death register (ICD-10 codes: I00-I99)
Hospitalisation for heart failure	Main diagnosis in NPR (ICD-10 codes: I50, I42, I43, I255, K761, I110, I130, I132, J81)
Hospitalisation for syncope	Main diagnosis in NPR (ICD-10 code: R55)
Hospitalisation for cancer	Main diagnosis in NPR (ICD-10 codes: C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C81-C85, C88, C90-C97)

NPR: National Patient Register; ICD: International Classification of Diseases; COPD: Chronic obstructive pulmonary disease.

Table S2. Guideline recommended beta-blocker agents and doses.

Beta-blocker	Target dose	Target dose percentage	N users in ≥80 years in the overall cohort	N users in <80 years in the overall cohort
Metoprolol			3130	6265
	200 mg daily	≥100%	470 (15.0%)	1855 (29.6%)
	100 – 200 mg	≥50 - 100%	1106 (35.3%)	2379 (38.0%)
	50 – 100 mg	≥25 – 50%	1071 (34.2%)	1552 (24.8%)
	0 – 50 mg	0 – 25%	483 (15.5%)	479 (7.6%)
Bisoprolol			2271	5285
	10 mg daily	≥100%	675 (29.7%)	2376 (45.0%)
	5 – 10 mg	≥50 - 100%	871 (38.4%)	1818 (34.4%)
	2.5 – 5 mg	≥25 – 50%	552 (24.3%)	862 (16.3%)
	0 – 2.5 mg	0 – 25%	173 (7.6%)	229 (4.3%)
Carvedilol			225	834
	25 mg 2x daily (<85 kg) 50 mg 2x daily (>85 kg)	≥100%	47 (20.9%)	195 (23.4%)
	25 - 50 mg (<85 kg) 50 – 100 mg (>85 kg)	≥50 - 100%	74 (32.9%)	316 (37.9%)
	12.5 – 25 mg (<85 kg) 25 - 50 mg (>85 kg)	≥25 – 50%	62 (27.5%)	186 (22.3%)
	0 – 12.5 mg (<85 kg) 0 – 25 mg (>85 kg)	0 – 25%	42 (18.7%)	137 (16.4%)

Table S3. Percentage missing for beta-blocker users and non-users in patients aged ≥80 years in the overall cohort.

	Beta-blocker non-users missing (%)	Beta-blocker users missing (%)
n		
Age (years)	0	0
Sex	0	0
Location	0.2	0.1
Follow-up location	9.5	6.1
NYHA class	35.1	28.8
Ejection fraction	0	0
Clinical measures		
BMI (kg/m^2)	52	45.5
SBP (mmHg)	1	1.5
DBP (mmHg)	1	1.6
MAP (mmHg)	1	1.6
Heart Rate (bpm)	6.0	5.5
eGFR (mL/min/1.73m^2)	1.0	0.6
NT-proBNP	68.8	61.6
Smoking (%)	30.0	28.1
Medical history (%)		
Atrial fibrillation	0	0
Anaemia	1.3	1.3
COPD	0	0
Dilated Cardiomyopathy	0	0
Diabetes	0	0
Hypertension	0	0
Ischaemic heart disease	0	0
Peripheral artery disease	0	0
Stroke and/or TIA	0	0
Valvular disease	0	0
Cancer in the previous 3 years	0	0
Dementia	0	0
Procedures (%)		
Coronary revascularisation	0	0
Devices	0	0

Table S3. Continued

	Beta-blocker non-users missing (%)	Beta-blocker users missing (%)
Medication use (%)		
RAS-inhibitors	0.1	0.4
MRA	0.8	0.6
Digoxin	0.3	0.3
Diuretics	0.4	0.8
Statins	0.1	0.3
Anticoagulants	0.5	0.4
Anti-platelets	0.3	0.4
Nitrates	0.3	0.4
Social economic characteristics (%)		
Education level	3.1	2.8
Income > median	0	0

NYHA: New York heart association; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; eGFR: Estimated glomerular filtration rate (calculated by CKD-epi formula); COPD: Chronic obstructive pulmonary disease; TIA: Transient ischaemic attack; CRT: Cardiac resynchronisation therapy; ICD: Implantable cardioverter defibrillator; RAS-inhibitor: Renin-angiotensin-system inhibitor; MRA: Mineralocorticoid receptor antagonist.

Table S4. Baseline characteristics for beta-blocker users and non-users in patients aged <80 years in the overall and matched cohorts.

	Overall cohort					Matched cohort		
	Beta-blocker non-users	Missing (%)	Beta-blocker users	Missing (%)	p-value	Beta-blocker non-users	Beta-blocker users	Absolute standardised difference*
n	893 (6.7%)		12458 (93.3%)			831 (50%)	831 (50%)	
Age (years, mean (SD))	69.0 (9.3)	0	67.2 (9.8)	0	<0.001	68.6 (9.4)	68.2 (9.2)	5.1%
Sex = Female (%)	26.3	0	23.8	0	0.095	26.4	25.2	2.8%
Location = Out-patient (%)	54.7	0.1	62.6	0.2	<0.001	57.2	58.6	2.8%
Follow-up location = Specialty (%)	68.4	5.5	78.7	4.4	<0.001	71.3	73.9	5.8%
NYHA class (%)		23.0		18.3	<0.001			6.6%
NYHA-I	9.2		10.1			9.5	10.7	
NYHA-II	39.1		46.0			41.1	38.1	
NYHA-III	44.3		40.4			44.3	46.0	
NYHA-IV	7.4		3.5			5.1	5.3	
Clinical measures								
BMI (kg/m^2, mean (SD))	26.8 (5.4)	50.0	27.8 (5.4)	44.0	<0.001	26.9 (5.4)	27.2 (5.3)	5.7%
SBP (mmHg, mean (SD))	122.6 (20.4)	2.0	122.1 (19.8)	2.0	0.470	122.9 (20.4)	122.6 (20.3)	1.8%
DBP (mmHg, mean (SD))	72.4 (12.1)	2.0	72.7 (11.6)	2.0	0.507	72.4 (12.0)	72.9 (11.7)	4.1%
MAP (mmHg, mean (SD))	89.2 (13.4)	2.0	89.2 (12.8)	2.0	0.960	89.2 (13.2)	89.4 (13.2)	1.5%
Heart Rate (bpm, median [IQR])	73.0 [64.0, 84.0]	8.0	70.0 [62.0, 80.0]	5.0	<0.001	72.0 [63.0, 83.0]	70.0 [62.0, 80.0]	1.3%
<60 bmp	14.0%		15.9%			14.8%	13.9%	
eGFR (mL/min/1.73m^2 , median [IQR])	62.7 [47.0, 79.3]	1.3	64.6 [47.8, 82.5]	1.3	0.038	63.4 [47.4, 79.6]	63.9 [47.6, 81.9]	3.7%
>60	54.3%		57.0%			54.9%	57.2%	
30-60	38.4%		36.6%			38.2%	35.9%	
<30	7.4%		6.4%			7.0%	6.9%	
NT-proBNP (pg/L, median [IQR])	2090.0 [922.0, 5265.0]	65.0	2187.0 [913.5, 5074.8]	59.0	0.716	2036.0 [872.0, 5140.0]	2592.0 [982.0, 5476.0]	9.7%

Table S4. Continued

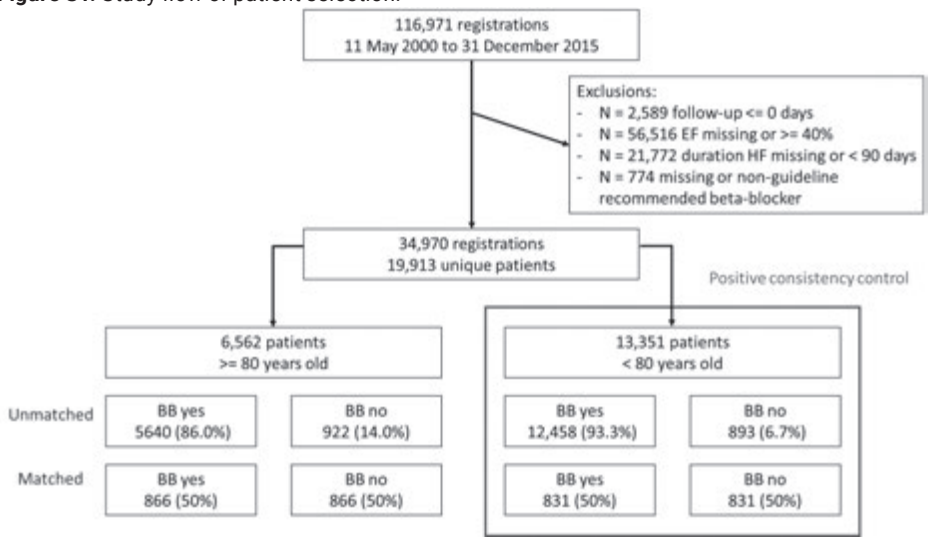
	Overall cohort					Matched cohort		
	Beta-blocker non-users	Missing (%)	Beta-blocker users	Missing (%)	p-value	Beta-blocker non-users	Beta-blocker users	Absolute standardised difference*
Smoking (%)		20.0		18.1	0.589			2.5%
never	35.6		34.2			35.2	34.1	
former	48.7		48.7			48.8	49.9	
current	15.7		17.0			16.0	16.0	
Medical history (%)								
Atrial fibrillation	50.4	0	53.1	0	0.120	50.8	48.0	5.5%
Anaemia	35.1	1.3	30.1	2.0	0.002	33.7	32.5	2.4%
COPD	23.5	0	15.7	0	<0.001	22.0	21.8	0.6%
Dilated Cardiomyopathy	28.8	0	30.2	0	0.393	29.4	31.9	5.5%
Diabetes	31.2	0	34.1	0	0.084	32.0	32.7	1.5%
Hypertension	52.9	0	59.7	0	<0.001	53.8	53.8	0.0%
Ischaemic heart disease	60.9	0	62.4	0	0.399	61.5	58.5	6.1%
Peripheral artery disease	13.0	0	12.1	0	0.489	13.0	13.1	0.4%
Stroke and/or TIA	16.8	0	13.7	0	0.011	16.1	15.9	0.7%
Valvular disease	33.4	0	27.1	0	<0.001	31.5	30.4	2.3%
Cancer in the previous 3 years	10.4	0	9.2	0	0.261	10.7	9.3	4.8%
Dementia	1.5	0	0.9	0	0.161	1.1	1.1	0.0%
Procedures (%)								
Coronary revascularisation	35.5	0	41.5	0	<0.001	36.5	34.2	4.8%
Devices (CRT or ICD)	8.8	0	14.6	0	<0.001	9.0	9.7	2.5%
Pacemaker (CRT-D, CRT-P or pacemaker)	16.1	0	15.4	0	<0.001	16.6	13.7	9.7%
Medication use (%)								

Table S4. Continued

	Overall cohort					Matched cohort		
	Beta-blocker non-users	Missing (%)	Beta-blocker users	Missing (%)	p-value	Beta-blocker non-users	Beta-blocker users	Absolute standardised difference*
RAS-inhibitors	84.0	0.3	94.4	0.2	<0.001	89.0	88.3	2.2%
MRA	41.0	0.6	43.5	0.5	0.147	41.1	43.1	4.0%
Digoxin	15.8	0.6	17.2	0.4	0.283	16.2	15.2	2.8%
Diuretics	77.0	1.2	79.6	0.6	0.074	77.0	76.7	0.6%
Statins	45.0	0.4	58.2	0.3	<0.001	47.8	47.9	0.4%
Anticoagulants	39.0	0.4	47.3	0.2	<0.001	40.6	40.3	0.7%
Anti-platelets	45.5	0.6	47.2	0.4	0.356	46.7	45.8	1.9%
Nitrates	12.4	0.9	13.9	0.3	0.232	12.8	12.9	0.4%
Social economic characteristics (%)								
Marital status		0.2		0.2	0.014			5.8%
Married	51.3		51.5			51.6	52.2	
Single	36.1		38.8			36.1	37.3	
Widowed	12.6		9.7			12.3	10.5	
Education level		1.5		2.2	0.085			5.1%
Compulsory school	46.1		42.3			45.7	43.7	
Secondary school	39.0		41.6			39.2	41.7	
University	14.9		16.1			15.0	14.6	
Income > median	46.0	0	53.9	0	<0.001	47.2	47.7	1.0%

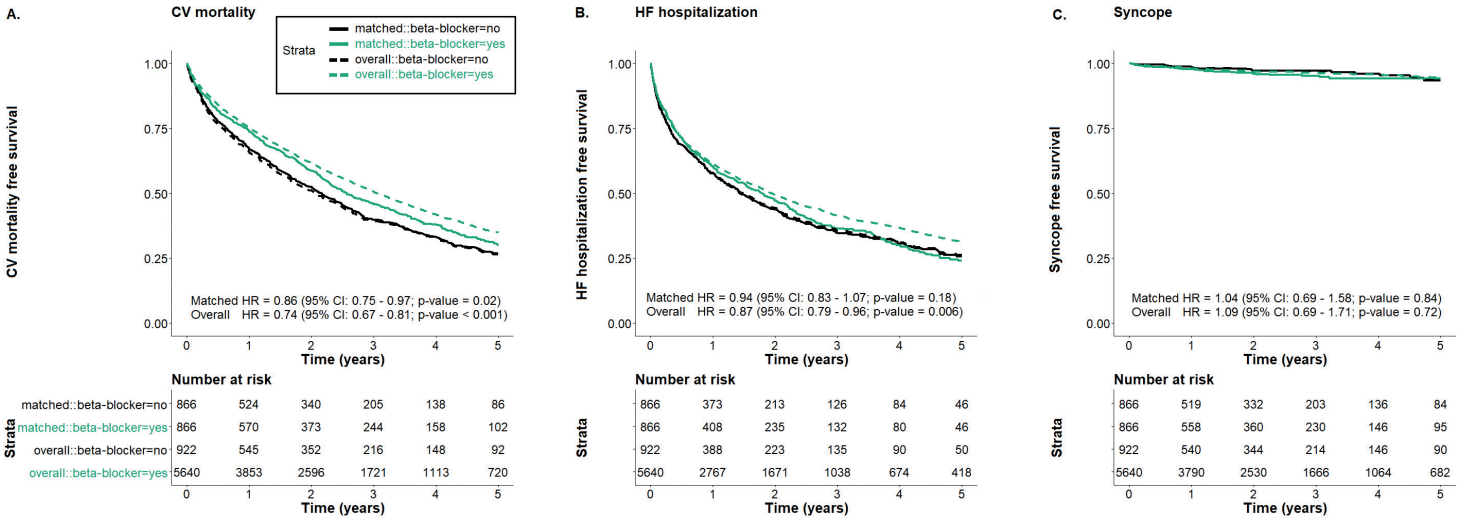
NYHA: New York heart association; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; eGFR: Estimated glomerular filtration rate (calculated by CKD-epi formula); COPD: Chronic obstructive pulmonary disease; TIA: Transient ischaemic attack; CRT: Cardiac resynchronisation therapy; ICD: Implantable cardioverter defibrillator; RAS-inhibitor: Renin-angiotensin-system inhibitor; MRA: Mineralocorticoid receptor antagonist; SD: Standard deviation; IQR: Interquartile range. * = Absolute standardised differences are defined as the difference in means, proportions or ranks divided by the mutual standard deviation.

Figure S1. Study flow of patient selection.



EF: left ventricular ejection fraction; HF: heart failure, BB: beta-blocker.

Figure S2. The association between beta-blocker use with cardiovascular (CV) mortality, heart failure (HF) hospitalisation and syncope for patients aged ≥80 years in the matched and overall cohort, displayed by Kaplan-Meier curves.



PART III – PROGNOSIS AFTER HEART FAILURE

CHAPTER 6

OPTIMIZING USE OF BIOMARKERS AS SURROGATE ENDPOINTS FOR HEART FAILURE WITH REDUCED EJECTION FRACTION PHASE II TRIALS: FINDINGS FROM BIOSTAT-CHF

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Abstract

Background. For early phase heart failure (HF) trials, there is a lack of suitable surrogate endpoints. We assessed whether and to what extent changes over time in multiple circulating biomarkers are associated with subsequent mortality/morbidity in HF with reduced ejection fraction (HFrEF).

Methods. Among 1327 patients from BIOSTAT-CHF, we assessed associations between 9-month changes in 30 biomarkers and all-cause death/HF hospitalisation with multivariable Cox regression models including the BIOSTAT-CHF risk score, changes in biomarkers modelled as splines and adjustments for baseline level of the biomarker. C-statistic was calculated to assess discriminatory power of our models.

Results. Of 30 biomarkers tested, 9-month reductions in concentrations for the following biomarkers were separately associated with reduced risk of outcome after adjustments for baseline biomarker levels and the BIOSTAT-CHF risk score: ANP, BNP, CRP, GDF-15, NT-proCNP, Neuropilin, Osteopontin, Procalcitonin, Pentraxin-3, Polymeric immunoglobulin receptor, Pro-adrenomedulin, RAGE, sST2, Syndecan-1, TNF-1α, VEGFR-1 WAP-4C. Of these biomarkers, changes in ANP, sST2, CRP and WAP-4C were independently associated with the risk of outcome on top of all the other biomarkers tested. The c-statistic increased from 0.69 for the BIOSTAT-CHF risk model to 0.73 by including changes + baseline levels of these 4 biomarkers. Changes in NT-proBNP were measured in a subset of 246 patients. In this subgroup, reductions in NT-proBNP and CRP predicted reduced risk of outcome on top of all the other biomarkers tested.

Conclusions. 9-Month reductions in ANP, NT-proBNP, CRP, sST2 and WAP4C levels are associated with improved mortality/morbidity over clinical characteristics and biomarker baseline values alone. Changes in these biomarkers' may be used as surrogate endpoints for early phase HFrEF trials.

Introduction

Development of pharmacological and other therapies is a long and expensive process. In order to justify investment in phase III randomised controlled trials (RCT) for regulatory approval, novel interventions need to be effective on surrogate endpoints in phase II RCTs. Indeed, a surrogate endpoint lies on the pathway between the disease and the outcome and thus, changes induced by a therapy on a surrogate endpoint may predict an effect on clinically relevant endpoints.

Currently, there are no accepted surrogate endpoints for HF trials.[1] Although several phase II RCTs have shown superiority of the tested intervention in terms of chosen surrogate endpoints, successful phase III RCTs have often not followed.[2] The identification of new easy-to-measure, reproducible and broadly available biomarkers as surrogate endpoints, where a change in the biomarker reflects an improved outcome, would improve and expedite the design and development of phase II trials, improve confidence among investors and health care companies in pursuing later phase interventional trials, and ultimately provide more therapeutic options and benefits to patients.

Therefore, the aim of the present study was, for multiple circulating biomarkers, to assess whether and to what extent changes over time are associated with subsequent mortality/morbidity in HF with reduced ejection fraction (HFrEF), and thus whether these biomarkers may serve as feasible surrogate endpoints in HFrEF phase II trials.

Methods

Study protocol and setting

We studied patients from the prospective BIOSTAT-CHF cohort which has been previously described.[3] Briefly, BIOSTAT-CHF enrolled 2516 patients from 11 European countries. Inclusion criteria were: 1) age ≥18 years; 2) symptoms of new-onset or worsening HF; 3) objective evidence of cardiac dysfunction documented either by EF ≤ 40% or plasma concentrations of B-type natriuretic peptide (BNP) and/or N-terminal pro-brain NP (NT-proBNP) >400 pg/mL or >2000 pg/ml, respectively; 4) treatment with either oral or intravenous furosemide ≥40 mg/day or equivalent at the time of inclusion 5) not previously treated with angiotensin-converting enzyme inhibitors (ACEi) /angiotensin receptor

antagonists (ARBs) and beta-blockers or receiving ≤50% of target doses of these drugs at the time of inclusion 5) be anticipated to be initiated or uptitrated with ACEi/ARBs and/or beta-blockers by the treating physician.

Patients were enrolled between December 2010 and December 2012. At baseline, medical history, current use of medication, physical examination and data on quality of life were recorded, and plasma, serum and urine were sampled. Echocardiographic exam was recommended but not compulsory. During the first 3 months, HF treatments were optimised according to the 2012 European Society of Cardiology guidelines.[4] In the following 6 months no further optimisation was undergone unless necessary for changes in clinical status (maintenance phase). At 9 months, all clinical and laboratory assessments from baseline were repeated. Patients were then followed-up till April 1st, 2015. The primary outcome was time to first of all-cause death or HF hospitalisation. HF hospitalisations were reported by sites but not adjudicated. The study complied with the Declaration of Helsinki. The local ethics committee approved the research protocol, and all patients provided written informed consent.

Patients and biomarkers

In the current study, patients with HFrEF (EF<40%) and biomarkers measurements at both baseline and month 9 were included. All the biomarkers considered in our analysis are listed in **Table 1**. Assay characteristics have been previously reported (5).

Statistical analyses

Baseline characteristics were reported as frequencies (percentages) if categorical and as mean $\pm$ standard deviation or median (interquartile range) if continuous. Median biomarker levels at baseline vs. month 9 were compared by the Wilcoxon-Mann-Whitney test. A p-value <0.05 was considered statistically significant. As index date we considered the date of the second biomarkers levels measurement (at 9 months from the baseline).

Changes in biomarkers levels were included in the analyses as the percent variation between the 2 consecutive measurements (% Δ biomarker levels = [9-month biomarker level − baseline biomarker level]/baseline biomarker level * 100). Changes in biomarkers levels were modelled as a quantitative predictor of outcome. Specifically, we used restricted cubic splines to flexibly model potential nonlinearity (3 knots at fixed percentiles). The associations between changes

in biomarkers and outcome was assessed by Cox proportional regressions according to 2 different sequential models. In Model 1, which was performed separately for each biomarker, we included the change in biomarker levels from baseline to month 9, the baseline levels of the biomarker and the compact BIOSTAT risk score for 2-year mortality and HF hospitalisation.[6] This risk score included age, previous HF hospitalisation in the last year peripheral oedema, systolic blood pressure, eGFR, log-BUN, log-NT-proBNP, haemoglobin, sodium, HDL and beta-blocker use at baseline.[6] Adjustment for multiple testing with the Holm method was used.[7] In Model 2 we assessed which changes in biomarkers were independently and significantly associated with prognosis on top of all the others (Wald test $p<0.05$). In this model we included those biomarkers whose changes in levels were associated with the risk of outcome with p-value <0.05 after Holm correction in Model 1. The discriminatory power for biomarkers was assessed by C-statistic.

Because practical criteria for changes in biomarkers as surrogate endpoints would likely have some cut-off rather than a continuous change, for those biomarkers whose changes in levels over the time were significantly associated with outcome in Model 1, we also repeated the analysis modelling the change as categorical instead of as restricted cubic splines, i.e. ≤ -50%, -50 to -25%, ≥-25% to ≤+25% (reference, labelled as 0%, i.e. no change), +25 to +50% and ≥ +50%.

Not all patients included in this study had N-terminal pro-B-type natriuretic peptide (NT-proBNP) measured. Therefore, changes in NT-proBNP were not assessed in the main analysis, but included in a sensitivity analysis performed on 246 patients with complete data for baseline and 9-month NT-proBNP levels.

Several BIOSTAT-CHF patients were excluded from our analyses due to the lack of repeated biomarker measurements. Thus, in order to evaluate the presence of a potential mortality bias, in a sensitivity analysis we compared characteristics of patients who did have repeated measurements vs. those who did not. All the statistical analyses were run by R version 3.5.1.

Table 1. Biomarker measurements at Baseline and at Month 9, absolute and percent variations over the time.

Biomarker	Baseline (median [IQR])	Month 9 (median [IQR])	Absolute difference (Baseline – Month 9) (median [IQR])	% difference (Baseline – Month 9)	p-value
NT-proBNP (ng/L)	3688.00 [1948.00, 7185.00]	1550.00 [586.00, 4010.00]	-960.30 [-3437.00, 234.50]	**-42.38 [-75.21, 15.20]**	< 0.0001
ANP (ng/mL)	18.31 [11.22, 28.62]	23.42 [13.15, 35.94]	4.38 [-2.80, 13.86]	**26.98 [-15.59, 86.77]**	< 0.0001
BNP (pg/mL)	187.80 [75.31, 395.05]	126.86 [46.21, 322.97]	-13.39 [-174.56, 74.87]	**-12.75 [-67.81, 79.85]**	< 0.0001
ESAM (ng/mL)	62.36 [56.24, 69.45]	67.28 [61.36, 74.57]	5.57 [-1.04, 12.20]	**8.70 [-1.45, 20.04]**	< 0.0001
LTßR (ng/mL)	0.14 [0.09, 0.21]	0.16 [0.11, 0.23]	0.02 [-0.02, 0.06]	**17.36 [-10.63, 58.08]**	< 0.0001
Mesothelin (ng/mL)	52.42 [46.39, 59.68]	56.39 [48.21, 65.34]	3.54 [-2.72, 11.60]	**6.81 [-4.98, 23.06]**	< 0.0001
MPO (ng/mL)	27.70 [23.08, 35.08]	28.57 [23.60, 35.78]	0.92 [-5.48, 7.13]	**3.34 [-17.69, 29.80]**	< 0.0001
Neuropilin (ng/mL)	20.31 [15.98, 25.60]	22.25 [17.57, 27.52]	1.69 [-2.18, 6.27]	**9.34 [-10.60, 33.85]**	< 0.0001
NT-proCNP (pg/mL)	5.20 [5.20, 12.17]	8.50 [3.23, 16.10]	-0.51 [-1.98, 6.00]	**-5.80 [-38.00, 81.48]**	< 0.0001
Osteopontin (ng/mL)	207.29 [169.38, 248.68]	218.20 [181.68, 257.55]	13.17 [-22.54, 47.70]	**6.39 [-9.96, 27.29]**	< 0.0001
PCT (pg/mL)	13.29 [4.55, 29.28]	18.51 [10.19, 34.02]	3.70 [-4.67, 13.74]	**32.53 [-23.05, 158.79]**	< 0.0001
PSAP-ß (ng/mL)	30.59 [21.75, 36.73]	28.66 [19.79, 37.65]	-0.64 [-9.20, 8.71]	**-2.00 [-29.53, 33.58]**	< 0.0001
VEGFR-1 (ng/mL)	0.14 [0.14, 0.21]	0.16 [0.16, 0.22]	0.02 [-0.00, 0.03]	**12.51 [-0.96, 15.33]**	< 0.0001
D-dimer (ng/mL)	101.92 [101.92, 129.62]	98.91 [98.91, 98.91]	-3.01 [-3.01, -3.01]	**-2.95 [-2.95, -2.95]**	< 0.0001
Pentraxin-3 (ng/mL)	1.84 [1.10, 3.10]	1.79 [1.21, 2.68]	0.03 [-0.92, 0.76]	**2.11 [-38.73, 65.95]**	0.067
PIGR (ng/mL)	110.06 [67.29, 177.31]	182.00 [109.48, 316.45]	65.34 [11.14, 161.03]	**70.41 [11.55, 163.50]**	< 0.0001
RAGE (ng/mL)	2.67 [1.87, 3.91]	2.98 [2.26, 4.11]	0.41 [-0.47, 1.21]	**17.25 [-16.01, 59.48]**	< 0.0001
Syndecan-1 (ng/mL)	1.95 [0.99, 3.52]	2.45 [1.46, 3.75]	0.38 [-0.71, 1.60]	**28.59 [-28.35, 130.06]**	< 0.0001
TNF-R1α (ng/mL)	0.92 [0.53, 1.52]	1.11 [0.67, 1.77]	0.18 [-0.19, 0.64]	**24.12 [-20.22, 98.73]**	< 0.0001
Troy (ng/mL)	0.21 [0.12, 0.37]	0.29 [0.17, 0.48]	0.07 [-0.03, 0.21]	**39.66 [-11.13, 123.14]**	< 0.0001

Table 1. Continued

Biomarker	Baseline (median [IQR])	Month 9 (median [IQR])	Absolute difference (Baseline – Month 9) (median [IQR])	% difference (Baseline – Month 9)	p-value
GDF-15 (ng/mL)	3.25 [2.61, 4.08]	3.67 [2.78, 4.77]	0.37 [-0.36, 1.28]	**12.35 [-11.38, 42.53]**	< 0.0001
proADM (ng/mL)	0.44 [0.29, 0.69]	0.61 [0.40, 0.96]	0.15 [-0.01, 0.37]	**40.99 [-1.53, 104.61]**	< 0.0001
sST2 (ng/mL)	6.98 [3.29, 15.05]	7.87 [4.44, 13.84]	0.97 [-3.39, 4.73]	**20.98 [-38.22, 117.54]**	0.0028
WAP-4C (ng/mL)	1.22 [0.68, 2.34]	1.22 [0.62, 2.64]	-0.04 [-0.52, 0.67]	**-5.05 [-39.09, 62.61]**	0.207
Periostin (ng/mL)	5.67 [3.31, 9.25]	7.48 [4.82, 12.17]	1.71 [-0.71, 4.44]	**36.76 [-10.05, 108.39]**	< 0.0001
Angiogenin (ng/mL)	4712.31 [3224.45, 7358.54]	2707.91 [1802.12, 4152.87]	-1898.94 [-4129.76, -433.17]	**-44.82 [-65.69, -12.87]**	< 0.0001
Cystatin-c (ng/mL)	14909.84 [10256.28, 21550.40]	11671.57 [6568.59, 19649.23]	-2861.12 [-9402.52, 5237.27]	**-19.59 [-57.39, 43.99]**	< 0.0001
CRP (ng/mL)	11300.75 [4824.61, 23328.45]	4515.72 [2074.54, 9804.65]	-4694.93 [-15660.36, -0.43]	**-51.90 [-80.92, -0.23]**	< 0.0001
GAL-3 (ng/mL)	19.84 [14.53, 27.08]	22.96 [18.08, 30.02]	3.14 [-2.44, 7.91]	**18.32 [-10.14, 50.39]**	< 0.0001
NGAL (ng/mL)	54.36 [35.77, 87.70]	83.51 [56.53, 133.40]	28.61 [2.53, 59.96]	**59.09 [4.53, 130.59]**	< 0.0001

Abbreviations. NT-proBNP: N-terminal pro-B-type natriuretic peptide; ANP: Atrial natriuretic peptide; ESAM: Endothelial cell-selective adhesion molecule; LTßR: Lymphotoxin ß receptor; MPO: myeloperoxidase; NT-proCNP: N-terminal pro-C-type natriuretic peptide; PCT: Procalcitonin; PSAP-ß: Prosaposin- ß; VEGFR-1: Vascular endothelial growth receptor; PIGR: Polymeric immunoglobulin receptor; RAGE: Receptor for advanced glycation end product; TNF-R1α: Tumor necrosis factor-receptor 1α; GDF-15: Growth differentiation factor; proADM: Pro-adrenomedulin; sST2: soluble ST2; WAP-4C: WAP 4-disulphide core domain protein HE; CRP: C-reactive protein; GAL-3: Galectin-3; NGAL: Neutrophil gelatinase-associated lipocalin.

Table 2. Patient characteristics at Baseline and at Month 9

	Baseline (N = 1327)*	Month 9 (N = 1327)*	P-value	N missing Baseline	N missing Month 9
Demographics/Organisational					
Age	66.8 (12.0)	67.5 (12.0)	< 0.0001	0	0
Sex (Female)	23.1%	23.1%	-	0	0
Previous hospitalisation	31.6%	31.6%	-	0	0
Smoking	15.1%	15.1%	-	1	1
Clinical					
BMI, kg/m^2	27.9 (5.2)	28.0 (5.6)	0.201	13	34
eGFR, mL/min/1.73 m^2	62.8 (23.6)	59.8 (24.9)	< 0.0001	114	428
Hb, g/dL	13.5 (1.8)	72.4 (16.0)	0.0026	164	570
Heart rate, bpm	79.1 (19.2)	13.3 (1.7)	< 0.0001	4	12
SBP, mmHg	125.0 (20.6)	124.4 (20.3)	0.227	2	12
DBP, mmHg	76.4 (12.6)	74.9 (12.0)	0.0006	2	13
MAP, mmHg	92.6 (13.9)	91.4 (13.4)	0.0071	2	14
NYHA, Class III/IV	56.9	24.2	< 0.0001	42	27
Comorbidities					
Smoking (Current)	15.1%	15.1%	-	1	1
Hypertension	61.3%	61.3%	-	0	0
Atrial fibrillation	41.1%	41.1%	-	0	0
COPD	16.1%	16.1%	-	0	0
Diabetes	30.4%	30.4%	-	0	0
Myocardial infarction	36.8%	36.8%	-	0	0
Stroke	8.3%	8.3%	-	0	0
PAD	9.0%	9.0%	-	0	0
Renal disease	21.6%	21.6%	-	0	0
Medication use					
Beta-blocker use	84.9%	94.2%	< 0.0001	0	0
Beta-blocker % target dose	25.0 [6.25, 50.0]	25.0 [12.5, 50.0]	< 0.0001	0	0
RASi use	76.3%	91.7%	< 0.0001	0	0
RASi % target dose	25.0 [7.63, 50.0]	50.0 [25.0, 100.0]	< 0.0001	0	0
Digoxin	17.6%	17.8%	0.872	0	3

Table 2. Continued

	Baseline (N = 1327)*	Month 9 (N = 1327)*	P-value	N missing Baseline	N missing Month 9
MRA	55.1%	60.0%	< 0.0001	0	3
Loop diuretics	99.5%	90.9%	< 0.0001	0	3
Device therapy (ICD or CRT)	17.1%	17.1%	-	0	0

*Categorical variables are reported as percentages, continuous variables as mean ± standard deviation except for RASi and Beta-blockers target doses that are reported as median [interquartile range].
Abbreviations: BMI: Body mass index; eGFR: Estimated glomerular filtration rate; Hb: Haemoglobin; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; NYHA: New York heart association; COPD: Chronic obstructive pulmonary disease; PAD: Peripheral artery disease; RASi: Renin-angiotensin-system; MRA: Mineralocorticoid receptor antagonist; ICD: Implantable cardioverter defibrillator; CRT: Cardiac resynchronisation therapy.

Results

Baseline characteristics

Of 2,516 patients enrolled in BIOSTAT-CHF, 1,327 had HFrEF and repeated biomarker measurements (i.e. at baseline and month 9) and thus were included in our analysis (**Supplementary Figure 1**).

Table 1 reports median (IQR) baseline and 9-month biomarkers levels, together with the absolute and percent variations in concentrations between the 2 assessments. In particular, median concentrations of 2 of 30 biomarkers did not significantly change over the time, 8 of 30 showed a significant decrease and 20 of 30 an increase in median levels. Patient characteristics are reported in **Table 2**. Mean age was 67±12 years and 23% were female.

Prognostic impact of changes in biomarkers levels

Over a median follow-up of 1.12 [IQR: 0.69 – 1.54] years after the 9 month (i.e. 2nd biomarker measurement), 253 of 1,327 (19%; 17 per 100 patient-years) patients experienced a hospital admission for HF or died.

In Model 1, after adjustments for baseline biomarker concentrations and the BIOSTAT risk score, changes in 17 of 30 biomarkers were separately associated with reduced risk of outcome [Atrial natriuretic peptide (ANP), BNP, C-reactive

protein (CRP), Growth differentiation factor (GDF-15), N-terminal pro-C-type natriuretic peptide (NT-proCNP), Neuropilin, Osteopontin, Procalcitonin (PCT), Pentraxin-3, Polymeric immunoglobulin receptor (PIGR), Pro-adrenomedulin (proADM), Receptor for advanced glycation end product (RAGE), Soluble ST2 (sST2), Syndecan-1, Tumor necrosis factor-receptor 1α (TNF-R1α), Vascular endothelial growth receptor (VEGFR-1) and WAP 4-disulphide core domain protein HE (WAP-4C)] (modelled as splines in **Figure 1**; modelled as categorical variables in **Supplementary Table 1**). Conversely, changes in Angiogenin, Cystatin-c, D-Dimer, Endothelial cell selective adhesion molecule (ESAM), Galectin-3 (GAL-3), Lymphotoxin ß receptor (LTßR), Mesothelin, myeloperoxidase (MPO), neutrophil gelatinase associated lipocalin (NGAL), Periostin, Prosaposin-ß (PSAP-ß), and Troy did not predict subsequent outcomes (**Figure 2**).

Model 2 included all the biomarkers whose changes were associated with prognosis in Model 1, together with their baseline concentrations and the BIOSTAT risk score. Changes in ANP, CRP, sST2 and WAP-4C were independently associated with the risk of outcome on top of all the other biomarkers tested (**Figure 3**).

Discriminative power

In our study population, a model fitted with only the BIOSTAT risk score at baseline, i.e. not including baseline biomarkers other than NT-proBNP or changes in biomarkers, resulted in a c-statistic of 0.69 for HF hospitalisation or any death. **Table 3** shows the c-statistics of models including only the baseline biomarker levels and of the models including the change in biomarker adjusted for baseline biomarker levels (Model 1). Adding only the baseline biomarkers levels to the BIOSTAT risk score did not change the c-statistic for prediction of HF hospitalisation or any death. However, adding changes in biomarker levels over time did increase the predictive ability of the model for most of the investigated biomarkers. The c-statistic for Model 2 including all significant biomarkers from Model 1 was 0.717, while the best c-statistic was obtained in the model including only the significant biomarkers from Model 2, i.e. ANP, sST2, WAP-4C and CRP, with a value of 0.731.

NT-proBNP subset analysis

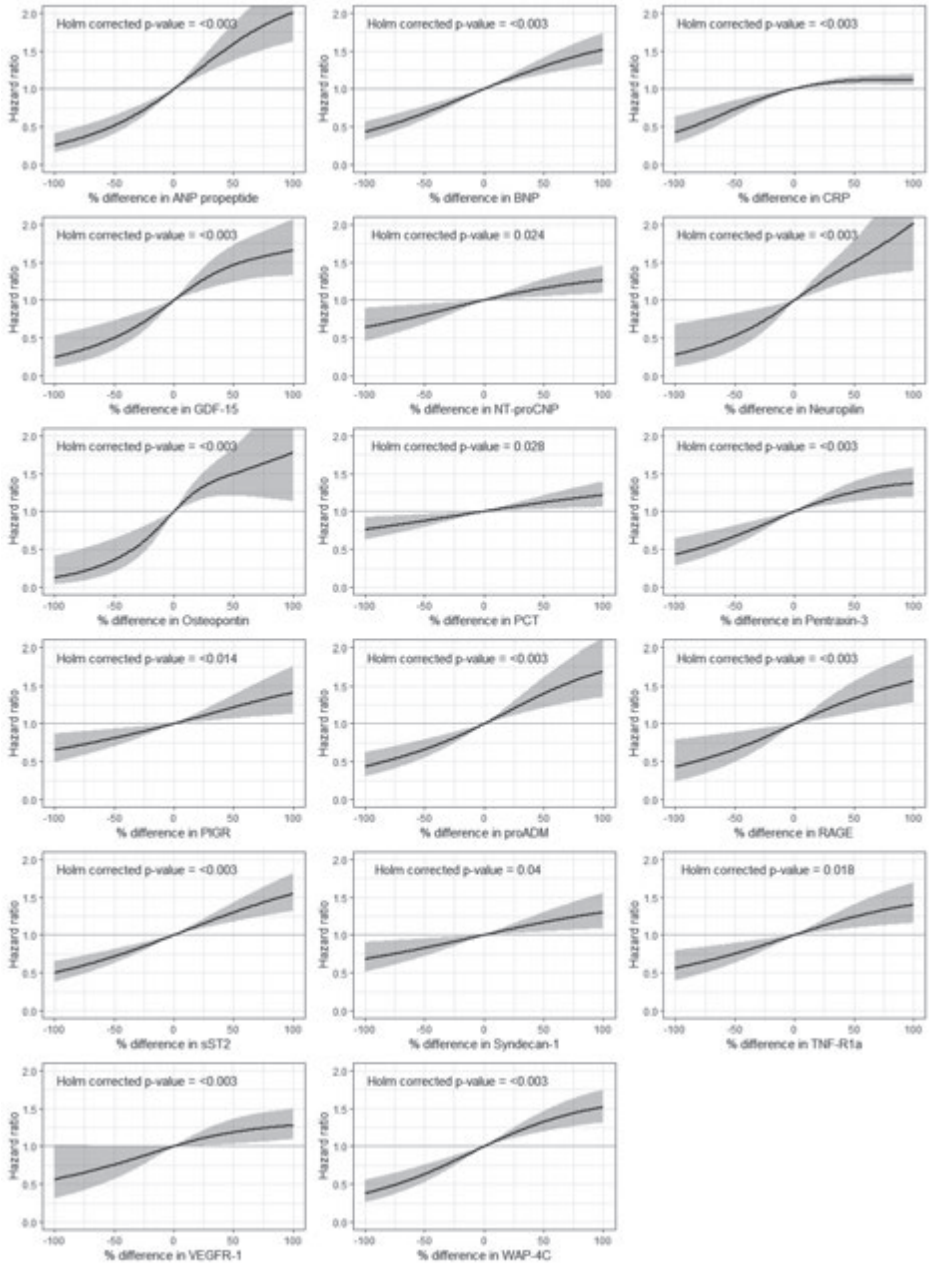
In the subset of patients with NT-proBNP levels collected, over a median follow-up of 1.21 (IQR: 0.72 – 1.57) years, 58 of 246 subjects (23%; 20 per 100 patients-years) experienced the occurrence of the outcome. Of 30 tested biomarkers in

sensitivity Model 1, NT-proBNP, ANP, CRP, sST2, BNP, Neuropilin, Pentraxin-3, and WAP-4C entered sensitivity Model 2 (**Supplementary Figure 2**). Among these, reductions in NT-proBNP and CRP were significantly and independently associated with improved prognosis in the multivariable sensitivity Model 2 (**Figure 4**). The c-statistic of the BIOSTAT risk model was 0.63 in this subset of patients with 2 NT-proBNP measurements. The discriminative power improved when change in NT-proBNP was added to the model to a c-statistic of 0.68. Change in CRP + baseline CRP levels added to the model resulted in a c-statistic of 0.66, while the multivariable model including both change in NT-proBNP and CRP + baseline biomarker levels resulted in a c-statistic of 0.69.

Sensitivity analysis

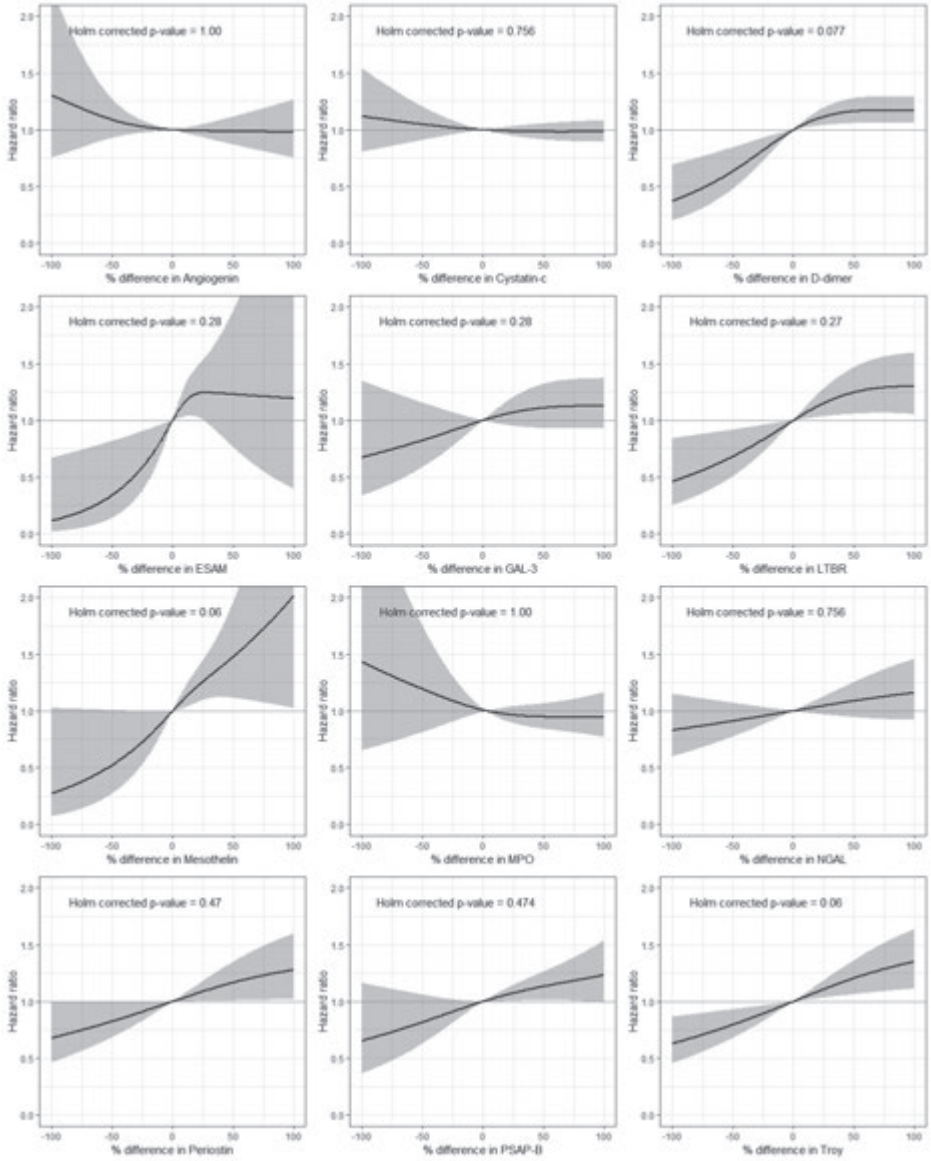
Supplementary Table 2 shows the comparison of baseline characteristics between patients with vs. without repeated biomarker measurements. Those who had only one measurement were generally older, more often had NYHA class III/IV, device therapy, previous hospitalisation in the last year, higher NT-proBNP levels, and more often had comorbidities and lower use of beta-blockers and RASi.

Figure 1. Statistically significant associations between continuous percent changes in biomarkers levels from Baseline to Month 9 and subsequent risk of all-cause death/heart failure (HF) hospitalisation, adjusted for the BIOSTAT risk score and baseline biomarker levels but not for other biomarkers (Model 1).



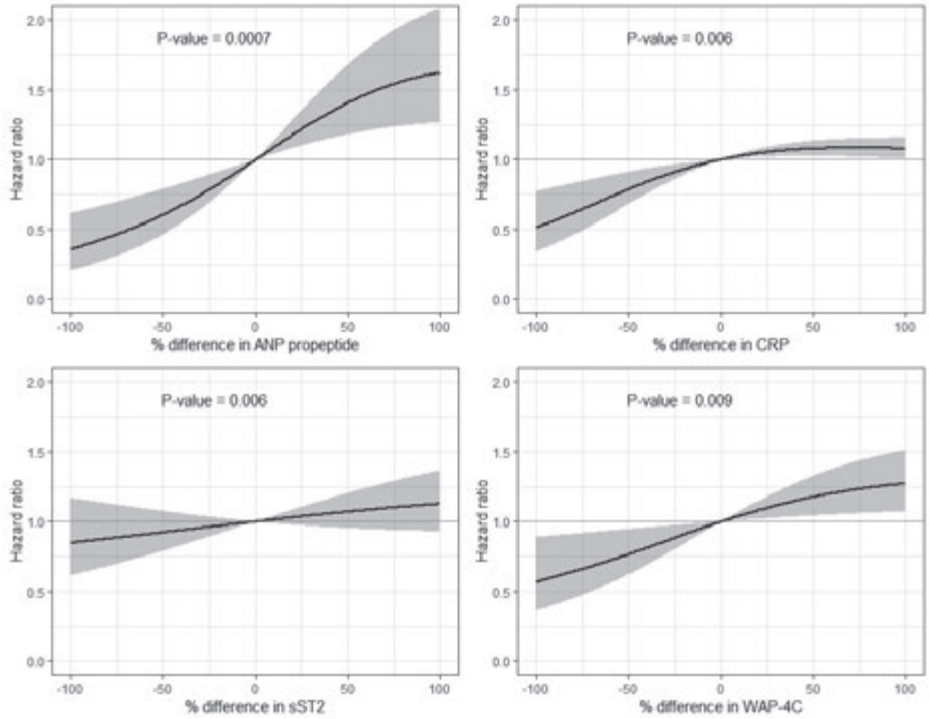
Hazard ratios adjusted for baseline biomarker levels and the BIOSTAT risk score. Abbreviations as in Table 1.

Figure 2. Non-statistically significant associations between continuous percent changes in biomarkers levels from Baseline to Month 9 and subsequent risk of all-cause death/heart failure (HF) hospitalisation, adjusted for the BIOSTAT risk score and baseline biomarker levels but not for other biomarkers (Model 1).



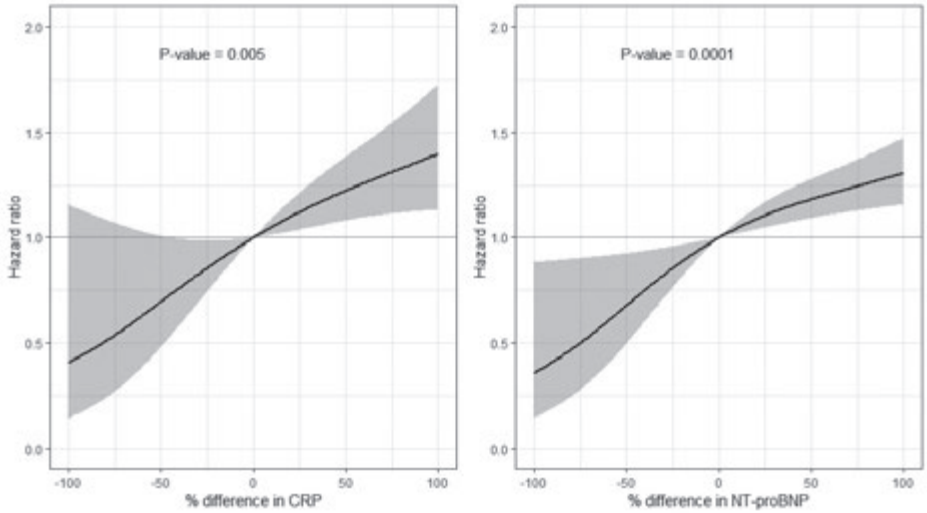
Hazard ratios adjusted for baseline biomarker levels and the BIOSTAT risk score. Abbreviations as in Table 1.

Figure 3. Percent changes in levels of biomarkers from Baseline to Month 9 independently and significantly associated with all-cause death/heart failure (HF) hospitalisation (Model 2).



All the changes in biomarkers levels significantly associated with all-cause death/HF hospitalisation at Model 1 entered Model 2 together with their baseline levels and BIOSTAT risk score. Hazard ratios adjusted for baseline biomarker levels, percentage change in biomarker levels (from Model 1, listed in **Figure 1**) and the BIOSTAT risk score Abbreviations as in Table 1.

Figure 4. Percent changes in levels of biomarkers from Baseline to Month 9 independently and significantly associated with prognosis (Model 2) at the sensitivity analysis (subset of patients with no missing data for N-terminal pro-B-type natriuretic peptide).



Subset of patients with N-terminal pro-B-type natriuretic peptide measured (n = 246 patients with n = 69 events). Hazard ratios adjusted for baseline biomarker levels, percentage change in biomarker levels (from Model 1, listed in **Supplementary Figure 2**) and the BIOSTAT risk score. Abbreviations as in Table 1.

Table 3. C-statistics for the change in biomarker + baseline biomarker + BIOSTAT risk model compared to the BIOSTAT risk model alone.

Model	**C-statistic**	
Biostat Risk Model	0.692	
	Baseline biomarker	**Baseline biomarker + change in biomarker (Model 1)**
	C-statistic	**C-statistic**
+ ANP (ng/mL)	0.688	0.713
+ BNP (pg/mL)	0.695	0.707
+ Neuropilin (ng/mL)	0.689	0.703
+ NT-proCNP (pg/mL)	0.688	0.690
+ Osteopontin (ng/mL)	0.694	0.697
+ PCT (pg/mL)	0.686	0.694
+ VEGFR-1 (ng/mL)	0.696	0.702
+ Pentraxin-3 (ng/mL)	0.685	0.693
+ PIGR (ng/mL)	0.689	0.696
+ RAGE (ng/mL)	0.686	0.697
+ Syndecan-1 (ng/mL)	0.692	0.693
+ TNF-R1α (ng/mL)	0.691	0.694
+ GDF-15 (ng/mL)	0.687	0.701
+ proADM (ng/mL)	0.688	0.693
+ sST2 (ng/mL)	0.689	0.708
+ WAP-4C (ng/mL)	0.691	0.707
+ CRP (ng/mL)	0.691	0.700
	Multivariable model with baseline biomarkers	**Multivariable model with baseline biomarker + change in biomarker (Model 2)**
+ all above biomarkers	0.676	0.717
+ ANP, sST2, WAP-4C and CRP	0.683	0.731

Abbreviations as in Table 1.

Discussion

In the HFrEF patients enrolled in BIOSTAT-CHF, 9-month improvements in concentrations of ANP, BNP, CRP, GDF-15, NT-proCNP, Neuropilin, Osteopontin, PCT, Pentraxin-3, PIGR, proADM, RAGE, sST-2, Syndecan-1, TNFR-1, VEGFR-1, and WAP-4C were associated with reduced risk of subsequent all-cause mortality or HF hospitalisation after adjustments for corresponding baseline levels and other patient characteristics. Among these biomarkers, changes in CRP, ANP, sST2 and WAP-4C predicted prognosis independently of all the others, and the model including only these 4 biomarkers had the best discriminatory power with an AUC of 0.731. In the sensitivity analysis, changes in NT-proBNP and CRP predicted the outcome independently of all the other biomarkers and their baseline levels. However, adding baseline and changes in CRP to the model including changes in NT-proBNP and BIOSTAT model did not improve discriminatory power. The discriminatory power of changes in biomarkers (AUCs up to 0.731) may at a first glance not appear any better than that of many single measurement single or composite biomarkers or risk scores (AUCs generally in the low 0.70's in HF). However, it is actually remarkable that changes in biomarkers could achieve AUCs above 0.70 *on top of* baseline biomarkers, clinical characteristics and risk scores. It is not unexpected that a baseline biomarker reflecting severity of HF correlates with outcomes, but a onetime measurement cannot be used to estimate treatment efficacy. In contrast, if a change in a biomarker can correlate with outcomes with an AUC >0.70, then this may be a highly relevant surrogate for a potential treatment effect.

Need for surrogate end-points in HFrEF

The use of surrogate endpoints in RCTs is convenient and necessary in early phase non-outcomes driven clinical trials since it reduces the sample size and thus the number of subjects exposed to pharmacological compounds that may not be beneficial or may be even harmful, and reduces the trial duration from years to months and thus the overall costs. Furthermore, use of surrogate endpoints in trials provides important mechanistic insights about the drug under investigation. However, treatments usually target multiple pathways and thus may have multiple effects, and there is continued misunderstanding of the difference between risk markers (associations) and risk factors (causality).[8,9] Consequently, assessing the efficacy of a drug focusing only on one intermediate effect, i.e. one surrogate endpoint targeting only one pathway, may lead to neglecting other beneficial or even harmful effects. Indeed, inappropriate

surrogate endpoints may lead to positive phase II trials followed by neutral (or negative) phase III trials, and to negative phase II trials preventing consequent successful phase III trials.

Thus, there is a critical need for feasible surrogate endpoints in HF.[1] Indeed, changes in hemodynamic measurements, quality of life, left ventricular performance and exercise capacity have been inconsistently shown to be associated with prognosis.[10,11] Among neurohormones, worse prognosis has been reported in patients with higher norepinephrine concentrations and with increasing norepinephrine levels over time.[12] However, RCTs showed that inotropes, although significantly reducing norepinephrine levels over the time, also increased the risk of mortality, excluding a role of norepinephrine as potential surrogate endpoint.[11,13,14] Both BNP and NT-proBNP concentrations have been associated with mortality and HF hospitalisation risk in patients with HFrEF.[15,16] However, although meta-analyses of RCTs reported a link between a reduction in natriuretic peptides levels over the time and reduced risk of HF hospitalisation, similar findings were not shown for mortality risk.[17,18] Additionally, whether NT-proBNP/BNP guided therapy may be a beneficial approach in HFrEF patients is still debated, with several RCTs and meta-analyses reporting contrasting results.[19,20] These observations raise important questions regarding the use of natriuretic peptides in phase II RCTs for decision making regarding phase III RCTs.

Potential surrogate end-points in HFrEF

Previous studies have reported a prognostic role for natriuretic peptides plasma concentrations and improved prognosis associated with a reduction in natriuretic peptides levels over the time.[15-18] Our analysis contributes to stress a potential use for biomarkers linked with the cardiomyocyte stretch/injury pathophysiological domain as surrogates for hard outcomes in trials. Indeed, we showed an association between reductions in both ANP, BNP and NT-proBNP levels over the time and improved overall mortality/HF hospitalisation after adjustment for patients' characteristics and baseline biomarker levels. Additionally, changes in ANP, BNP and NT-proBNP improved discrimination for any death/HF hospitalisation on top of baseline levels of these biomarkers. Surprisingly, changes in ANP predicted prognosis on top of changes in BNP and with higher discrimination, although ANP is not currently considered as an interesting biomarker because of its instability and shorter half-time (3-5 minutes) compared to BNP (23 minutes) and NT-proBNP (120 minutes).[21] Further, in our

sensitivity analysis we observed changes in NT-proBNP predicting prognosis on top of BNP and ANP, and thus, according to our data, it may be the preferred choice as surrogate endpoint among the other natriuretic peptides. However, a previous study showed midregional proANP (MR-proANP) outperforming BNP and NT-proBNP in the prediction of death, potentially due to the even higher biological stability of this molecule (i.e. lower short-term variability compared to BNP and no degradation/polymerisation vs. NT-proBNP).[22] Whether this finding may be extended to changes in MR-proANP remains unknown. However, the higher predictive and discriminative power of changes in ANP vs. changes in BNP shown in our study, together with the previous evidence of the prognostic superiority of MR-proANP vs. NT-proBNP and BNP, may suggest to adopt surrogates targeting atrial rather than ventricular cardiomyocyte stretch.

The link between HF and inflammation has been extensively investigated. According to the current HF with preserved EF (HFpEF)/HFrEF paradigm, comorbidities may induce HFpEF by fostering microvascular inflammation and endothelial activation that affect the adjacent cardiomyocytes, leading to cardiac abnormalities.[23] Conversely, direct cardiomyocyte injury (i.e. acute myocardial infarction, toxicity, etc) may be more determinant in HFrEF pathogenesis.[23] Recent findings from BIOSTAT-CHF support this paradigm, showing higher levels of inflammatory biomarkers in HFpEF vs. higher levels of biomarkers linked with cardiac stretch in HFrEF.[5] However, inflammation is not limited to HFpEF. Indeed, in HFrEF it is linked with atherosclerosis and ischaemic heart disease and, notably, increased wall stress and ventricular remodelling in failing heart triggers inflammatory processes.[24]

Previous studies showed CRP, a major inflammatory mediator, predicting mortality and morbidity independently of ischaemic/non-ischaemic aetiology and BNP levels in patients with HFrEF, thus a prognostic role for CRP in HFrEF has been hypothesised.[25] Our analysis reported changes in several inflammatory biomarkers predicting prognosis in HFrEF. In particular, a reduction of CRP over the time, together with decreases in natriuretic peptides, sST2 and WAP-4C levels, predicted improved prognosis on top of all the other biomarkers tested. Whether treatments reducing CRP levels affect also hard outcomes is still debated. Indeed, in GISSI trial, rosuvastatin reduced CRP levels vs. placebo but did not affect morbidity/mortality in HF.[26] In CORONA, enrolling HFrEF patients aged ≥60 years, although rosuvastatin significantly reduced CRP levels by 32% over a median follow up of 33 months, it had no significant impact on

the risk of the primary outcome (cardiovascular death, non-fatal myocardial infarction or stroke) but significantly reduced the number of cardiovascular and HF hospitalisations.[27] Atorvastatin use has also been shown to be associated with significantly reduced levels of CRP over the time, and in the Treating to New Target (TnT) trial higher dose of atorvastatin significantly reduced the risk of HF hospitalisation, in particular in those with pre-existing HF (28). Given that a *reduction* in CRP was associated with lower risk in the present study, but *reducing* CRP in these trials was not, CRP may very well represent a marker of some other drive of poor prognosis.

Our analysis reports also evidence supporting a potential role for WAP-4C and sST2 as prognostic marker and surrogate endpoint in HFrEF. Indeed, we showed that on top of all the other tested biomarkers, a reduction of both WAP-4C and sST2 over 9-month follow-up was associated with improved prognosis, and adding changes in levels of each of these biomarkers to a model including patient characteristics and corresponding biomarker baseline levels improved discrimination for all-cause death/HF hospitalisation. Previous studies report higher WAP-4C concentrations independently predicting increased risk of all-cause death/HF hospitalisation in HF populations including mainly HFrEF patients.[29,30] WAP-4C is a protein with antimicrobial and immunomodulatory properties and an accepted biomarker for ovarian carcinoma.[31] Its role in HF has not been fully elucidated but may be linked to inflammation and immunomodulation. Whether changes in WAP-4C levels over the time may predict HF treatments' effect requires future investigation and this question and similar questions on novel surrogate endpoints can quite feasibly be addressed in ancillary studies in future trials. High sST2 levels have been linked with mechanically overloaded cardiac myocytes and reflect myocardial stress, ventricular remodeling and fibrosis, but also inflammation, which are pathways heavily involved in HFrEF.[3] In the PARADIGM-HF and PIONER-HF, changes in sST2 levels over the time predicted outcome and, at the same time, biomarker levels were significantly reduced by sacubitril/valsartan vs. enalapril.[32,33] Our and trials findings strongly suggest a role for sST2 as surrogate endpoint in phase II HFrEF trials.

Study limitations

We tested the association between changes in several biomarker levels and outcomes, thus there could be chance of false positive findings although we did adjust for multiple testing in our main analysis. We did not have repeated

NT-proBNP measurements in the overall cohort, so changes in NT-proBNP levels were tested only in a smaller subset of patients. Finally, our analysis could be prone to mortality bias. Indeed, at the sensitivity analysis we showed that patients with 2 biomarker levels measurements were less sick as compared with those with only the baseline assessment.

Conclusions

In HFrEF, an improvement over time in the concentrations of several biomarkers was associated with reduced mortality/morbidity. In particular, 9-month changes in ANP, NT-proBNP, CRP, sST2 and WAP-4C predicted the outcome on top of baseline levels of these biomarkers, patient characteristics and all the other biomarkers tested. It may be premature to formally incorporate changes in these or any other biomarkers as primary endpoints in phase II trials. However, phase II trials do indeed take place in most drug (and other interventions) development programs; and sponsors must make decisions regarding continued development based on these imperfect phase II trials. Therefore, we suggest that in considering the totality of the evidence, use of changes in these biomarkers may add incremental utility for sponsors and other stake holders in assessing the potential benefit of an intervention and making decisions whether to continue development and engage in costly outcomes and/or pivotal trials.

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Supplemental material

Supplementary Table 1. Hazard Ratios (HR) and 95% Confidence Intervals (95% CI) for the associations between categorical percent changes in biomarkers levels from Baseline to Month 9 and risk of all-cause death/heart failure (HF) hospitalisation, adjusted for the BIOSTAT risk score and baseline biomarker levels (Model 1).

Biomarkers	% change biomarkers	N	HR (95% CI)*	p-value
ANP	≤ - 50%	137	0.49 (0.26, 0.94)	0.031
	- 50% to -25%	141	0.41 (0.22, 0.78)	0.007
	≥-25% to ≤25%	367	1 (ref)	
	25% to 50%	157	1.42 (0.93, 2.16)	0.101
	≥ 50%	525	1.94 (1.41, 2.66)	<0.001
BNP	≤ - 50%	478	0.39 (0.26, 0.58)	<0.001
	- 50% to -25%	122	0.68 (0.41, 1.11)	0.123
	≥-25% to ≤25%	236	1 (ref)	
	25% to 50%	80	1.02 (0.60, 1.72)	0.946
	≥ 50%	411	1.21 (0.87, 1.69)	0.262
CRP	≤ - 50%	681	0.58 (0.41, 0.83)	0.003
	- 50% to -25%	178	0.90 (0.59, 1.36)	0.609
	≥-25% to ≤25%	228	1 (ref)	
	25% to 50%	42	1.06 (0.52, 2.15)	0.869
	≥ 50%	198	1.03 (0.69, 1.53)	0.894
GDF-15	≤ - 50%	41	0.79 (0.34, 1.84)	0.590
	- 50% to -25%	141	0.82 (0.50, 1.35)	0.439
	≥-25% to ≤25%	655	1 (ref)	
	25% to 50%	208	1.42 (1.00, 2.02)	0.051
	≥ 50%	282	1.80 (1.32, 2.44)	<0.001
NT-proCNP	≤ - 50%	18	0.40 (0.10, 1,62)	0.199
	- 50% to -25%	134	0.55 (0.34, 0.89)	0.016
	≥-25% to ≤25%	737	1 (ref)	
	25% to 50%	234	1.15 (0.81, 1.64)	0.436
	≥ 50%	204	1.98 (1.39, 2.81)	<0.001
Neuropilin	≤ - 50%	143	0.43 (0.24, 0.77)	0.004
	- 50% to -25%	414	0.91 (0.63, 1.31)	0.606
	≥-25% to ≤25%	251	1 (ref)	
	25% to 50%	77	0.94 (0.54, 1.64)	0.822
	≥ 50%	442	1.15 (0.82, 1.60)	0.427
Osteopontin	≤ - 50%	9	0.63 (0.08, 4.82)	0.658
	- 50% to -25%	115	0.57 (0.33, 0.97)	0.039

Supplementary Table 1. Continued

Biomarkers	% change biomarkers	N	HR (95% CI)*	p-value
	≥-25% to ≤25%	841	1 (ref)	
	25% to 50%	226	1.21 (0.87, 1.70)	0.261
	≥ 50%	136	1.50 (0.96, 2.33)	0.072
PCT	≤ - 50%	129	0.98 (0.62, 1.54)	0.923
	- 50% to -25%	198	1.11 (0.68, 1.80)	0.685
	≥-25% to ≤25%	304	1 (ref)	
	25% to 50%	95	1.56 (0.93, 2.60)	0.092
	≥ 50%	601	1.42 (1.01, 1.98)	0.043
Pentraxin-3	≤ - 50%	232	0.71 (0.45, 1.11)	0.132
	- 50% to -25%	215	0.92 (0.62, 1.38)	0.700
	≥-25% to ≤25%	366	1 (ref)	
	25% to 50%	117	1.12 (0.68, 1.86)	0.659
	≥ 50%	397	1.65 (1.20, 2.27)	0.002
PIGR	≤ - 50%	48	0.61 (0.24, 1.53)	0.289
	- 50% to -25%	88	0.88 (0.47, 1.63)	0.686
	≥-25% to ≤25%	280	1 (ref)	
	25% to 50%	135	0.75 (0.44, 1.30)	0.310
	≥ 50%	776	1.47 (1.04, 2.06)	0.027
proADM	≤ - 50%	68	1.10 (0.57, 2.11)	0.780
	- 50% to -25%	114	1.44 (0.87, 2.38)	0.154
	≥-25% to ≤25%	348	1 (ref)	
	25% to 50%	204	1.29 (0.81, 2.06)	0.281
	≥ 50%	593	2.31 (1.65, 2.23)	< 0.001
RAGE	≤ - 50%	65	0.58 (0.28, 1.19)	0.135
	- 50% to -25%	187	0.58 (0.37, 0.93)	0.022
	≥-25% to ≤25%	478	1 (ref)	
	25% to 50%	208	1.38 (0.94, 2.03)	0.101
	≥ 50%	389	1.51 (1.10, 2.07)	0.010
sST2	≤ - 50%	250	0.54 (0.34, 0.86)	0.010
	- 50% to -25%	164	0.73 (0.45, 1.19)	0.203
	≥-25% to ≤25%	263	1 (ref)	
	25% to 50%	108	1.33 (0.81, 2.20)	0.265
	≥ 50%	542	1.62 (1.14, 2.31)	0.007
Syndecan-1	≤ - 50%	180	0.45 (0.26, 0.77)	0.004
	- 50% to -25%	181	1.01 (0.66, 1.54)	0.958
	≥-25% to ≤25%	287	1 (ref)	

Supplementary Table 1. Continued

Biomarkers	% change biomarkers	N	HR (95% CI)*	p-value
	25% to 50%	108	1.42 (0.92, 2.19)	0.117
	≥ 50%	571	1.10 (0.79, 1.52)	0.588
TNF-R1α	≤ - 50%	105	0.45 (0.24, 0.84)	0.013
	- 50% to -25%	190	0.60 (0.39, 0.91)	0.018
	≥-25% to ≤25%	374	1 (ref)	
	25% to 50%	146	0.66 (0.41, 1.05)	0.076
	≥ 50%	512	1.09 (0.81, 1.46)	0.572
VEGFR-1	≤ - 50%	108	0.78 (0.43, 1.42)	0.416
	- 50% to -25%	114	1.15 (0.73, 1.80)	0.556
	≥-25% to ≤25%	796	1 (ref)	
	25% to 50%	66	1.08 (0.61, 1.92)	0.782
	≥ 50%	243	1.69 (1.26, 2.26)	<0.001
WAP-4C	≤ - 50%	227	0.60 (0.38, 0.94)	0.026
	- 50% to -25%	222	0.81 (0.52, 1.24)	0.332
	≥-25% to ≤25%	386	1 (ref)	
	25% to 50%	110	1.30 (0.80, 2.09)	0.287
	≥ 50%	382	1.68 (1.23, 2.30)	0.001

* HR (95% CI) = hazard ratio (95% confidence interval); Hazard ratios adjusted for baseline biomarker levels and the BIOSTAT risk score (Model 1).[¶] Abbreviations as in Table 1.

Supplementary Table 2. Baseline patient characteristics of patients with and without repeat measurements (i.e. both at Baseline and Month 9)

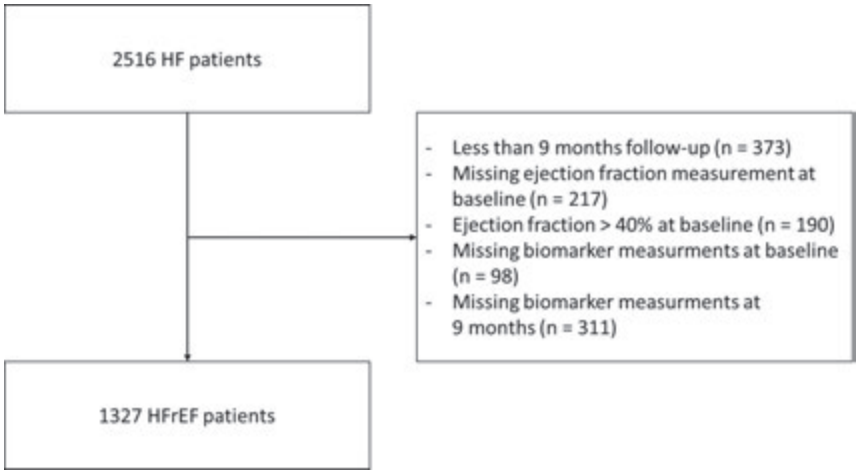
	No repeated measurements	Repeated measurements	p-value
n	558	1331	
Demographics			
Age (mean (sd))	70.14 (11.59)	66.79 (12.02)	<0.001
Sex (Female (%))	145 (26.0)	309 (23.2)	0.220
Smoking (Current (%))	73 (13.1)	203 (15.3)	0.235
HF related measurments			
NYHA (Class III/IV (%))	380 (69.9)	745 (56.9)	<0.001
Previous hospitalisation (%)	212 (38.0)	419 (31.5)	0.007
Device therapy (%)	123 (22.0)	227 (17.1)	0.013
NT-proBNP (mean (sd))	3682.0 [1732.0, 7710.5]	2143.5 [941.8, 4522.5]	<0.001
Ischaemic aetiology (Yes (%))	350 (62.7)	737 (55.4)	0.004
Peripheral oedema (Yes (%))	403 (72.2)	791 (59.4)	<0.001

Supplementary Table 2. Continued

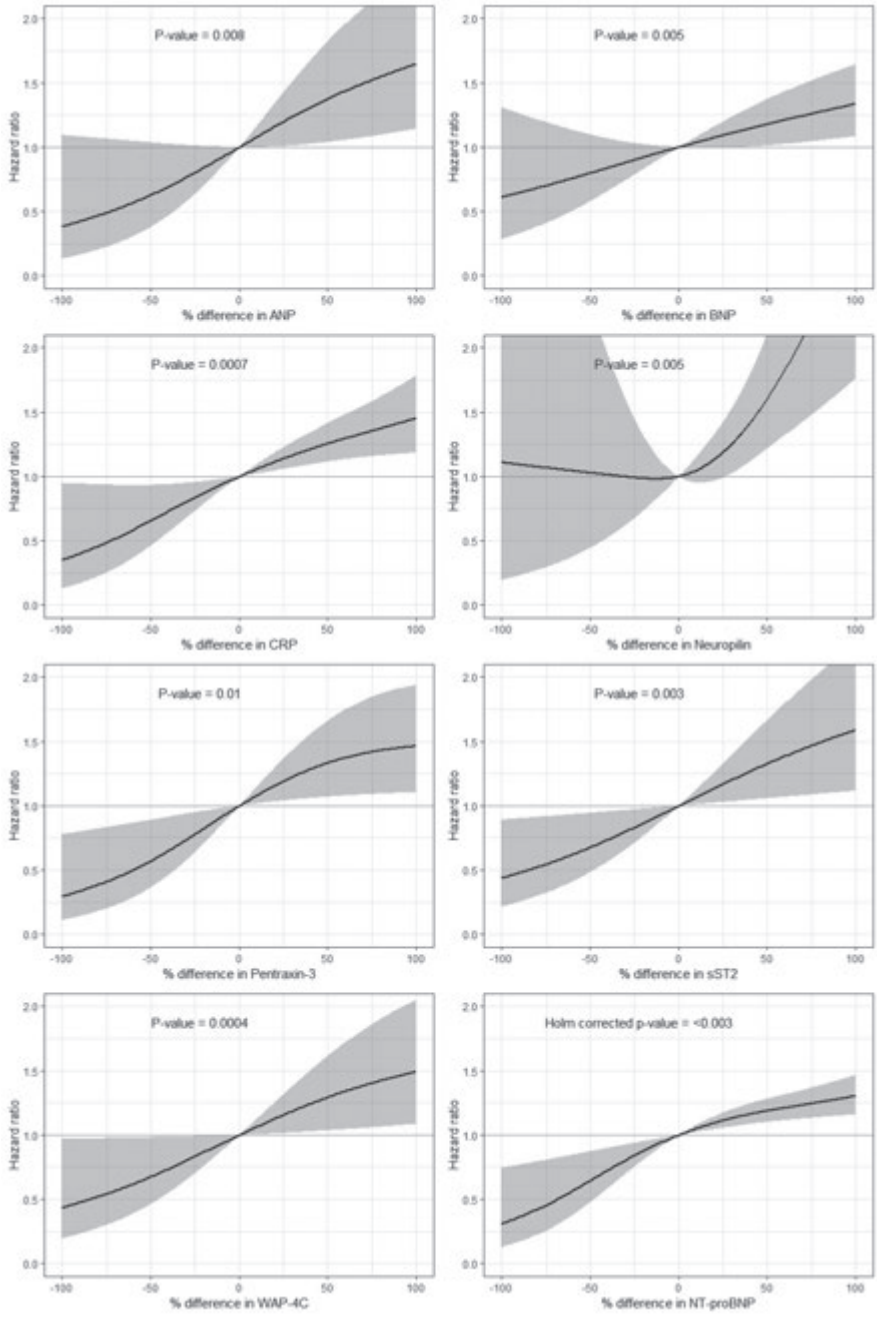
	No repeated measurements	Repeated measurements	p-value
Clinical measurements (mean (sd))			
BMI (kg/m2)	27.34 (5.48)	27.88 (5.19)	0.041
eGFR (mL/min/1.73 m2)	56.64 (22.27)	63.78 (22.34)	<0.001
hb (g/dL)	12.91 (1.97)	13.52 (1.78)	<0.001
Heart rate (bpm)	80.35 (18.20)	79.09 (19.13)	0.188
SBP (mmHg)	121.77 (21.42)	125.06 (20.57)	0.002
DBP (mmHg)	73.32 (12.24)	76.40 (12.61)	<0.001
HDL (mmol/L)	1.07 (0.40)	1.12 (0.38)	0.046
Sodium (mmol/L)	138.91 (4.51)	139.55 (3.62)	0.002
Comorbidities (%)			
Hypertension	342 (61.3)	816 (61.3)	1.000
AF	271 (48.6)	546 (41.0)	0.003
COPD	106 (19.0)	215 (16.2)	0.152
Diabetes	210 (37.6)	405 (30.4)	0.003
MI	257 (46.1)	489 (36.7)	<0.001
Stroke	62 (11.1)	110 (8.3)	0.061
PAD	69 (12.4)	120 (9.0)	0.033
Renal disease	200 (35.8)	289 (21.7)	<0.001
Medication use			
Beta-blocker use (%)	449 (80.5)	1130 (84.9)	0.021
Beta-blocker % target dose (median [IQR])	12.50 [4.16, 36.22]	25.00 [6.25, 50.00]	0.001
RAS-inhibitor use (%)	378 (67.7)	1014 (76.2)	<0.001
RAS-inhibitor % target dose (median [IQR])	25.00 [0.00, 50.00]	25.00 [7.14, 50.00]	<0.001
Aldosterone-inhibitor (%)	307 (55.0)	733 (55.1)	1.000
Loop diuretics (%)	556 (99.6)	1325 (99.5)	1.000
Digoxin (%)	115 (20.6)	234 (17.6)	0.138

Abbreviations: BMI: Body mass index; eGFR: Estimated glomerular filtration rate; Hb: Haemoglobin; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; NYHA: New York heart association; COPD: Chronic obstructive pulmonary disease; PAD: Peripheral artery disease; RASi: Renin-angiotensin-system; MRA: Mineralocorticoid receptor antagonist; ICD: Implantable cardioverter defibrillator; CRT: Cardiac resynchronisation therapy.

Supplementary Figure 1. Flow chart reporting patients' inclusion



Supplementary Figure 2. Sensitivity analysis: statistically significant associations between continuous percent changes in biomarkers levels from Baseline to Month 9 and risk of all-cause death/heart failure (HF) hospitalisation, adjusted for the BIOSTAT risk score and baseline biomarker levels but not for other biomarkers (Model 2), at the sensitivity analysis.



Subset analysis in patients with N-terminal pro-B-type natriuretic peptide measured (n = 246 patients with n = 69 events). Hazard ratios adjusted for baseline biomarker levels and the BIOSTAT risk score. Abbreviations as in Table 1.

CHAPTER 7

HEART FAILURE CHARACTERISTICS, TREATMENT AND SURVIVAL: A EUROPEAN COMPARISON

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Abstract

Background. International comparisons of healthcare systems might yield important knowledge of distinct differences in quality of care and outcomes. We harmonised and studied heart failure (HF) care in three different real-world datasets across Europe with respect to case mix, medication use and survival.

Methods and results. 13,334 patients from the CALIBER resource in the UK, 18,862 patients from ABUCASIS in Spain and 11,050 patients from the Swedish HF registry were selected. All patients were included at first HF registration between 2010 and 2016. Data was harmonised between the countries with ICD (International Classification of Diseases) codes. Age and sex distribution was similar across countries, with a median age of 80 years and 45-54% women. Cardiovascular risk factors and co-morbidities were most prevalent in Spanish HF patients with higher rates of hypertension, COPD, diabetes, chronic renal disease, valvular disease and cancer. Medication use was not consistent across the countries, with more RAS-inhibitors and beta-blockers prescribed in Sweden and more MR-antagonists and diuretics prescribed in Spain. We found a higher crude all-cause mortality in Spain compared to Sweden and the UK.

Conclusions. Despite highly similar age and sex distribution, there are differences between case mix, medication use and crude survival of heart failure patients across three different countries in Europe. International data harmonisation is needed to be able to assess the quality of care and outcomes across Europe. Implementation of a common data model is key to achieve this goal. This study might stimulate an initiative to improve interoperability of databases across Europe.

Introduction

International comparisons of healthcare systems might yield important knowledge of distinct differences in quality of care and outcomes. Data already shows that cancer, ischaemic heart disease and myocardial infarction survival could be improved in the United Kingdom (UK), suggesting that the performance of the health care system could be improved.[1] The healthcare system in Spain, like most other European countries, has had to deal with the economic recession and cutbacks on government healthcare expenditure. However, the Spanish population has actually seen a decrease in self-reported health problems related to socioeconomic inequalities over the last 10 years and cardiovascular risk factors have stabilised.[2] Healthcare in Sweden has been regarded as high quality, however with life expectancy and aging population increasing, it is testing the quality of the current health system.[3,4]

The Institute of Medicine (IOM) recommends that more attention should be given to cardiovascular diseases (CVD) in comparative effectiveness research.[5] In 2015, there were 6.1 million new cases of CVD in the European Union, with the absolute number of CVD cases increasing over time.[6] One of the main presentations of CVD is heart failure (HF), with a prevalence in the UK estimated at 500.000 patients, and in Spain and Sweden around 2% of the population having HF.[7,8] HF is associated with mortality exceeding most cancers, with 5-year survival ranging between 20-50% and frequent (re)hospitalisations.[9–14]

Limited information is known about differences in HF care in Europe. Comparison between European countries is complicated by differences in patient characteristics, also called case mix. The aim of this study was to compare the case mix, medication use and survival of heart failure patients between Sweden, Spain and the UK.

Methods

Data sources

In the UK, patients were selected from the CALIBER resource, which is a research platform consisting of reproducible data variables extracted from three linked databases: The Clinical Practice Research Datalink (CPRD) with primary care electronic health records (EHR), Hospital Episodes Statistics (HES) containing coded diagnoses and surgical procedures from inpatient hospital admissions,

and the Office for National Statistics (ONS) registry containing cause-specific mortality data. CALIBER has previously been described in detail.[15] Briefly, information is available for 5 million UK residents consisting of diagnoses, blood laboratory results, prescriptions, cause of death and more. Preceding work has shown that these patients are representative of the general population in the UK.[16–18]

In Sweden, we selected patients from the Swedish heart failure registry (SwedeHF). This registry was established in 2000 and broadly implemented throughout Sweden by 2003. SwedeHF has been previously described in detail.[19] The only inclusion criterion is clinician-judged HF. Patients are registered at discharge from hospital or after outpatient clinic visit on a web-based care report form and entered into the database (managed by Uppsala Clinical Research Center, Uppsala, Sweden). All permanent residents in Sweden have unique personal identification numbers that allows linking of disease-specific health registries and governmental health and statistical registries. For the current analysis, we linked SwedeHF to the National Patient Registry and the Cause of Death Registry, which provided data on baseline comorbidities, cause-specific outcomes (i.e. HF readmission) and all-cause mortality. In SwedeHF, patients do not provide written informed consent, but are informed of entry into national quality registries and allowed to opt out.

Lastly, in Spain, patients were selected from ABUCASIS, a regional EHR platform in Valencia. The sample was recruited from beneficiaries of the Valencian Health Agency's universal health care system, a population of 3,799,885 people older than 18 years in 2012. Data was extracted using the health information exchange function of ABUCASIS for the period of time between 1st January 2012 and 31st December 2016. ABUCASIS includes information on patient demographics, medications, vital status, past medical history and laboratory data among others. Patients' data collected from the system during the study were documented by a process of pseudo-anonymization and posterior anonymization. The data generated during the study was handled according to the Spanish Law 3/2018 of Data Protection and Guaranty of Digital Rights and corresponding European norms.

Ethical approval was obtained in all countries. In the UK, this study was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency (protocol 18_159), in Sweden by the

Ethical Review Board of SwedeHF and in Spain by the Committee for Ethics and Clinical Trials of the Hospital Clinico of Valencia.

Study population

Patients were included at their first hospital record of HF between 1 January 2010 and 31 December 2015 in Sweden and the UK, while in Spain patients were included between 1 January 2012 and 31 December 2016. The first hospital record was considered a patient's index date. HF hospitalisations were defined based on the ICD-10 classification (International Statistical Classification of Diseases) in the UK, ICD-9 in Spain and in Sweden all patients recorded in the registry had clinician-judged HF. Because information was also obtained in primary care with regard to clinical variables and medication, patients in the UK and Spain were to have a HF diagnosis recorded in primary care as well. All ICD codes can be found in **Table S1**. All patients were eligible for inclusion if they were aged 35 years or older and had a minimum follow-up ≥ 1 day. Patients were censored at the earliest date from the last data collection date, the date of death or at the study end date.

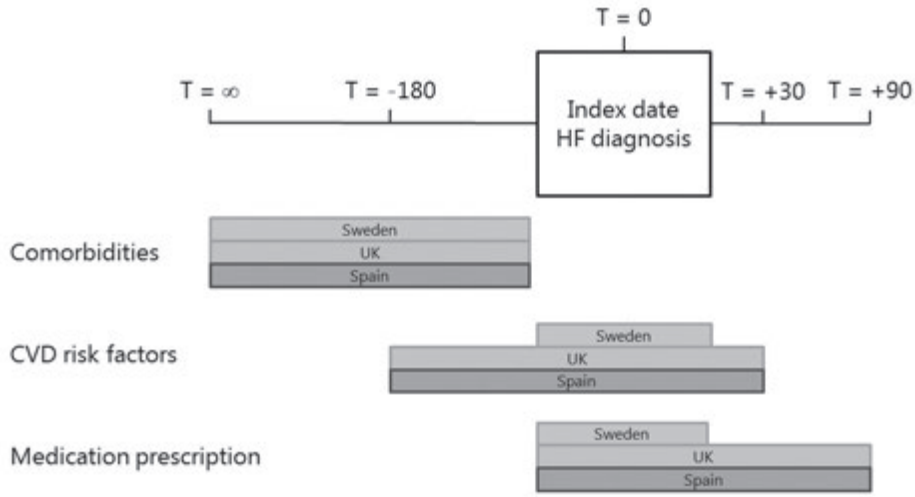
Case mix variables

Baseline patient characteristics were based on EHR records prior to index date in the UK and Spain and at the date of registration in Sweden, including demographics (age, sex), cardiovascular risk factors (smoking, BMI, diastolic blood pressure (DBP), systolic blood pressure (SBP), creatinine, haemoglobin, and estimated glomerular filtration rate (eGFR)), comorbidities (a medical history of atrial fibrillation, chronic obstructive pulmonary disease (COPD), diabetes, hypertension, ischaemic heart disease, stroke/transient ischaemic attack (TIA), cancer [in the past three years] and valvular disease) and medication prescription, classified as: RAS-inhibitors (Angiotensin converting enzyme-inhibitors and/or angiotensin II receptor blockers), beta-blockers, mineralocorticoid receptor-antagonists (MR-antagonists) and diuretics. Anaemia was defined as haemoglobin < 120 g/L for women and <130 g/L for men.

Figure 1 shows the timing of the measurement selection. Cardiovascular risk factors were obtained in primary care in the UK and Spain, and from the registry in Sweden. In primary care (Spain and UK) we selected the closest measurement to index date between 180 days before up to 30 days after index date, in the registry data entered in the SwedeHF database at patient registration was used. Comorbidities were defined based on ICD-10 classification (International

Statistical Classification of Diseases) in the UK and Sweden, while in Spain ICD-9 classification was used, records all time before up to index date were used to define medical history. Medication prescription in Sweden was entered in the database at patient registration, while in the UK and Spain this information was obtained from prescription data with CPRD product codes and Anatomical Therapeutic Chemical (ATC) classification respectively. Records in the UK and Spain between index date and up to 90 days after index date were used to define prescription use. Definitions of all variables can be found in **Table S1**.

Figure 1. Timing of the measurement selection in days.



T = Time; HF = Heart failure; CVD = Cardiovascular disease; UK = United Kingdom. In Sweden CVD risk factors and medication prescription were recorded at index date, i.e. hospital discharge.

Outcomes

Our primary outcome was all-cause death, which was obtained from the country-specific national death registries. We furthermore collected information all time HF readmission and 30-day HF readmission information. This was defined as the first HF hospitalisation since index date based on the ICD-10 classification in the UK and Sweden and ICD-9 classification in Spain (**Table S1**).

Statistical methods

Patient characteristics were summarised as mean (SD) or median [IQR] for continuous variables and percentages for categorical variables. The population distribution for each country was stratified by age and sex, with age categorised in 5-year intervals from 35 years to 95+ years. Unadjusted survival and HF

hospitalisation estimates were visualised with the Kaplan-Meier method for each country.

In a sensitivity analysis we applied an ejection fraction (EF) prediction model (*Uijl et al, unpublished;* **Chapter 8**) to predict EF subphenotypes based on EF>50%. The following variables were included in the prediction model: age, sex, comorbidities (history of ischemic heart disease, atrial fibrillation, COPD, diabetes, hypertension, anaemia, cancer in the previous 3 years and valvular disease), and treatments (device therapy [implantable cardioverter defibrillator or cardiac resynchronisation therapy], RAS-inhibitors, beta-blockers, diuretics, MRAs and digoxin).

All analyses were performed using R version 3.6.1.

Results

Heart failure case mix characteristics

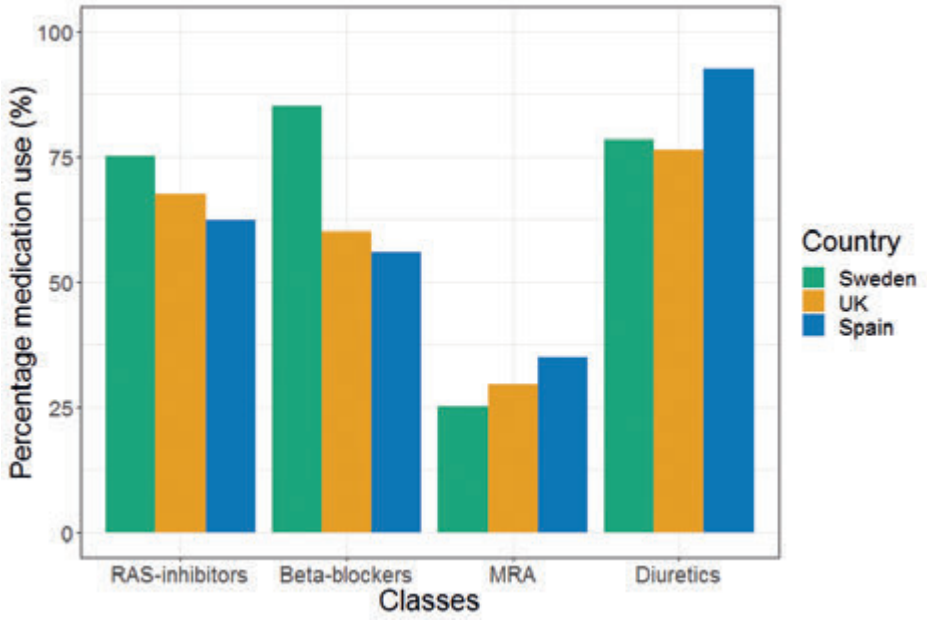
Case mix characteristics are summarised in **Table 1**. In Sweden we included 11,050 HF patients, in the UK 13,334 patients, and in Spain 18,862 patients. Median age was high, with Sweden at 79.0 years [69.0, 85.8], UK at 80.7 years [72.3, 86.9] and Spain at 79.2 years [74.0, 87.0]. Almost every country had an equal distribution of sex with 44%, 45% and 54% women for Sweden, UK and Spain respectively. Many HF patients had comorbidities, of which most common in all countries were hypertension, ischaemic heart disease and atrial fibrillation. Spain more frequently had patients with hypertension, COPD, diabetes, chronic renal disease, valvular disease and cancer compared to Sweden and the UK. While in Sweden more patients were revascularised compared to the UK and Spain. In the UK patients seemed to have less stroke/TIA in their medical history than in Sweden or Spain.

Table 1. Case mix characteristics in Sweden, UK and Spain.

	Sweden	UK	Spain
N	11,050	13,334	18,862
Age (Years, median [IQR])	79 [69, 86]	81 [72, 87]	79 [74, 87]
Sex (Female (%))	43.5	45.4	54.1
Clinical measurements			
DBP (mean (SD))	74 (13)	73 (12)	72 (14)
SBP (mean (SD))	129 (21)	128 (21)	131 (23)
BMI (mean (SD))	27 (6)	29 (7)	31 (6)
Creatinine (median [IQR])	92 [75, 117]	99 [79, 128]	96 [74, 127]
eGFR (median [IQR])	62 [44, 79]	56 [41, 72]	57 [40, 77]
Anaemia (%)	40.5	54.4	36.5
Comorbidities (%)			
Atrial Fibrillation	52.8	51.1	56.4
COPD	13.9	19.2	29.5
Diabetes	25.0	26.6	46.9
Hypertension	60.9	72.6	88.4
Ischaemic heart disease	49.4	51.5	37.2
Chronic renal disease	10.2	17.3	30.9
Stroke/TIA	16.0	6.8	20.9
Valvular disease	19.3	27.3	39.0
Cancer in the past 3 years	7.9	11.1	18.2
Procedures (%)			
Revascularisation	25.9	12.1	9.6
Device implantation*	2.6	2.8	4.3
Medication (%)			
RAS-inhibitors	75.2	67.5	62.4
Beta-blockers	85.1	60.2	56.0
MR-antagonists	25.2	29.6	35.1
Diuretics	78.5	76.4	92.5
Digoxin	15.2	20.1	16.6

*Device implantation = implantable cardioverter defibrillator or cardiac resynchronisation therapy. DBP = Diastolic Blood Pressure; SBP = Systolic blood pressure; BMI = Body Mass Index; eGFR = estimated Glomerular Filtration Rate; COPD = Chronic Obstructive Pulmonary Disease; TIA = Transient Ischaemic Attack.

Figure 2. Treatment for HF patients in Sweden, UK and Spain.



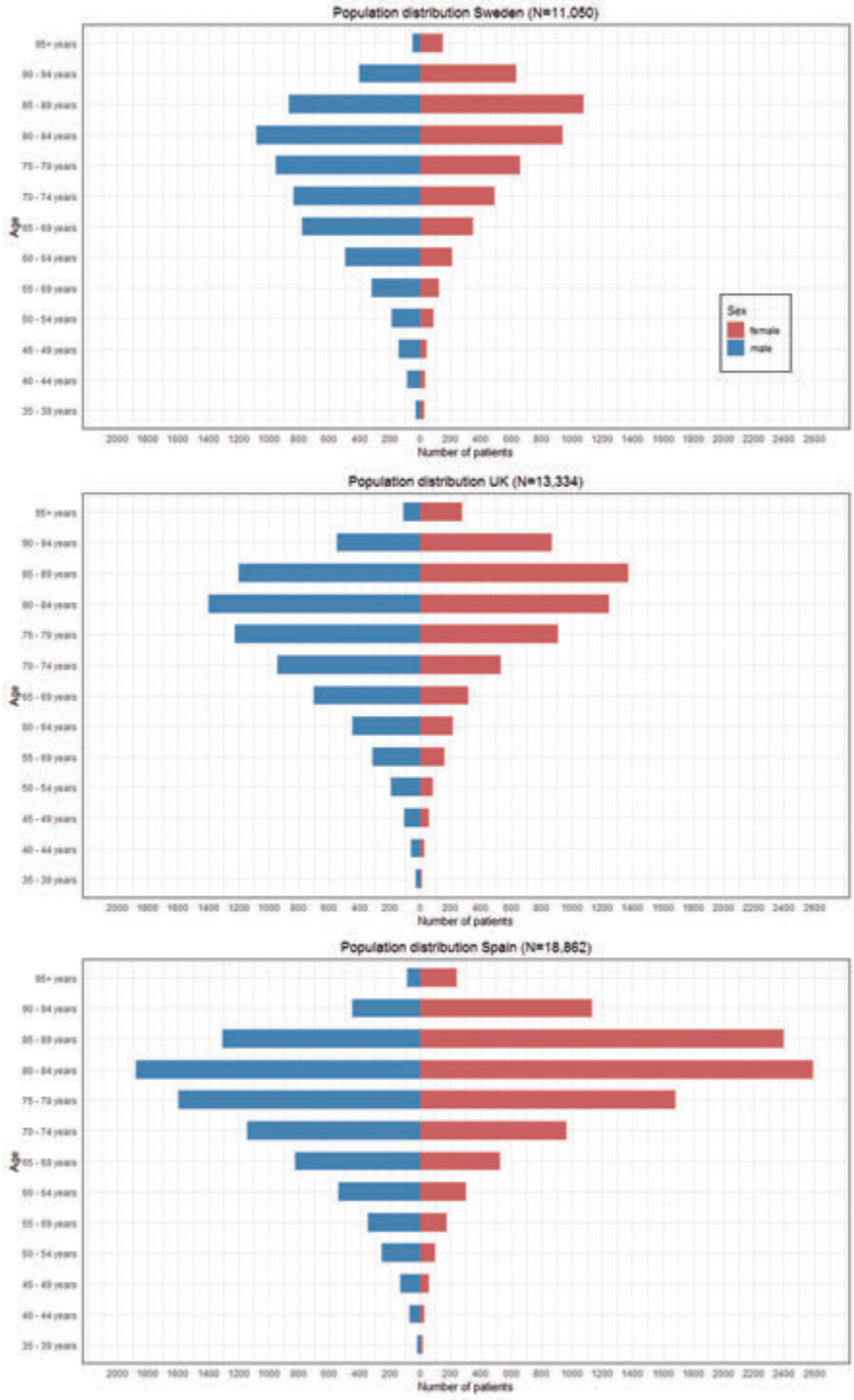
Medication prescription for heart failure patients

The highest proportion of RAS-inhibitor (75%) and beta-blocker (85%) use was observed in Sweden, however MR-antagonists were prescribed in a higher proportion of UK (30%) and Spanish patients (35%) (**Figure 2**). Diuretic were prescribed for most Spanish patients (92%) but was lower in Swedish (79%) and UK patients (76%).

Population distribution

The population distribution stratified by age and sex was similar for each country, shown in **Figure 3**. Male patients were slightly younger, whereas female patients tended to be older. Most male patients were between 80-84 years old, while female patients were 85-89 years old.

Figure 3. Population distribution of HF patients in Sweden, UK and Spain.



Unadjusted all-cause mortality

The median follow-up in Sweden was the longest, with 2.9 years [IQR 1.4-4.1], while the UK and Spain were very similar with 1.4 years [IQR 0.5-2.7] and 1.7 years [IQR 0.7-2.9] respectively. In Sweden 45.2% of patients died during follow-up, while in the UK 34.8% and in Spain 55.8% of patients died. 30-day patient readmission for HF was 10.1% in Sweden, 14.3% in the UK and 13.7% in Spain. Patients in Sweden and Spain had a median hospital stay of 5 days [IQR 3-8], while in the UK this was 6 days [IQR 2-13]. The Kaplan-Meier plot for all-cause mortality is shown in **Figure 4A**.

The 1-year risk for all-cause mortality was 20.7% (95% CI: 19.6-21.8%) in Sweden, 21.5% (95% CI: 20.8-22.2%) in the UK and 30.5% (95% CI: 29.8-31.1%) in Spain, the 3-year risk was 40.2% (95% CI: 39.2-41.2%) in Sweden, 42.8% (95% CI: 41.7-43.9%) in the UK and 56.8% (95% CI: 56.0-57.6%) in Spain, while the 5-year risk of all-cause mortality was 54.2% (95% CI: 53.1-55.3%) in Sweden, 57.6% (95% CI: 56.1-59.1%) in the UK and 72.4% (95% CI: 71.0-73.8%) in Spain.

Figure 4B. shows the Kaplan Meier plot for HF hospitalisation. The risk for 30-day rehospitalisation was 6.4% (95% CI: 5.9 – 6.9%) in Sweden, 14.2% (95% CI:13.6 – 14.8%) in the UK and 12.6% (95% CI: 12.1 – 13.1%) in Spain. The 1-year risk for rehospitalisation was 23.7% (95% CI:22.9 – 24.5%) in Sweden, 51.9% (51.0 – 52.8%) in the UK and in Spain it was 42.6% (95% CI: 41.8 – 43.3%). After the first year the rehospitalisation rate stabilised and the 5-year risk of rehospitalisation was 44.7% (95% CI: 43.5% - 45.9%) in Sweden, 82.1% (95% CI: 80.8 – 83.4%) in the UK and 61.6% (95% CI: 60.6 – 62.5%) in Spain.

Ejection fraction subphenotypes

HF patients were divided based on EF≥50%, baseline characteristics are shown in **Table 2**. EF was registered in Sweden, while in UK and Spain it was calculated based on a prediction model (*Uijl et al.,* **Chapter 8**). In Sweden EF was not recorded in 15.4% of patients, in the UK and Spain we were unable to calculate EF in 32.9% and 27.7% respectively. Of the patients with registered or calculated EF in Sweden, UK and Spain, 28%, 22% and 14% had an EF≥50% respectively.

Figure 4. Kaplan Meier curves for A. all-cause mortality and B. HF rehospitalisation in Sweden, UK and Spain.

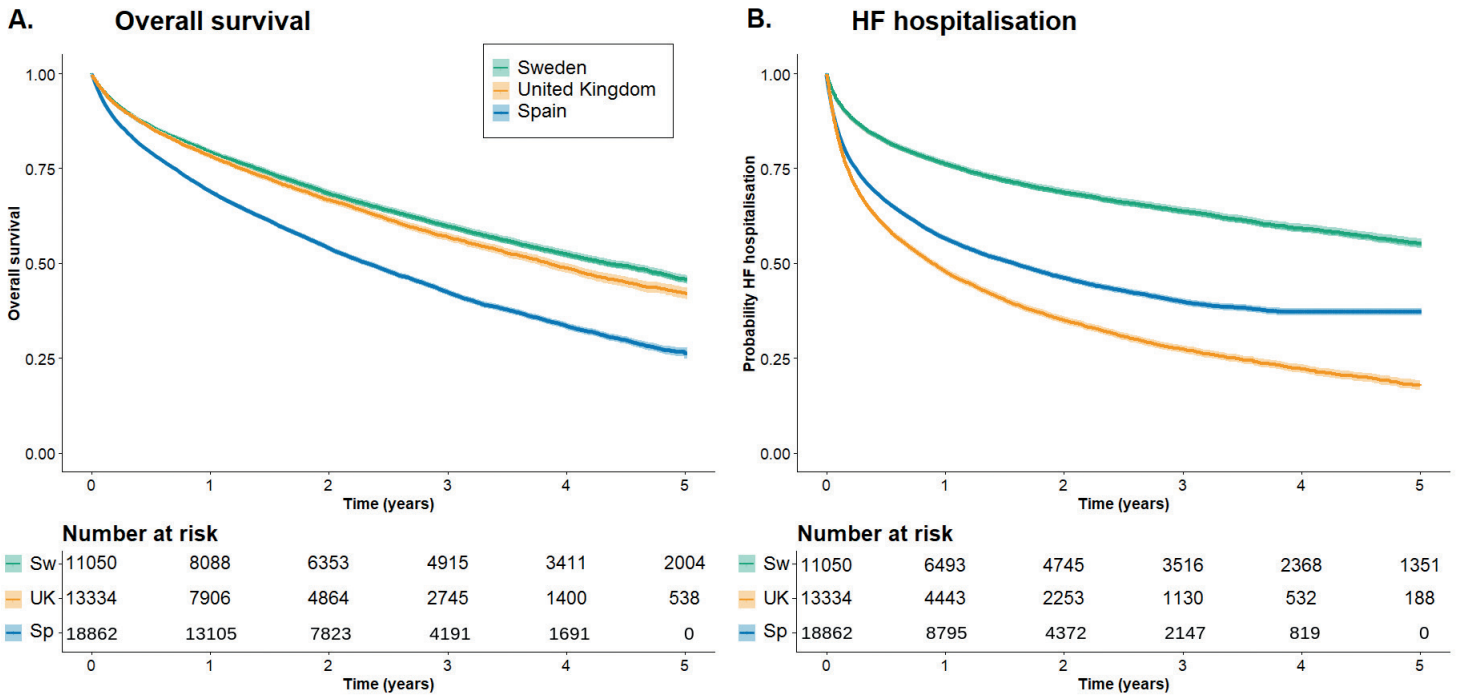


Table 2. Case mix characteristics in Sweden, UK and Spain, stratified by EF≥50%.

	Sweden		UK		Spain	
	EF<50	**EF≥50**	**EF<50**	**EF≥50**	**EF<50**	**EF≥50**
N	6736 (72%)	2614 (28%)	7015 (78.4%)	1928 (21.6%)	11760 (86.2%)	1885 (13.8%)
Age (Years, median [IQR])	75 [66, 83]	80 [73, 86]	79 [71, 86]	86 [80, 90]	80 [73, 86]	85 [80, 89]
Sex (Female (%))	35.3	56.2	36.2	78.1	54.1	55.3
Clinical measurements						
DBP (mean (SD))	74 (13)	73 (13)	72 (12)	72 (12)	73 (14)	70 (12)
SBP (mean (SD))	126 (20)	133 (22)	127 (21)	130 (21)	131 (23)	129 (21)
BMI (mean (SD))	26.6 (5.5)	27.5 (6)	28.6 (6.6)	27.1 (7.2)	30.9 (6.2)	29.7 (6.4)
Creatinine (median [IQR])	91 [75, 116]	92 [74, 119]	99 [80, 128]	99 [77, 137]	94 [73, 124]	104 [76, 141]
eGFR (median [IQR])	65 [48, 82]	58 [41, 76]	57 [42, 73]	49 [34, 66]	58 [41, 78]	50 [33, 69]
Anaemia (%)	36.9	46.5	51.4	65.7	48.0	63.3
Comorbidities (%)						
Atrial Fibrillation	48.7	60.1	48.6	64	53.7	72.3
COPD	12.1	17.8	17.2	27.9	26.5	49.9
Diabetes	24	28.3	28.9	27.4	47.1	46.4
Hypertension	55.8	71.0	70.7	85.9	86.9	96.4
Ischaemic heart disease	52.4	45.0	58.4	29.3	41.0	14.6
Chronic renal disease	9.2	12.0	17.5	26.5	17.7	27.6
Stroke/TIA	13.8	17.8	6.2	8.3	14.1	18.2
Valvular disease	18.4	26.6	29.8	41.5	37.6	47.4
Cancer in the past 3 years	7.5	9.0	15.2	19.7	16.8	26.8

Table 2. Continued

	Sweden		UK		Spain	
	EF<50	**EF≥50**	**EF<50**	**EF≥50**	**EF<50**	**EF≥50**
Procedures (%)						
Revascularisation	30.3	21.3	14.4	4.6	8.5	2.7
Device implantation*	3.6	1.1	3.6	0	2.4	0
Medication (%)						
RAS-inhibitors	84.4	64.2	80.6	20.0	71.3	6.2
Beta-blockers	90.2	79.0	71.5	21.2	63.6	8.5
MR-antagonists	27.5	24.1	35.2	14.7	38.1	16.9
Diuretics	74.9	83.8	81.7	69.1	94.1	82.7
Digoxin	15.1	14.8	20.5	21.1	16.8	15.8

*Device implantation = implantable cardioverter defibrillator or cardiac resynchronisation therapy.
DBP = Diastolic Blood Pressure; SBP = Systolic blood pressure; BMI = Body Mass Index; eGFR = estimated Glomerular Filtration Rate; COPD = Chronic Obstructive Pulmonary Disease; TIA = Transient Ischaemic Attack.

Patients in the subset of Sweden with measured EF were generally 5 years younger than those in Spain or the UK. In Sweden more patients with EF≥50% had ischaemic heart disease, which was comparable to those with EF<50%. In patients with EF<50% we observed almost 20% more women in Spain compared to Sweden and the UK. While in those with EF≥50% we observed over 20% more women in the UK compared to Sweden and Spain. RAS-inhibitor, beta-blocker and MR-antagonist use was lower in patients with EF≥50%, however the difference was much less pronounced in Sweden compared to the UK and Spain. In Sweden, patients with EF≥50% were prescribed more diuretics than patients with EF>50%, this was not observed in the UK or Spain.

Discussion

In this study we described the data harmonisation of real-world datasets to compare the case mix, medication use and survival of heart failure patients across three different countries in Europe. Patients in all three countries had similar age and sex distributions. Many HF patients had comorbidities, with Spanish patients more frequently having hypertension, COPD, diabetes, chronic renal disease, valvular disease and cancer compared to Sweden and the UK. Uptake of MRAs was lower in Sweden compared to the UK and Spain, while RAS-inhibitors and beta-blockers were more prescribed in Sweden compared to the other countries. Survival seemed to be similar for the UK and Sweden, but lower in Spain.

Heart failure case mix across Europe

In the case mix of HF patients in Europe, we found that HF in contemporary real-world data can be seen as a disease of the elderly, with a median age of 80 years old at first HF hospitalisation. Men and women were almost equally represented in all countries, but women were on average slightly older. The clinical measures blood pressure, creatinine and eGFR seem to be very similar across countries, however BMI seemed to be lower in Sweden than in the UK or Spain. A study from 2014 showed that more Swedes achieve the recommended 150 min of moderate-intensity physical activity compared to people in the UK and Spain.[20] This could potentially contribute to a lower BMI also observed in Swedish HF patients. Other lifestyle related factors such as diabetes and hypertension were also lower in Sweden and to an extend in the UK, compared to Spain. However, patients in Sweden seemed to have many cardiovascular related indications, such as ischaemic heart disease, a prior revascularisation or stroke, yet atrial

fibrillation (AF) occurred similarly across all countries. It is known that AF and HF often co-exist, with a prevalence estimated between 20-50%.[21,22] We found that consistently more than 50% of HF patients in Sweden, the UK and Spain had AF. When AF and HF are both present, it has been reported that these patients have poor prognosis and increased risk of stroke, emphasising there is a need for preventive and treatment strategies for these patients.[22,23] Of the non-cardiovascular comorbidities, patients in Sweden seemed to have less chronic renal disease and COPD than the UK or Spain. It is relevant to note that some differences between countries might be influenced due to differences in coding practice (i.e. first or secondary diagnosis or coding for billing purposes) and transition mapping between ICD-9 and ICD-10 code.[24] Lastly, it has been proposed that HFpEF / HFrEF proportions are 50% – 50% among real-world patients.[25] We found a 20% – 80% proportion in our study for EF≥50% and EF<50% respectively. The ESC HF Long-Term Registry shows similar proportions, as well as the MAGGIC cohort.[26,27] However, the Get With The Guideline registry shows a more even division across EF subphenotypes.[28] This could reflect the selection of inpatients into the study. Patients with HFpEF are commonly more seen in outpatient clinics for worsening HF, such as reported in community-based cohorts.[29,30]

Heart failure medication use in Europe

Sweden and Spain follow the European Society of Cardiology (ESC) guidelines for heart failure diagnosis and treatment, whereas in the UK the National Institute for Health and Care Excellence (NICE) are followed.[9,31] The ESC and NICE guidelines are similar, with diuretics for treating congestive symptoms and fluid retention for all patients, and HFrEF treatment consisting of RAS-inhibitors and beta-blockers, followed by MR-antagonists if a patient remains symptomatic.

In an international comparison of new health innovations, it was shown that Sweden is generally a high uptake country, whereas Spain and the UK were slow adoptors.[32] Unexpectedly, we found that Sweden had a lower proportion of patients on MR-antagonists than Spain and the UK, while the proportion of patients prescribed a RAS-inhibitor or beta-blocker is higher. In all data sources the prescription of diuretics was high. One of the reasons could be that Spanish and English patients might have more severe HF compared to those in Sweden, since diuretics and MR-antagonists are more often prescribed to patients with worse/symptomatic HF.[9] Another reason for potential differences in medication use could be related to the registry. In the UK and Spain, we included 3-month

follow-up after patient discharge from the hospital for medication prescription, this was done due to lag time between HF hospitalisation and medication prescription obtained from GP records, whereas in the Swedish registry, medication use is a snapshot at discharge. MR-antagonists are not the first line treatment in treatment guidelines (for HFrEF), but rather RAS-inhibitors and beta-blockers, it could be that MR-antagonists will be started later, after the patient has been up titrated with first line medication. Indeed, the ESC HF Long Term Registry shows that MR-antagonists are prescribed more often 1 year after HF discharge than directly after hospital discharge.[33]

In contrast to HFrEF patients, in HFpEF, patient comorbidities such as hypertension and atrial fibrillation should be managed accordingly. Several European studies have shown that RAS-inhibitor, beta-blocker and MRA use among HFpEF patients is generally high.[26,34–36] This was similar for Sweden, however not for Spain and the UK. A potential reason for this could be that there is a difference between registry patients and EHR patients. Even though the information we used to compare patients was obtained from the Swedish National Patient Registry (NPR), the patients that were included in the registry, compared to those in the NPR, were more often male, younger and had higher education. Enrolment in SwedeHF was associated with an increased survival, related to demographic difference and higher uptake of HF medication.[37] A second reason could be related to the EF prediction model, most medication uses were predictors for HFrEF, diuretics were the only predictors for HFpEF.

Outcomes of heart failure patients in Europe

There are many similarities between patients in Europe, such as an aging population, increase in CVDs, concomitant comorbidities, and in particular for HF: readmission and monitoring, which contributes to increases in healthcare expenditures and the economic burden on the healthcare system.[40,41] We observed a high morbidity among patients in Sweden, UK and Spain, with 6% in Sweden, 12% in Spain and 14% in the UK rehospitalised for HF within 30 days. This finding is similar for other European countries.[42]

In unadjusted survival analysis we observed a better survival of Swedish patients compared to Spanish or English patients. The ESC HF Long-term registry has previously shown that 1-year all-cause mortality was 24% for hospitalised patients, and has also shown that the risk of all-cause death was lower in northern regions vs. southern regions of Europe, however this finding was

potentially biased due to a much smaller number of patients in the northern region.[33] On the other hand the United States based Get With The Guidelines Registry showed a 1-year all-cause mortality rate of 35%.[38] Trends in the UK show that 1-year survival was 81.2% and 5-year survival was 51.8%, this improved over time, but less for inpatients than for outpatients.[39] In our study we found a 21% 1-year all-cause mortality rate for Sweden and the UK, however this was over 30% for Spain. These results thus confirm the trend seen in the ESC HF Long-Term registry. The higher risk of all-cause mortality might be related to differences in case mix, with more patients in Spain with chronic kidney disease, cancer and other comorbidities.

Data harmonisation

The UK, Swedish and Spanish data sources differ with regard to logical organisation, terminologies, vocabularies and coding schemes and their systematic analysis in a comparable manner is therefore challenging. To be able to compare patients from these different data sources the data had to be mapped into a common format. All terms were standardised according to ICD-codes, between Sweden and the UK there was an exact match as a result of both data sources using ICD-10 coding, however in Spain ICD-9 had to be mapped to their ICD-10 counterpart. Data standardisation in this study was a manual labour intensive process, therefore we suggest for future analyses between these data sources and others to transform the data to a Common Data Model (CDM).[43–45] In this process data from the individual data sources is converted to the CDM and the clinical terminologies are mapped using standard SNOMED (Systematized Nomenclature of Medicine) vocabularies, both ICD-10 and ICD-9, as well as procedural and medication codes can be mapped to the SNOMED vocabularies. The CDM preserves all data and codes from the original data source, but adds the standardised vocabulary to facilitate collaborative research across data platforms, resources and countries. The UK resource has previously been converted to the OMOP CDM and future plans include extending this work to Swedish and Spanish data.

Strengths and Limitations

This study has several strengths and limitations. First, in this large contemporary study we were able to collect information on more than 43,000 patients across Europe. Furthermore, we used common data definitions to define study variables across datasets. Several limitations should be addressed. First, we were unable to differentiate between HF phenotypes based on EHRs, since there was no

access to detailed echocardiography estimates to assess systolic function in Spain and the UK. We did however apply a prediction model based on SwedeHF to predict ejection fraction phenotypes in EHRs. Second, differences in healthcare that were not measured might explain differences between countries. Third, data sets had to be analysed separately and no data exchange took place at any point in time. Fourth, we were unable to gather information on dosage and adherence to drugs, which could explain more of differences in healthcare. Last, the inclusion criterion for SwedeHF is clinician-judged HF, which differs from the ICD definition of HF in EHRs.

Conclusions

In this study we compared the case mix, medication use and survival of heart failure patients across three different countries in Europe. Medication use was not consistent across the countries, with more RAS-inhibitors and beta-blockers prescribed in Sweden and more MR-antagonists and diuretics prescribed in Spain. We found a higher all-cause mortality in Spain compared to Sweden and the UK, which might be related to case-mix of baseline characteristics, with Spanish patients more frequently having hypertension, COPD, diabetes, chronic renal disease, valvular disease and cancer. International data harmonisation is needed to be able to assess the quality of care and outcomes across Europe. Implementation of a common data model is key to achieve this goal. This study might stimulate an initiative to improve interoperability of databases across Europe.

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Supplemental material

Table S1. Coding for all variables

	ICD-10 codes	ICD-9 codes
Heart failure	I50, I11, I13.0, I13.2, I26.0	428, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 402.01, 402.11, 402.91, 415.0
CV comorbidities		
Atrial fibrillation/flutter	I48	427.3, 427.31, 427.32
Hypertension	I10, I11, I12, I13, I15	401, 402, 403, 404, 405
Ischemic Heart Disease	I20, I21, I22, I23, I24, I25	410, 411, 412, 413, 414, 429
Stroke	I61, I62, I63, I64	430, 431, 432, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436
Transient Ischemic Attack	G458, G459, I639	435, 435.8, 435.8
Valvular disease	I05, I06, I07, I08, I34, I35, I36, I37, I38, I39, Q22, Q23	394, 395, 396, 397, 424, 746
Revascularised: CABG, PCI	OPCS: Z955, K40, K41, K42, K43, K44, K45, K46, K49, K50, K75	E87.82, V45.82
Devices	OPCS: K59	V45.02, 00.50, 00.51, 00.53, 00.54
Non-CV comorbidities		
COPD	J40, J41, J42, J43, J44	490, 491, 492, 494, 495, 496
Diabetes Mellitus	E10, E11, E12, E13, E14	249, 250
Malignant Cancer 3 years prior HF diagnosis	C00 - C26, C30 - C34, C37 - C41, C43, C45 - C58, C60 - C76, C81 - C85, C88, C90 - C97	140-149, 150-159, 160-165, 170-176, 179-189, 190-199, 200-209
Renal disease chronic	N18.3-N18.9, N19	585.3-585.9, 586
Medication	**READ***	**ATC**
RAS-inhibitors	Hypertension and heart failure related: 3 - Angiotensin-converting enzyme inhibitors 4 - Angiotensin-II receptor antagonists	C09A-C09D
Beta-blockers	Beta-adrenoceptor blocking drugs: 1- Beta-adrenoceptor blocking drugs	C07A-C07D, C07F

Table S1. Continued

	ICD-10 codes	ICD-9 codes
MR-antagonists	Diuretics: 4 - Loop diuretics with potassium-sparing diuretics or aldosterone antagonists 8 - Potassium-sparing diuretics and aldosterone antagonists 10 - Thiazides with potassium-sparing diuretics or aldosterone antagonists	C03DA, C03EA, C03EB
Diuretics	Diuretics: 2 – loop diuretics with potassium 3 – loop diuretics 4- Loop diuretics with potassium-sparing diuretics or aldosterone antagonists 9 – Thiazides and related diuretics 10 - Thiazides with potassium-sparing diuretics or aldosterone antagonists 11 - Thiazide-like diuretics with potassium	C03A, C03C, and combinations with diuretics in: C07BA, C07BB, C07CA-CB-CG-DZ-DB, C08GA, C09BA, C09BX, C09DA, C09DX, C02LA-LB-LC-LG-LK-LL-LX
Digoxin	Positive inotropic drugs: 1 - Cardiac glycosides	C01AA

* Full code list available on www.caliberresearch.org/portal/codelists

PART IV – PHENOTYPING HEART FAILURE

CHAPTER 8

A REGISTRY-BASED ALGORITHM TO PREDICT EJECTION FRACTION IN ELECTRONIC HEALTH RECORDS

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Abstract

Background. Left ventricular ejection fraction (EF) is required to categorize heart failure (HF) [i.e. HF with preserved (HFpEF), mid-range (HFmrEF) and reduced (HFrEF) EF], but is often not captured in electronic health records (EHRs). The aim was to create an algorithm that identifies EF phenotypes for research purposes.

Methods & results. We included 42,061 HF patients from the Swedish Heart Failure Registry. As primary analysis we performed two logistic regression models including 22 variables to predict 1) EF ≥ vs. <50%; and 2) EF ≥ vs. <40%. In the secondary analysis we performed a multivariable multinomial analysis with 22 variables to create a model for all 3 separate EF phenotypes: HFrEF vs. HFmrEF vs. HFpEF. The models were validated in the database from the CHECK-HF study, a cross-sectional survey of 10,627 patients from the Netherlands.

The C-statistic (discrimination) was 0.78 (95% confidence interval 0.77-0.78) for EF ≥50%, and 0.76 (95% CI 0.75–0.76) for EF ≥40%, Similar results were achieved for HFrEF and HFpEF in the multinomial model, but the c-statistic for HFmrEF was lower: 0.63 (95% CI 0.63–0.64). The external validation showed similar discriminative ability to the development cohort.

Conclusions. Routine clinical characteristics can be used to identify different EF phenotypes in EHRs where EF is not documented. Accuracy was good for the prediction of HFpEF and HFrEF but lower for HFmrEF. The proposed algorithm enables more effective research on heart failure in the big data setting.

Introduction

Left ventricular ejection fraction (EF) is used in heart failure (HF) for diagnosis, characterization and treatment selection, and is a key inclusion criterion for HF trials.[1] Current European guidelines classify HF according to EF as HF with preserved EF (HFpEF; EF≥50%), HF with mid-range EF (HFmrEF; EF 40-49%) and HF with reduced EF (HFrEF; HF<40%).[2]

Electronic health records (EHRs) provide an abundance of routine clinical care data, which may contribute to assess quality of care and uncover the current unmet needs in HF, i.e. identifying underuse of evidence-based therapies and reasons for undertreatment in order to implement care.[3–5] Furthermore, phenotyping real-world HF patients could facilitate the development of new treatments or the establishment of new uses of existing treatments, and may also help in designing of and pre-screening for randomized trials in all EF categories. However, EHRs frequently lack phenotypic information that is needed to discern relevant sub-phenotypes. In the case of HF, EF is often missing or not documented in EHRs, thereby preventing analyses focusing on specific EF phenotypes and limiting EHRs use in HF research.

A few algorithms have been developed for the purpose of identifying EF phenotypes (i.e. HFpEF vs. HFmrEF vs. HFrEF) in routine care data using International Classification of Diseases (ICD) codes, but none have considered routine clinical information which may be relevant for EF prediction in trials datasets, registries and EHRs.[6,7]

Therefore, we aimed to develop and validate algorithms to discern HFrEF, HFmrEF and HFpEF phenotypes using two representative, large, contemporary HF registries.

Methods

Development cohort

The Swedish Heart Failure Registry (SwedeHF) has been previously described.[8] Briefly, it was created in 2000 and broadly implemented throughout by 2003. The only inclusion criterion is clinician-judged HF. Patients are registered at discharge from hospital or after outpatient clinic visit on a web-based care report

form and entered into the database (managed by Uppsala Clinical Research Center, Uppsala, Sweden).

All permanent residents in Sweden have unique personal identification numbers that allows linking of disease-specific health registries, governmental health and statistical registries. For the current analysis, we linked SwedeHF to the National Patient Registry, which provided more data on baseline comorbidities.

In this study we included 42,061 patients with known EF registered between 11 May 2000 and 31 December 2012. In SwedeHF, EF is recorded as a categorical variable, i.e. <30%, 30 – 39%, 40 – 49% and ≥50%. We defined HFrEF as EF <40%, HFmrEF as EF = 40 – 49% and HFpEF as EF ≥50%. The Study flow diagram is reported in **Figure S1a**.

Validation cohort

The CHECK-HF (Chronic Heart Failure ESC-guideline based Cardiology Practice Quality project) registry is a cross-sectional registration of unselected patients with the diagnosis of chronic HF treated at outpatient HF clinics (96%) of 34 Dutch hospitals or encountered at the general cardiology outpatient clinic of the same hospitals (4%) between September 2013 and September 2016. The registry contains 10,910 patients with chronic HF.[9] Inclusion criteria for this study were 18 years of age or older and known EF (n = 10,627). EF was recorded as a continuous variable, but recoded to: HFrEF <40%, HFmrEF 40–49% and HFpEF ≥50%. The study flow diagram is reported in **Figure S1b**.

Statistical methods

Baseline characteristics and missing data

Patient characteristics were summarized by HF sub-phenotype as mean (SD) or median [IQR] for continuous variables and percentages for categorical variables. Multiple imputation using the *mice* algorithm in the statistical software package R was used to impute missing data for the variables included in the models. **Table S1** shows the variables included in the multiple imputation models and the amount of missing records in the SwedeHF dataset. We created 10 imputed datasets and analyses were performed on each imputed dataset separately. Results were pooled using Rubin's rules. All the analyses, except for descriptive statistics, were performed on imputed data.

Development of predictive models

In the primary analysis we used multivariable logistic regression to fit two different predictive models, one for ≥50% (HFpEF) vs. EF <50% (HFrEF and HFmrEF), and one for EF <40% (HFrEF) vs. ≥40% (HFmrEF and HFpEF). For the secondary analysis we used a multinomial logistic model to separately predict HFpEF, HFmrEF and HFrEF (HFrEF was used as reference).

We screened several sources of EHR for commonly available variables to assess as potential predictors of EF phenotypes in our analyses and we selected the following[10–13]: age, sex, clinical characteristics (N-terminal pro b-type natriuretic peptide [NT-proBNP], New York Heart Failure Association [NYHA] class, mean arterial pressure, heart rate, Body Mass Index [BMI], estimated Glomerular Filtration Rate [eGFR]), comorbidities (history of ischemic heart disease, atrial fibrillation, chronic obstructive pulmonary disease [COPD], diabetes, hypertension, anemia, cancer in the previous 3 years, valvular disease), and treatments (device therapy [implantable cardioverter defibrillator or cardiac resynchronization therapy], renin–angiotensin system [RAS] inhibitors, beta-blockers, diuretics, mineralocorticoid receptor antagonist [MRA], digoxin).

Variance inflation factor was used to test for multicollinearity among predictors. If a pair of predictors was highly correlated (Variance inflation factor > 10), we included only one of the predictors in the multivariable model. We performed backward selection on the multivariable model based on Akaike's Information Criterion to regress the full model towards the final model. Predicted probability threshold cut-offs for the prediction of EF phenotypes were investigated to maximize accuracy, sensitivity and specificity of the model.

Model discrimination

Area under the Receiver Operating Curves were used to discern model discrimination. The c-statistic was used to assess model performance. For the secondary analysis, i.e. multinomial models, discrimination and calibration were calculated with a 1-vs-rest approach. The outcome for each EF category *j* was dichotomized, i.e. HFrEF vs. HFmrEF and HFpEF. The c-statistic was then obtained by evaluating the predicted risk of EF category *j* versus the predicted risk of the remaining categories.[14,15] Observed versus predicted plots were created to visually assess model calibration. We externally validated the models in the CHECK-HF registry.

Sensitivity analysis

In a sensitivity analysis we simplified the models by excluding the clinical variables (NT-proBNP, NYHA class, mean arterial pressure, heart rate, BMI and eGFR), and therefore only investigated demographics, comorbidities and treatments. This was done because many EHRs, such as claim databases, include categorical data but not clinical variables that are often continuous (e.g. chronic kidney disease rather than eGFR) or ordinal (e.g. NYHA class). In further sensitivity analyses we excluded only NT-proBNP and then NT-proBNP + NYHA class, since both are HF specific variables that are not always recorded in EHRs.

All statistical analyses were performed in R software version 3.5.1.

Results

Baseline characteristics

Baseline patient characteristics are summarized in **Table 1**. Overall, HFpEF patients were older, more often female, had higher blood pressure and BMI. Generally, comorbidities were more often observed in HFpEF compared to HFrEF and HFmrEF, except for history of myocardial infarction, which was considerably more common in HFrEF and HFmrEF. HFrEF but also HFmrEF patients were more likely to receive RAS-inhibitors, beta-blockers, MRAs, and device therapy compared to HFpEF patients, though diuretics were more often prescribed in HFpEF patients. Baseline characteristics of the external validation cohort are summarized in **Table S2**. Similar characteristics were observed in the CHECK-HF population and its phenotypes.

Table 1. Baseline characteristics of the SwedeHF cohort

	HFrEF	HFmrEF	HFpEF	p-value
N	23402 (55.6%)	9019 (21.4%)	9640 (22.9%)	
Demographics				
Age (years, mean (SD))	71.7 (12.3)	74.3 (11.7)	77.4 (10.6)	<0.001
Sex (Female (%))	28.8	39.2	54.6	<0.001
HF measures				
NYHA Class (Class III/IV (%))	45.8	31.7	38.8	<0.001
NT-proBNP (≥ median (%))	55.8	44.2	41.6	<0.001
Clinical variables				
SBP (mean (SD))	124.4 (20.5)	130.6 (20.9)	133.4 (21.9)	<0.001
DBP (mean (SD))	73.4 (12.3)	73.8 (12.1)	73.1 (12.4)	0.001

Table 1. Continued

	HFrEF	HFmrEF	HFpEF	p-value
MAP (≥90 mmHg (%))	51.8	59.5	60.6	<0.001
Heart rate (≥70 BPM (%))	60.5	55.7	59.7	<0.001
BMI (%)				<0.001
< 18.5 kg/m2	3.1	2.7	3.4	
18.5 - 24.9 kg/m2	40.1	35.3	34.5	
25 - 29.9 kg/m2	35.8	35.6	33.1	
≥30 kg/m2	21.0	26.4	29.0	
eGFR (%)				<0.001
≥ 90 mL/min/1.73m2	11.8	11.2	9.6	
60 - 89.9 mL/min/1.73m2	41.3	40.0	35.3	
30 - 59.9 mL/min/1.73m2	39.7	41.2	46.0	
< 30 mL/min/1.73m2	7.2	7.5	9.1	
Anemia (%)	31.4	34.5	40.9	<0.001
Ischemic heart disease (%)	57.8	57.1	46.3	<0.001
Revascularized (%)	32.2	32.6	22.1	<0.001
Comorbidities (%)				
Atrial fibrillation	51.0	58.0	63.6	<0.001
COPD	15.9	17.4	21.7	<0.001
Diabetes	26.7	26.7	28.1	0.035
Hypertension	54.1	62.9	70.6	<0.001
Myocardial infarction	42.6	41.1	29.1	<0.001
Peripheral artery disease	9.7	10.1	10.2	0.338
Cancer previous 3yr	12.4	13.4	15.1	<0.001
Valvular disease	23.4	25.4	33.6	<0.001
Therapy (%)				
RAS-inhibitor	90.4	83.6	71.7	<0.001
Beta-blocker	90.3	85.7	78.4	<0.001
Loop diuretic	79.6	74.2	84.7	<0.001
MRA	32.7	23.5	26.2	<0.001
Digoxin	17.6	15.9	18.1	<0.001
Device therapy	6.1	2.2	1.0	<0.001

HFrEF = Heart failure with reduced ejection fraction, HFmrEF = Heart failure with mid-range ejection fraction, HFpEF = Heart failure with preserved ejection fraction, mean (SD) = mean (standard deviation), NYHA Class = New York Heart Association Class, NT-proBNP = N-terminal pro b-type natriuretic peptide, MAP = Mean arterial pressure, BPM = beats per minute, BMI = Body mass index, eGFR = estimated Glomerular filtration rate, COPD = Chronic obstructive pulmonary disease, RAS-inhibitor = renin-angiotensin system inhibitor, MRA = Mineralocorticoid receptor antagonist.

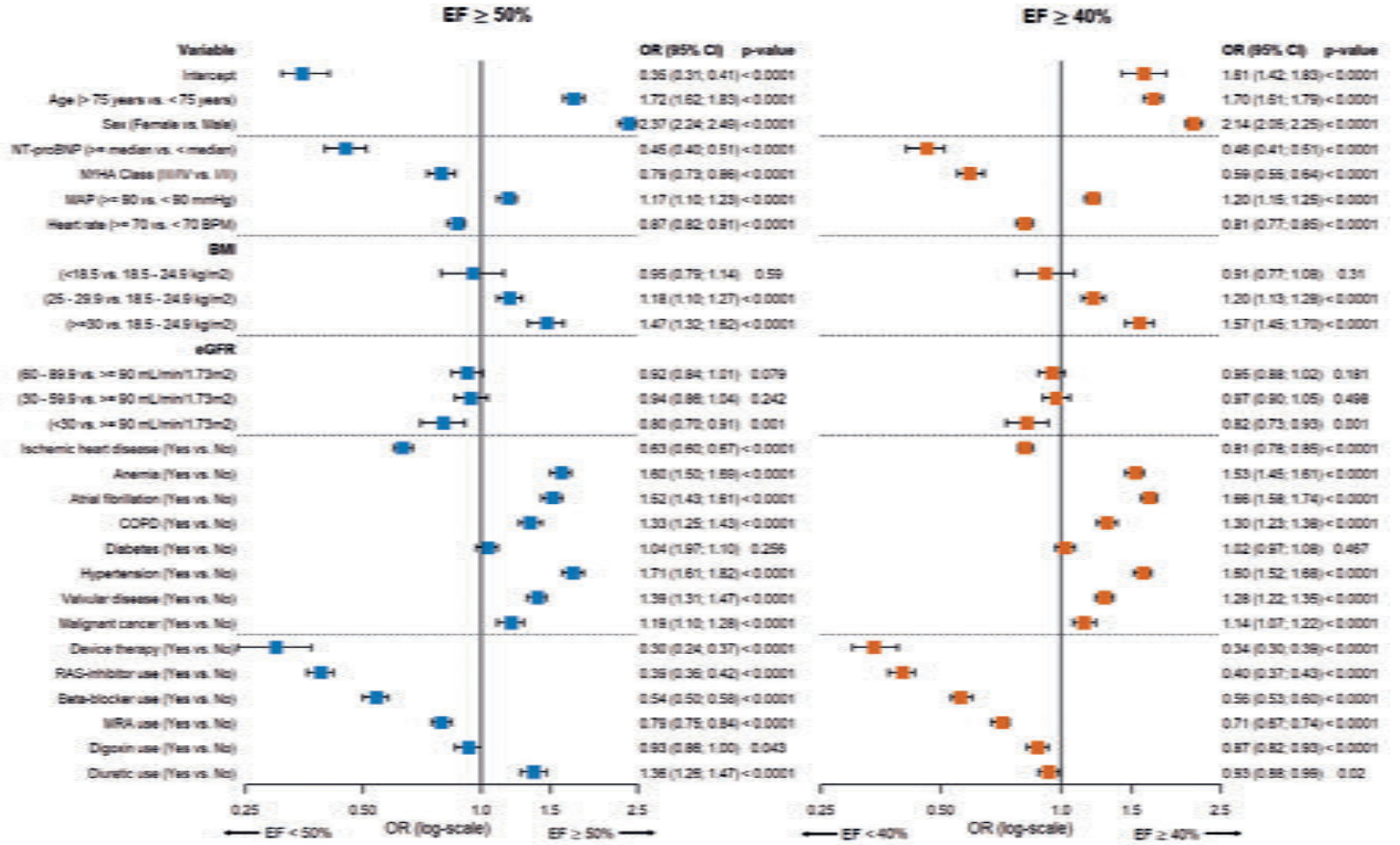
Prediction models

Primary analysis

The model predicting EF ≥50% vs. <50% is presented in **Figure 1**. The strongest predictors for EF ≥50% were older age, female sex, hypertension, anemia and atrial fibrillation, while device therapy, use of RAS-inhibitors and beta-blockers and higher NT-proBNP levels were associated with EF <50%. The model discriminated well, with a c-statistic of 0.775 [95% confidence interval (95% CI) 0.770 – 0.780] (**Figure 3a**). There was a slight overestimation for the predicted probabilities between 0.4 – 0.6 (**Figure 4a**). With a predicted probability threshold of 0.21 we maximized the sensitivity and specificity of predicting EF ≥50%, while a higher threshold of 0.44 led to a higher overall accuracy and higher specificity to predict EF <50% (**Table S3**).

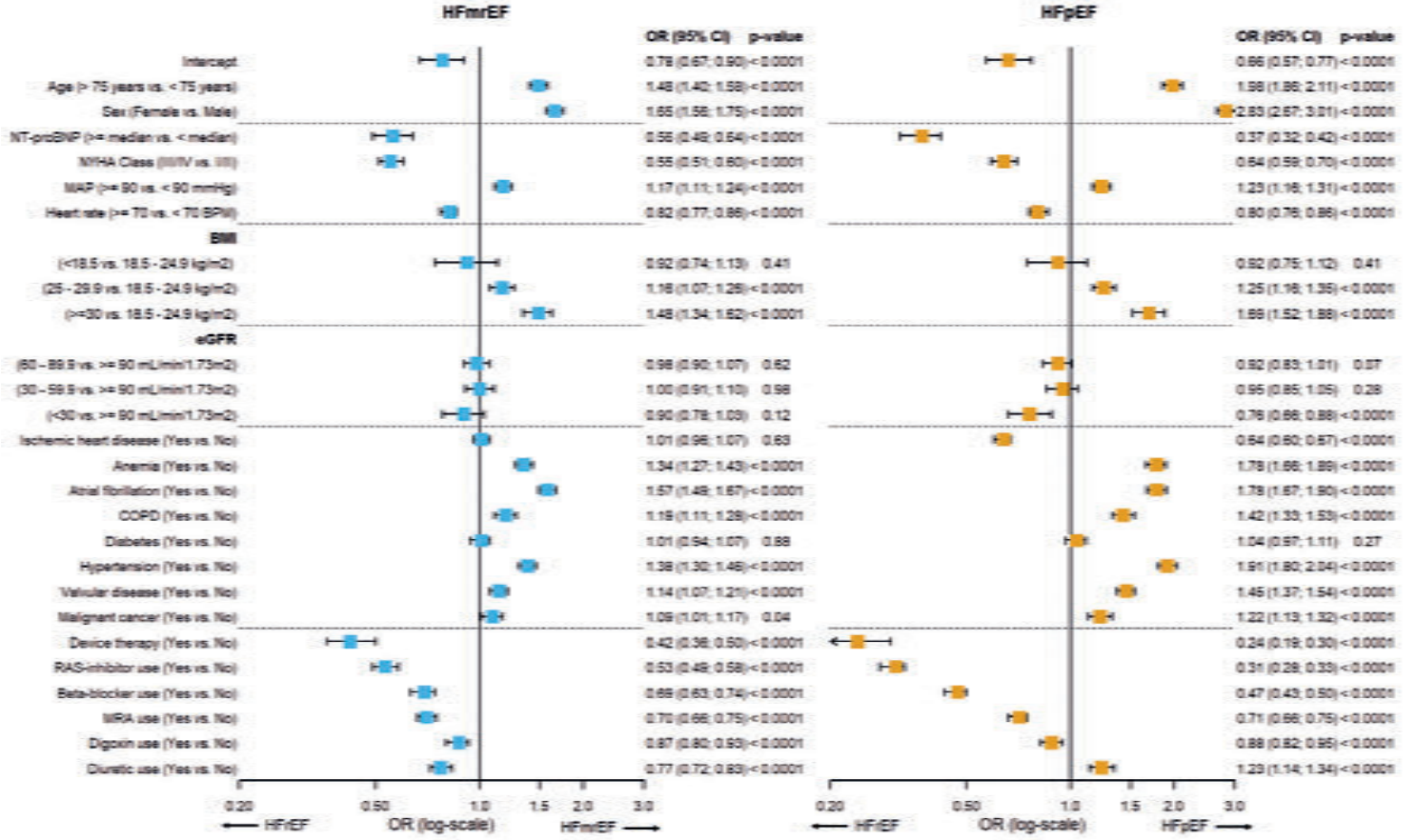
Comparable results were observed for the model predicting EF ≥40% vs. <40%, with older age and female sex as strong predictors for EF ≥40% (**Figure 1**). Furthermore, BMI ≥30 kg/m^2, atrial fibrillation, hypertension and anemia were strong predictors for EF ≥40%, while device therapy, RAS-inhibitors and higher NT-proBNP levels were the strongest predictors for EF <40%. The discrimination of this model was good, with a c-statistic of 0.757 (95% CI 0.752 – 0.763) (**Figure 3b)** and slight under- and overestimation in the lower and higher ends of the predicted probabilities (**Figure 4b**). Predicted probability thresholds to maximize overall accuracy or sensitivity + specificity was similar, with cut-offs of 0.48 and 0.45 respectively (**Table S3**).

Figure 1. Multivariable logistic prediction models predicting EF ≥50% vs. EF <50% and EF ≥40% vs. <40%.



NT-proBNP = N-terminal pro b-type natriuretic peptide, NYHA Class = New York Heart Association Class, MAP = Mean arterial pressure, BPM = beats per minute, BMI = Body mass index, eGFR = estimated Glomerular filtration rate, COPD = Chronic obstructive pulmonary disease, RAS-inhibitor = renin-angiotensin system inhibitor, MRA = Mineralocorticoid receptor antagonist.

Figure 2. Multinomial prediction model predicting HFmrEF or HFpEF with HFrEF as reference category.



HFmrEF = Heart failure with mid-range ejection fraction, HFpEF = Heart failure with preserved ejection fraction, NT-proBNP = N-terminal pro b-type natriuretic peptide, NYHA Class = New York Heart Association Class, MAP = Mean arterial pressure, BPM = beats per minute, BMI = Body mass index, eGFR = estimated Glomerular filtration rate, COPD = Chronic obstructive pulmonary disease, RAS-inhibitor = renin-angiotensin system inhibitor, MRA = Mineralocorticoid receptor antagonist.

Secondary analysis

The results from the multinomial model are shown in **Figure 2**. HFrEF was the reference category. Compared with HFrEF, older age, female sex, higher BMI and atrial fibrillation were the strongest predictors for HFmrEF. Predictors for HFpEF were similar to those for HFmrEF, but the associations were much stronger. C-statistics according to the one-vs-rest approach for HFrEF and HFpEF were similar to the logistic models for EF ≥40% or EF ≥50% in the primary analysis, 0.758 (95% 0.754 – 0.763) and 0.775 (95% 0.770 – 0.780) respectively (**Figure 3c**). However, the discriminative performance for predicting HFmrEF was only moderate, with a c-statistic of 0.633 (95% CI 0.627 – 0.640). Model calibration was not optimal (**Figure 4c**). Overall accuracy was much lower for the multinomial model than the primary analyses with an accuracy of 58.1 - 60.8% (**Table S3**).

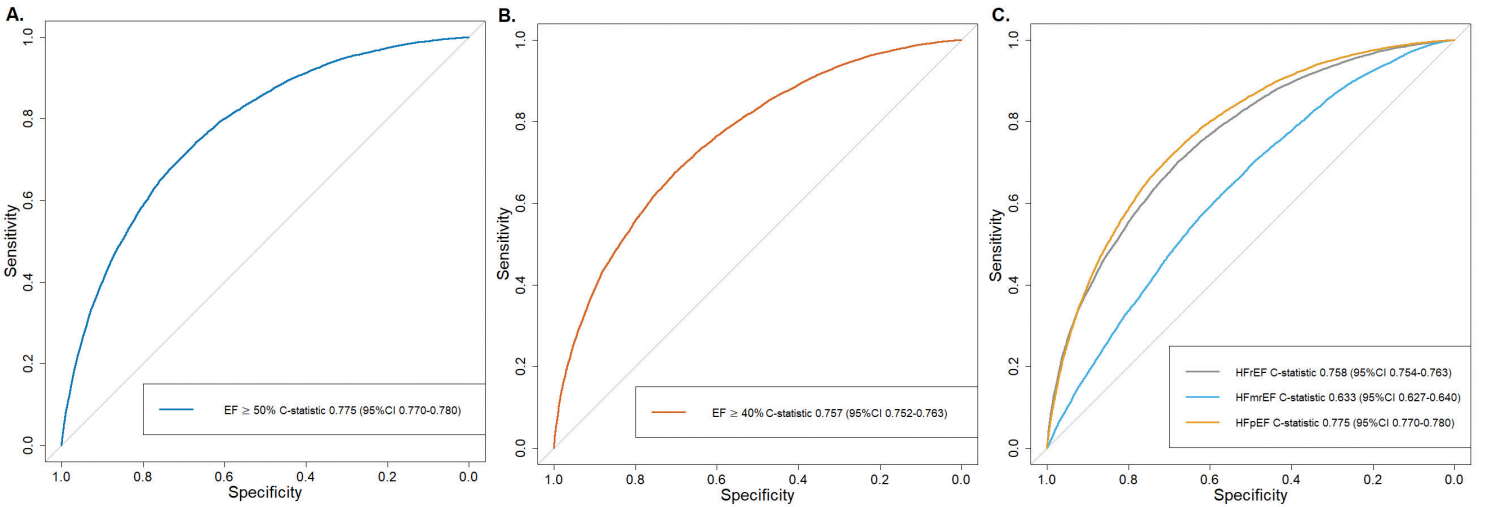
External validation

Models were externally validated in the CHECK-HF dataset, with good discriminative performance which was comparable to the development cohort, and the EF ≥50% models performing best with a c-statistic of 0.728 (0.724 - 0.731) for the main model (**Table S4**).

Sensitivity analyses

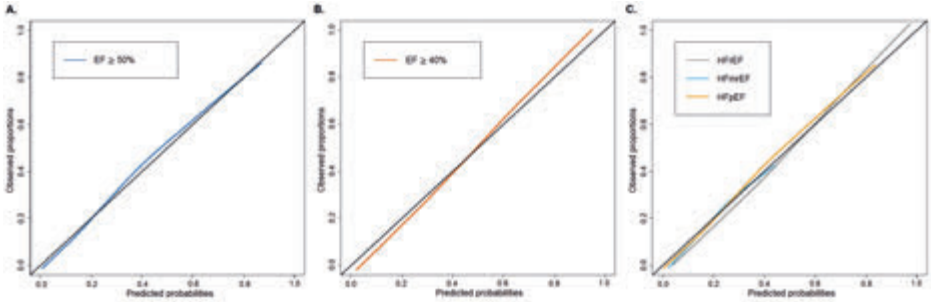
We performed sensitivity analyses to investigate simpler models, i.e. excluding clinical characteristics (NT-proBNP, NYHA class, mean arterial pressure, heart rate, BMI and eGFR) (**Table S5, Table S6** and **Table S11**) as well as models excluding only NT-proBNP (**Table S7, Table S8** and **Table S12**) and models excluding NT-proBNP and NYHA (**Table S9**, **Table S10** and **Table S13**).The models had lower, but good discriminative ability for the models with EF ≥50% vs. <50% (**Figure S2, Figure S4** and **Figure S6**), with a c-statistic for the simple model of 0.737 (95% CI 0.732 – 0.743), the model without NT-proBNP 0.753 (95% CI 0.748 – 0.759) and the model without NT-proBNP and NYHA 0.750 (95% CI 0.744 – 0.755). This was similar for the model predicting EF ≥40% vs. <40%, with a c-statistic of 0.703 (95% CI 0.698 – 0.708) for the simpler model, 0.734 (95% CI 0.729 – 0.739) for the model excluding NT-proBNP and 0.721 (95% CI 0.716 – 7.26) for the model excluding NT-proBNP and NYHA (**Figure S3, Figure S5** and **Figure S7**) at the logistic regression analysis, and HFrEF and HFpEF at the multinomial analysis, while predicting HFmrEF was only moderate (**Figure S8, Figure S9** and **Figure S10**).

Figure 3. Discrimination plots.



Discrimination plots displaying ROC curves for A. Logistic model EF cut-off ≥50%, B. Logistic model EF cut-off ≥40% and C. multinomial model predicting HFrEF, HFmrEF and HFpEF with the plot displaying one vs. all discrimination, i.e. HFrEF vs HFmrEF + HFpEF, HFmrEF vs. HFrEF + HFpEF and HFpEF vs. HFmrEF + HFrEF.

Figure 4. Calibration plots.



Calibration plots of observed proportions vs. predicted probabilities to assess the goodness-of-fit for A. Logistic model EF cut-off ≥50%, B. Logistic model EF cut-off ≥40% and C. multinomial model predicting HFrEF, HFmrEF and HFpEF with the plot displaying one vs. all calibration plots, i.e. HFrEF vs HFmrEF + HFpEF, HFmrEF vs. HFrEF + HFpEF and HFpEF vs. HFmrEF + HFrEF.

Sensitivity analyses

We performed sensitivity analyses to investigate simpler models, i.e. excluding clinical characteristics (NT-proBNP, NYHA class, mean arterial pressure, heart rate, BMI and eGFR) (**Table S5, Table S6** and **Table S11**) as well as models excluding only NT-proBNP (**Table S7, Table S8** and **Table S12**) and models excluding NT-proBNP and NYHA (**Table S9**, **Table S10** and **Table S13**).The models had lower, but good discriminative ability for the models with EF ≥50% vs. <50% (**Figure S2, Figure S4** and **Figure S6**), with a c-statistic for the simple model of 0.737 (95% CI 0.732 – 0.743), the model without NT-proBNP 0.753 (95% CI 0.748 – 0.759) and the model without NT-proBNP and NYHA 0.750 (95% CI 0.744 – 0.755). This was similar for the model predicting EF ≥40% vs. <40%, with a c-statistic of 0.703 (95% CI 0.698 – 0.708) for the simpler model, 0.734 (95% CI 0.729 – 0.739) for the model excluding NT-proBNP and 0.721 (95% CI 0.716 – 7.26) for the model excluding NT-proBNP and NYHA (**Figure S3, Figure S5** and **Figure S7**) at the logistic regression analysis, and HFrEF and HFpEF at the multinomial analysis, while predicting HFmrEF was only moderate (**Figure S8, Figure S9** and **Figure S10**).

We externally validated these sensitivity analyses in the CHECK-HF dataset, with similar discriminative performances as in the development cohort (**Table S4**).

Discussion

EHRs and routine clinical care data represent a great potential resource for HF research.[10–13] While these databases provide for large samples sizes ensuring generalizability and many clinically relevant variables, the main limitation is often the depth of phenotypic information required to identify and investigate specific HF sub-phenotypes. Currently, EF is the key to phenotype HF patients and is used for treatment selection in clinical practice and as inclusion criteria in HF trials. Moreover, as shown in numerous previous studies, patients have different risk profiles, disease trajectories and outcomes.[16–19] Absence of EF measurements limits research on HF in routine EHR data. Simple prediction models for EF could be used to gain more knowledge on HF phenotypic information in EHRs, claim databases, trials and large cohorts. With recent data on Angiotensin-receptor-Neprilysin-inhibitors (ARNi) and potentially emerging data on Sodium/Glucose cotransporter 2 (SGLT2)-inhibitors in HF, the use of these drugs may be expanded.[20,21] It would be important for regulators, payers and health systems to be able to use EF prediction models to assess implications of these new drugs in their own health care systems and databases.

We hereby propose prediction models that could be used to infer EF category in secondary care HF patients for research purposes based on patients' characteristics. The created models discriminated well, especially for HFpEF and HFrEF, while predicting HFmrEF was more challenging.

Two previous studies have aimed to create algorithms to predict EF category in HF patients.[6,7] Bovitz et al. realized a predictive model for EF based on ICD-9 codes for systolic and diastolic HF in 2714 patients encountered in a single center. The area under the curve for this model was 0.821 and had a predicted probability threshold cut-off for EF of 43.5%.[6] The main limitation was generalizability. Indeed, no external validation was performed, and this study enrolled a small cohort of patients from only one center, whereas ICD coding practice is highly varying from one center to another. Furthermore, this model did not incorporate clinical or laboratory data such as blood pressure, eGFR or NT-proBNP. A predictive model from Desai et al. included 11,073 patients (of which 7,105 patients in the development cohort) and aimed to predict HFrEF, HFmrEF or HFpEF as well as with EF < or ≥45% in patients with known EF from a center referring to Medicare (claim database).[7] The discriminative performance varied

between 0.84 – 0.88. This model was externally validated in a cohort of patients from a different hospital but still limited to Medicare patients only.

Compared to previous models which have been developed to be mainly applied to claim data, our model, that considers also clinically relevant variables, can be used as well in clinical cohorts or trials where HF is diagnosed at baseline, but EF is not collected.[22] Furthermore, we have developed predicted probability thresholds to optimize accuracy or sensitivity and specificity that can guide researchers in classifying patients based on our models.

We created prediction models for HFrEF, HFmrEF and HFpEF as well as for EF ≥40% vs <40% and EF ≥50% vs. <50% in SwedeHF. Our models had good performance, with the lowest c-statistic 0.633 for HFmrEF in the multinomial model and the highest performance for the EF ≥50% model with a c-statistic of 0.775. The lower c-statistic for HFmrEF may be explained by the heterogeneity that characterizes this phenotype,[17,23,24] with a large proportion of patients having transitioning EF for different reasons (e.g. atrial fibrillation and ischemic heart disease) which may make EF prediction more challenging.[25] Most trials use EF cut-offs at 40% or 50% and could thus use our models for those cut-offs. If a trial or other research program wishes to specifically select HFrEF, HFpEF or HFmrEF patients, our models can be applied, albeit that the area under the curve was worse (0.633) than for the dichotomous models (0.775 and 0.757, respectively).

Similar to the binary model by Desai et al,[7] male sex, implantable devices and use of ACE-inhibitors, beta-blockers and MRAs predicted HFrEF in both our ≥40% and ≥50% models, while anemia, valvular disease, obesity and hypertension were predictive of HFpEF. Out of the comorbidities we included in our model, only ischemic heart disease was predictive for HFrEF or EF <50%. This is comparable to what is known from recent studies, i.e. HFpEF is more related to ageing, female sex and comorbidities, while HFrEF (and HFmrEF) are more likely to be associated to ischemic heart disease.[16–19] Compared to HFpEF, the main variables associated with HFrEF were medication use and variables associated with worsening or symptomatic HF, such as higher NYHA class and higher NT-proBNP levels.[26] While medication use does not represent the biology of any HF phenotype, it is still helpful as a marker reflecting clinician decisions which in turn reflect EF. Interestingly, only severe renal disease (eGFR <30 ml/min/1.73 m^2) was associated with HFrEF, while mildly reduced kidney function was not associated with either EF phenotype.

Strengths and limitations

SwedeHF and CHECK-HF are both large, unselected, contemporary HF cohorts, collecting data on demographics, clinical characteristics, biomarkers, medication use and, notably, EF measurements. A strength of our analysis is that we were able to externally validate our models from SwedeHF in an independent sample with good discriminative performance (CHECK-HF). However, several limitations should be addressed. EF is collected as a categorical variable in SwedeHF; therefore, we were unable to investigate linear associations between predictors and EF. However, clinical guidelines and trials use EF categories as well and would not be improved by linear information. Based on our models, it remains difficult to classify HFmrEF, which may be wrongly defined as HFrEF or HFpEF. We therefore suggest to use models with a dichotomous cut-off. Many of the HF therapies were predictive for HFrEF/HFpEF. When applying our models to EHR data we suggest to consider use of medications 3-6 months after the initial HF diagnosis to allow for optimizing therapies and reflection of clinician decision making. Last, the inclusion criterion for SwedeHF is clinician-judged HF, which differs from the ICD definition of HF in EHRs and thus our model should be further evaluated in an EHR setting.

Conclusions

Our model based on patients' demographics, clinical characteristics and use of treatments could be applied to EHR, clinical trials and registries, and other "big data" datasets to identify EF phenotypes in HF when EF is not available. Accuracy was good for the prediction of HFpEF and HFrEF but lower for HFmrEF, perhaps due to the heterogeneity which characterizes this phenotype. Our model may significantly support more effective research in the "big data" setting.

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Supplemental material

Table S1. Missing data baseline characteristics and variables included in the multiple imputation for SwedeHF

	HFrEF		HFmrEF		HFpEF	
	N missing	**% missing**	**N missing**	**% missing**	**N missing**	**% missing**
Demographics						
Age	0	0	0	0	0	0
Sex	0	0	0	0	0	0
HF measures						
NYHA Class	5507	23.5	2482	27.5	3565	37.0
NT-proBNP	16202	69.2	6275	69.6	6568	68.1
Clinical variables						
SBP	265	1.1	100	1.1	162	1.7
DBP	289	1.2	110	1.2	172	1.8
MAP	302	1.3	113	1.3	173	1.8
Heart rate	1496	6.4	636	7.1	746	7.7
BMI	12511	53.5	4898	54.3	5423	56.3
eGFR	69	0.3	30	0.3	32	0.3
Anemia	0	0	0	0	0	0
IHD	921	3.9	248	2.7	283	2.9
Revascularized	0	0	0	0	0	0
Comorbidities						
AF	0	0	0	0	0	0
COPD	0	0	0	0	0	0
Diabetes	0	0	0	0	0	0
Hypertension	0	0	0	0	0	0
MI	0	0	0	0	0	0
PAD	0	0	0	0	0	0
Cancer previous 3yr	0	0	0	0	0	0
Valvular disease	619	2.6	249	2.8	250	2.6

Table S1. Missing data baseline characteristics and variables included in the multiple imputation for SwedeHF

	HFrEF		HFmrEF		HFpEF	
	N missing	**% missing**	**N missing**	**% missing**	**N missing**	**% missing**
Therapy						
RAS-inhibitor	126	0.5	58	0.6	104	1.1
Beta-blocker	94	0.4	45	0.5	73	0.8
Loop diuretic	112	0.5	42	0.5	50	0.5
MRA	166	0.7	57	0.6	81	0.8
Digoxin	130	0.6	50	0.6	63	0.7
Device therapy	227	1.0	90	1.0	114	1.2

HFrEF = Heart failure with reduced ejection fraction, HFmrEF = Heart failure with mid-range ejection fraction, HFpEF = Heart failure with preserved ejection fraction, Planned FU level = Planned follow-up level, NYHA Class = New York Heart Association Class, NT-proBNP = N-terminal pro b-type natriuretic peptide, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, MAP = Mean arterial pressure, BMI = Body mass index, eGFR = estimated Glomerular filtration rate, IHD = Ischaemic Heart Disease, COPD = Chronic obstructive pulmonary disease, MI = Myocardial Infarction, PAD = Peripheral Artery Disease, RAS-inhibitor = renin-angiotensin system inhibitor, MRA = Mineralocorticoid receptor antagonist.

Table S2. Baseline characteristics of the external validation cohort (CHECK-HF) including missing data

	HFrEF	Missing (%)	HFmrEF	Missing (%)	HFpEF	Missing (%)	p-value
N	6682 (64.4%)		1536 (14.8%)		2153 (20.8%)		
Demographics							
Age (years, mean (SD))	72.0 (11.7)	0.1	73.9 (11.5)	0.1	75.2 (11.2)	0.1	<0.001
Sex (Female (%))	34.8	0.5	41.6	0.2	54.5	0.3	<0.001
HF measures							
NYHA Class (Class III/IV (%))	27.5	1.2	27.3	1.0	31.1	1.6	0.004
NT-proBNP (=> median (%))	50.0	62.5	54.8	65.6	49.1	72.5	0.096
Clinical variables							
SBP (mean (SD))	124.5 (20.2)	1.3	129.3 (21.4)	1.1	134.8 (22.9)	0.6	<0.001
DBP (mean (SD))	71.0 (11.1)	1.3	71.6 (12.0)	0.9	72.7 (12.2)	0.5	<0.001
MAP (≥ 90 mmHg (%))	45.8	1.4	52.4	1.1	59.0	0.6	<0.001
Heart rate (≥ 70 BPM (%))	52.1	1.2	54.2	1.3	55.0	0.8	0.045
BMI (%)		8.4		7.2		7.8	<0.001
< 18.5 kg/m2	1.6		1.6		1.3		
18.5 - 24.9 kg/m2	35.1		32.8		28.9		
25 - 29.9 kg/m2	39.1		38.4		35.6		
≥ 30 kg/m2	24.3		27.2		34.2		
eGFR (%)		27.0		37.1		47.3	<0.001
≥ 90 mL/min/1.73m2	13.4		9.3		7.8		
60 - 89.9 mL/min/1.73m2	34.8		31.6		28.6		
30 - 59.9 mL/min/1.73m2	41.0		45.3		47.0		
< 30 mL/min/1.73m2	10.9		13.8		16.6		
Anemia (%)	5.0	10.4	6.0	10.0	7.1	7.1	0.002
Ischemic heart disease (%)	53.4	3.0	46.0	3.5	29.4	2.7	<0.001

Table S2. Continued

	HFrEF	Missing (%)	HFmrEF	Missing (%)	HFpEF	Missing (%)	p-value
Comorbidities (%)							
Atrial fibrillation	23.7	1.2	34.8	1.0	38.5	0.8	<0.001
COPD	18.0	10.4	21.0	10.0	20.6	7.1	0.005
Diabetes	29.4	10.4	28.4	10.0	32.2	7.1	0.023
Hypertension	39.0	10.4	44.0	10.0	54.6	7.1	<0.001
Myocardial infarction	32.7	3.0	32.9	3.5	24.5	2.7	<0.001
Peripheral artery disease	6.4	10.4	5.6	10.0	3.5	7.1	<0.001
History of cancer	12.8	23.2	13.5	23.1	14.0	19.8	0.384
Valvular disease	14.3	3.0	18.4	3.5	25.4	2.7	<0.001
Therapy (%)							
RAS-inhibitor	82.3	0	76.8	0	67.3	0	<0.001
Beta-blocker	85.6	0	82.2	0	78.3	0	<0.001
Loop diuretic	83.6	0.1	79.5	0.1	79.4	0	<0.001
MRA	54.8	0	45.1	0	38.5	0	<0.001
Digoxin	17.2	0	16.7	0	18.0	0	0.562
Device therapy	37.8	17.2	16.4	28.2	8.8	45.3	<0.001

HFrEF = Heart failure with reduced ejection fraction, HFmrEF = Heart failure with mid-range ejection fraction, HFpEF = Heart failure with preserved ejection fraction, NYHA Class = New York Heart Association Class, NT-proBNP = N-terminal pro b-type natriuretic peptide, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, MAP = Mean arterial pressure, BMI = Body mass index, eGFR = estimated Glomerular filtration rate, COPD = Chronic obstructive pulmonary disease, RAS-inhibitor = renin-angiotensin system inhibitor, MRA = Mineralocorticoid receptor antagonist.

Table S3. Prediction thresholds for maximizing accuracy and sensitivity + specificity

	Maximize accuracy	Maximize sensitivity + specificity
EF ≥50%*		
Threshold	0.44	0.25
Overall accuracy	79.1%	69.8%
Sensitivity (accurate HFpEF prediction)	30.7%	67.5%
Specificity (accurate HFrEF + HFmrEF prediction)	93.5%	73.6%
EF ≥50%: Simple model§		
Threshold	0.51	0.21
Overall accuracy	78.0%	65.1%
Sensitivity (accurate HFpEF prediction)	15.1%	72.4%
Specificity (accurate HFrEF + HFmrEF prediction)	96.7%	63.0%
EF ≥50%: NT-proBNP excluded¶		
Threshold	0.51	0.24
Overall accuracy	78.4%	70.0%
Sensitivity (accurate HFpEF prediction)	17.9%	66.8%
Specificity (accurate HFrEF + HFmrEF prediction)	96.4%	70.9%
EF ≥50%: NT-proBNP and NYHA class excluded¥		
Threshold	0.48	0.23
Overall accuracy	78.3%	68.2%
Sensitivity (accurate HFpEF prediction)	21.0%	66.9%
Specificity (accurate HFrEF + HFmrEF prediction)	95.4%	68.6%
EF ≥40%*		
Threshold	0.48	0.45
Overall accuracy	69.4%	65.8%
Sensitivity (accurate HFpEF + HFmrEF prediction)	62.2%	39.7%
Specificity (accurate HFrEF prediction)	75.1%	86.6%
EF ≥40%: Simple model§		
Threshold	0.51	0.44
Overall accuracy	65.5%	63.2%
Sensitivity (accurate HFpEF + HFmrEF prediction)	50.2%	38.2%
Specificity (accurate HFrEF prediction)	77.6%	83.1%
EF ≥40%: NT-proBNP excluded¶		
Threshold	0.5	0.45
Overall accuracy	67.7%	64.6%
Sensitivity (accurate HFpEF + HFmrEF prediction)	56.1%	38.3%
Specificity (accurate HFrEF prediction)	77.0%	85.6%

Table S3. Continued

	Maximize accuracy	Maximize sensitivity + specificity
EF ≥40%: NT-proBNP and NYHA class excluded[¥]		
Threshold	0.49	0.44
Overall accuracy	66.8%	63.6%
Sensitivity (accurate HFpEF prediction)	56.6%	39.1%
Specificity (accurate HFrEF + HFmrEF prediction)	74.9%	83.1%
Multinomial*		
Threshold HFrEF	HFrEF > HFpEF & HFrEF > HFmrEF	HFrEF > HFpEF & HFrEF > HFmrEF
Threshold HFmrEF	HFmrEF > HFrEF & HFmrEF > HFpEF	HFmrEF > HFrEF & HFmrEF > HFpEF
Threshold HFpEF	HFpEF > HFrEF & HFpEF > HFmrEF	0.225
Overall accuracy	60.8%	58.1%
HFpEF accuracy	42.8%	73.2%
HFrEF accuracy	90.6%	74.1%
Multinomial: Simple model[§]		
Threshold HFrEF	HFrEF > HFpEF & HFrEF > HFmrEF	HFrEF > HFpEF & HFrEF > HFmrEF
Threshold HFmrEF	HFmrEF > HFrEF & HFmrEF > HFpEF	HFmrEF > HFrEF & HFmrEF > HFpEF
Threshold HFpEF	HFpEF > HFrEF & HFpEF > HFmrEF	0.275
Overall accuracy	58.8%	57.8%
HFpEF accuracy	34.9%	58.2%
HFrEF accuracy	91.1%	79.8%
Multinomial: NT-proBNP excluded[¶]		
Threshold HFrEF	HFrEF > HFpEF & HFrEF > HFmrEF	HFrEF > HFpEF & HFrEF > HFmrEF
Threshold HFmrEF	HFmrEF > HFrEF & HFmrEF > HFpEF	HFmrEF > HFrEF & HFmrEF > HFpEF
Threshold HFpEF	HFpEF > HFrEF & HFpEF > HFmrEF	0.225
Overall accuracy	59.8%	56.7%
HFpEF accuracy	39.3%	70.8%
HFrEF accuracy	90.4%	72.7%

Table S3. Continued

	Maximize accuracy	Maximize sensitivity + specificity
Multinomial: NT-proBNP and NYHA class excluded[¥]		
Threshold HFrEF	HFrEF > HFpEF & HFrEF > HFmrEF	HFrEF > HFpEF & HFrEF > HFmrEF
Threshold HFmrEF	HFmrEF > HFrEF & HFmrEF > HFpEF	HFmrEF > HFrEF & HFmrEF > HFpEF
Threshold HFpEF	HFpEF > HFrEF & HFpEF > HFmrEF	0.23
Overall accuracy	59.8%	56.7%
HFpEF accuracy	38.7%	69.5%
HFrEF accuracy	91.1%	73.3%

EF = Ejection Fraction, HFrEF = Heart Failure with reduced Ejection Fraction, HFmrEF = Heart Failure with midrange Ejection Fraction, HFpEF = Heart Failure with preserved Ejection Fraction. * = The full model, [§] = model with demographics, comorbidities and treatments (i.e. excluding NT-proBNP, NYHA class, mean arterial pressure, heart rate, BMI and eGFR), [¶] = the full model excluding NT-proBNP, [¥] = the full model excluding NT-proBNP and NYHA class.

Table S4. External validation of the models in CHECK-HF

External validation	C-statistic
EF ≥50% model	
Main*	0.728 (0.724 – 0.731)
Simple§	0.725 (0.721 – 0.728)
Excluding NT-proBNP¶	0.727 (0.724 – 0.731)
Excluding NT-proBNP and NYHA class¥	0.731 (0.728 – 0.735)
EF ≥40% model	
Main*	0.709 (0.705 – 0.712)
Simple§	0.705 (0.702 – 0.709)
Excluding NT-proBNP¶	0.703 (0.700 – 0.706)
Excluding NT-proBNP and NYHA class¥	0.711 (0.708 – 0.714)
Multinomial model	
Main*	
HFrEF vs. Rest	0.709 (0.705 – 0.712)
HFmrEF vs. Rest	0.586 (0.581 – 0.591)
HFpEF vs. Rest	0.728 (0.724 – 0.731)
Simple§	
HFrEF vs. Rest	0.705 (0.702 – 0.709)
HFmrEF vs. Rest	0.579 (0.574 – 0.583)
HFpEF vs. Rest	0.725 (0.721 – 0.728)
Excluding NT-proBNP¶	
HFrEF vs. Rest	0.703 (0.700 – 0.706)
HFmrEF vs. Rest	0.583 (0.579 – 0.588)
HFpEF vs. Rest	0.727 (0.724 – 0.731)
Excluding NT-proBNP and NYHA class¶	
HFrEF vs. Rest	0.711 (0.708 – 0.714)
HFmrEF vs. Rest	0.584 (0.579 – 0.589)
HFpEF vs. Rest	0.731 (0.728 – 0.735)

EF = Ejection Fraction, HFrEF = Heart Failure with reduced Ejection Fraction, HFmrEF = Heart Failure with midrange Ejection Fraction, HFpEF = Heart Failure with preserved Ejection Fraction. * = The full model, § = model with demographics, comorbidities and treatments (i.e. excluding NT-proBNP, NYHA class, mean arterial pressure, heart rate, BMI and eGFR), ¶ = the full model excluding NT-proBNP.

Table S5. Simplified logistic model (i.e. not including NT-proBNP, NYHA class, mean arterial pressure, heart rate, BMI and eGFR) for EF cut-off ≥50%

	OR (95% CI)	p-value
Intercept	0.34 (0.30; 0.37)	< 0.001
Age (> 75 years vs. < 75 years)	1.39 (1.32; 1.47)	< 0.001
Sex (Female vs. Male)	2.24 (2.13; 2.36)	< 0.001
Ischemic heart disease (Yes vs. No)	0.61 (0.58; 0.64)	< 0.001
Anemia (Yes vs. No)	1.31 (1.24; 1.38)	< 0.001
Atrial fibrillation (Yes vs. No)	1.42 (1.35; 1.51)	< 0.001
COPD (Yes vs. No)	1.32 (1.24; 1.40)	< 0.001
Diabetes (Yes vs. No)	1.10 (1.03; 1.16)	0.002
Hypertension (Yes vs. No)	1.80 (1.71; 1.90)	< 0.001
Valvular disease (Yes vs. No)	1.25 (1.19; 1.33)	< 0.001
Malignant cancer (Yes vs. No)	1.14 (1.06; 1.23)	< 0.001
Device therapy (Yes vs. No)	0.29 (0.23; 0.36)	< 0.001
RAS-inhibitor use (Yes vs. No)	0.44 (0.41; 0.47)	< 0.001
Beta-blocker use (Yes vs. No)	0.52 (0.48; 0.55)	< 0.001
MRA use (Yes vs. No)	0.79 (0.74; 0.83)	< 0.001
Digoxin use (Yes vs. No)	0.88 (0.83; 0.95)	< 0.001
Diuretic use (Yes vs. No)	1.12 (1.05; 1.20)	0.001

OR (95% CI) = Odds Ratio (95% Confidence Interval), COPD = Chronic obstructive pulmonary disease, RAS-inhibitor = renin-angiotensin system inhibitor, MRA = Mineralocorticoid receptor antagonist.

Table S6. Simplified logistic model (i.e. not including NT-proBNP, NYHA class, mean arterial pressure, heart rate, BMI and eGFR) for EF ≥40%

	OR (95% CI)	p-value
Intercept	1.44 (1.31; 1.59)	< 0.001
Age (> 75 years vs. < 75 years)	1.32 (1.26; 1.38)	< 0.001
Sex (Female vs. Male)	1.99 (1.91; 2.08)	< 0.001
Ischemic heart disease (Yes vs. No)	0.78 (0.75; 0.81)	< 0.001
Anemia (Yes vs. No)	1.23 (1.17; 1.28)	< 0.001
Atrial fibrillation (Yes vs. No)	1.52 (1.45; 1.59)	< 0.001
COPD (Yes vs. No)	1.23 (1.16; 1.30)	< 0.001
Diabetes (Yes vs. No)	1.06 (1.01; 1.12)	0.015
Hypertension (Yes vs. No)	1.70 (1.62; 1.77)	< 0.001
Valvular disease (Yes vs. No)	1.13 (1.08; 1.19)	< 0.001
Malignant cancer (Yes vs. No)	1.09 (1.02; 1.16)	0.007
Device therapy (Yes vs. No)	0.34 (0.30; 0.39)	< 0.001
RAS-inhibitor use (Yes vs. No)	0.46 (0.43; 0.49)	< 0.001
Beta-blocker use (Yes vs. No)	0.55 (0.52; 0.59)	< 0.001
MRA use (Yes vs. No)	0.69 (0.66; 0.72)	< 0.001
Digoxin use (Yes vs. No)	0.82 (0.78; 0.87)	< 0.001
Diuretic use (Yes vs. No)	0.74 (0.70; 0.78)	< 0.001

OR (95% CI) = Odds Ratio (95% Confidence Interval), COPD = Chronic obstructive pulmonary disease, RAS-inhibitor = renin-angiotensin system inhibitor, MRA = Mineralocorticoid receptor antagonist.

Table S7. Sensitivity analysis of the logistic model EF ≥50% without NT-proBNP

	OR (95% CI)	p-value
Intercept	0.33 (0.29; 0.38)	< 0.001
Age (> 75 years vs. < 75 years)	1.61 (1.52; 1.71)	< 0.001
Sex (Female vs. Male)	2.33 (2.22; 2.46)	< 0.001
NYHA Class (III/IV vs. I/II)	0.73 (0.68; 0.79)	< 0.001
MAP (≥ 90 vs. < 90 mmHg)	1.17 (1.11; 1.24)	< 0.001
Heart rate (≥ 70 vs. < 70 BPM)	0.81 (0.77; 0.85)	< 0.001
BMI		
(<18.5 vs. 18.5 - 24.9 kg/m2)	0.88 (0.73; 1.07)	0.192
(25 - 29.9 vs. 18.5 - 24.9 kg/m2)	1.29 (1.20; 1.38)	< 0.001
(≥30 vs. 18.5 - 24.9 kg/m2)	1.77 (1.62; 1.93)	< 0.001
eGFR		
(60 - 89.9 vs. ≥ 90 mL/min/1.73m2)	0.87 (0.80; 0.95)	0.003
(30 - 59.9 vs. ≥ 90 mL/min/1.73m2)	0.84 (0.76; 0.92)	< 0.001
(<30 vs. ≥ 90 mL/min/1.73m2)	0.63 (0.55; 0.71)	< 0.001
Ischemic heart disease (Yes vs. No)	0.63 (0.60; 0.67)	< 0.001
Anemia (Yes vs. No)	1.46 (1.38; 1.54)	< 0.001
Atrial fibrillation (Yes vs. No)	1.45 (1.38; 1.54)	< 0.001
COPD (Yes vs. No)	1.37 (1.29; 1.46)	< 0.001
Diabetes (Yes vs. No)	1.03 (0.97; 1.09)	0.318
Hypertension (Yes vs. No)	1.68 (1.59; 1.78)	< 0.001
Valvular disease (Yes vs. No)	1.34 (1.27; 1.42)	< 0.001
Malignant cancer (Yes vs. No)	1.19 (1.11; 1.28)	< 0.001
Device therapy (Yes vs. No)	0.31 (0.25; 0.38)	< 0.001
RAS-inhibitor use (Yes vs. No)	0.40 (0.37; 0.42)	< 0.001
Beta-blocker use (Yes vs. No)	0.51 (0.48; 0.54)	< 0.001
MRA use (Yes vs. No)	0.80 (0.75; 0.84)	< 0.001
Digoxin use (Yes vs. No)	0.92 (0.86; 0.98)	0.012
Diuretic use (Yes vs. No)	1.20 (1.12; 1.29)	< 0.001

OR (95% CI) = Odds Ratio (95% Confidence Interval), NYHA Class = New York Heart Association Class, MAP = Mean arterial pressure, BMI = Body mass index, eGFR = estimated Glomerular filtration rate, COPD = Chronic obstructive pulmonary disease, RAS-inhibitor = renin-angiotensin system inhibitor, MRA = Mineralocorticoid receptor antagonist.

Table S8. Sensitivity analysis of the logistic model EF cut-off ≥40% without NT-proBNP

	OR (95% CI)	p-value
Intercept	1.50 (1.33; 1.69)	< 0.001
Age (> 75 years vs. < 75 years)	1.59 (1.51; 1.67)	< 0.001
Sex (Female vs. Male)	2.11 (2.02; 2.21)	< 0.001
NYHA Class (III/IV vs. I/II)	0.55 (0.52; 0.59)	< 0.001
MAP (≥ 90 vs. < 90 mmHg)	1.21 (1.15; 1.26)	< 0.001
Heart rate (≥ 70 vs. < 70 BPM)	0.76 (0.72; 0.79)	< 0.001
BMI		
(<18.5 vs. 18.5 - 24.9 kg/m2)	0.85 (0.72; 1.01)	0.064
(25 - 29.9 vs. 18.5 - 24.9 kg/m2)	1.30 (1.22; 1.39)	< 0.001
(≥30 vs. 18.5 - 24.9 kg/m2)	1.88 (1.75; 2.02)	< 0.001
eGFR		
(60 - 89.9 vs. ≥ 90 mL/min/1.73m2)	0.90 (0.84; 0.97)	0.004
(30 - 59.9 vs. ≥ 90 mL/min/1.73m2)	0.86 (0.80; 0.93)	< 0.001
(<30 vs. ≥ 90 mL/min/1.73m2)	0.66 (0.59; 0.73)	< 0.001
Ischemic heart disease (Yes vs. No)	0.81 (0.78; 0.85)	< 0.001
Anemia (Yes vs. No)	1.40 (1.33; 1.47)	< 0.001
Atrial fibrillation (Yes vs. No)	1.59 (1.51; 1.66)	< 0.001
COPD (Yes vs. No)	1.33 (1.26; 1.41)	< 0.001
Diabetes (Yes vs. No)	1.02 (0.97; 1.07)	0.545
Hypertension (Yes vs. No)	1.57 (1.50; 1.65)	< 0.001
Valvular disease (Yes vs. No)	1.24 (1.18; 1.31)	< 0.001
Malignant cancer (Yes vs. No)	1.15 (1.08; 1.22)	< 0.001
Device therapy (Yes vs. No)	0.36 (0.32; 0.41)	< 0.001
RAS-inhibitor use (Yes vs. No)	0.41 (0.38; 0.43)	< 0.001
Beta-blocker use (Yes vs. No)	0.53 (0.50; 0.57)	< 0.001
MRA use (Yes vs. No)	0.71 (0.68; 0.75)	< 0.001
Digoxin use (Yes vs. No)	0.86 (0.81; 0.92)	< 0.001
Diuretic use (Yes vs. No)	0.82 (0.78; 0.87)	< 0.001

OR (95% CI) = Odds Ratio (95% Confidence Interval), NYHA Class = New York Heart Association Class, MAP = Mean arterial pressure, BMI = Body mass index, eGFR = estimated Glomerular filtration rate, COPD = Chronic obstructive pulmonary disease, RAS-inhibitor = renin-angiotensin system inhibitor, MRA = Mineralocorticoid receptor antagonist.

Table S9. Sensitivity analysis of the logistic model EF ≥50% without NT-proBNP and NYHA class

LVEF >= 50%	OR (95% CI)	p-value
Intercept	0.32 (0.28, 0.37)	<0.001
Age (> 75 years vs. < 75 years)	1.58 (1.49, 1.67)	<0.001
Sex (Female vs. Male)	2.33 (2.22, 2.46)	<0.001
MAP (≥ 90 vs. < 90 mmHg)	1.20 (1.14, 1.26)	<0.001
Heart rate (≥ 70 vs. < 70 BPM)	0.79 (0.75, 0.84)	<0.001
BMI		
(<18.5 vs. 18.5 - 24.9 kg/m2)	0.86 (0.71, 1.04)	0.12
(25 - 29.9 vs. 18.5 - 24.9 kg/m2)	1.29 (1.20, 1.38)	<0.001
(≥30 vs. 18.5 - 24.9 kg/m2)	1.75 (1.60, 1.91)	<0.001
eGFR		
(60 - 89.9 vs. ≥ 90 mL/min/1.73m2)	0.87 (0.80, 0.96)	0.003
(30 - 59.9 vs. ≥ 90 mL/min/1.73m2)	0.82 (0.75, 0.90)	<0.001
(<30 vs. ≥ 90 mL/min/1.73m2)	0.60 (0.53, 0.67)	<0.001
Ischemic heart disease (Yes vs. No)	0.63 (0.59, 0.66)	<0.001
Anemia (Yes vs. No)	1.44 (1.36, 1.52)	<0.001
Atrial fibrillation (Yes vs. No)	1.45 (1.37, 1.53)	<0.001
COPD (Yes vs. No)	1.34 (1.26, 1.42)	<0.001
Diabetes (Yes vs. No)	1.01 (0.95, 1.07)	0.696
Hypertension (Yes vs. No)	1.68 (1.59, 1.78)	<0.001
Valvular disease (Yes vs. No)	1.31 (1.24, 1.39)	<0.001
Malignant cancer (Yes vs. No)	1.18 (1.10, 1.27)	<0.001
Device therapy (Yes vs. No)	0.30 (0.24, 0.37)	<0.001
RAS-inhibitor use (Yes vs. No)	0.40 (0.38, 0.43)	<0.001
Beta-blocker use (Yes vs. No)	0.51 (0.48, 0.55)	<0.001
MRA use (Yes vs. No)	0.78 (0.74, 0.83)	<0.001
Digoxin use (Yes vs. No)	0.91 (0.85, 0.98)	0.009
Diuretic use (Yes vs. No)	1.15 (1.07, 1.24)	<0.001

OR (95% CI) = Odds Ratio (95% Confidence Interval), NYHA Class = New York Heart Association Class, MAP = Mean arterial pressure, BMI = Body mass index, eGFR = estimated Glomerular filtration rate, COPD = Chronic obstructive pulmonary disease, RAS-inhibitor = renin-angiotensin system inhibitor, MRA = Mineralocorticoid receptor antagonist.

Table S10. Sensitivity analysis of the logistic model EF ≥40% without NT-proBNP and NYHA class

LVEF >= 40%	OR (95% CI)	p-value
Intercept	1.39 (1.23, 1.56)	<0.001
Age (> 75 years vs. < 75 years)	1.51 (1.44, 1.58)	<0.001
Sex (Female vs. Male)	2.10 (2.01, 2.19)	<0.001
MAP (≥ 90 vs. < 90 mmHg)	1.25 (1.20, 1.30)	<0.001
Heart rate (≥ 70 vs. < 70 BPM)	0.73 (0.70, 0.77)	<0.001
BMI		
(<18.5 vs. 18.5 - 24.9 kg/m2)	0.82 (0.70, 0.96)	0.015
(25 - 29.9 vs. 18.5 - 24.9 kg/m2)	1.30 (1.22, 1.38)	<0.001
(≥30 vs. 18.5 - 24.9 kg/m2)	1.83 (1.70, 1.96)	<0.001
eGFR		
(60 - 89.9 vs. ≥ 90 mL/min/1.73m2)	0.90 (0.84, 0.97)	0.006
(30 - 59.9 vs. ≥ 90 mL/min/1.73m2)	0.83 (0.77, 0.90)	<0.001
(<30 vs. ≥ 90 mL/min/1.73m2)	0.60 (0.54, 0.67)	<0.001
Ischemic heart disease (Yes vs. No)	0.79 (0.76, 0.83)	<0.001
Anemia (Yes vs. No)	1.36 (1.30, 1.43)	<0.001
Atrial fibrillation (Yes vs. No)	1.56 (1.49, 1.64)	<0.001
COPD (Yes vs. No)	1.26 (1.19, 1.33)	<0.001
Diabetes (Yes vs. No)	0.98 (0.93, 0.03)	0.434
Hypertension (Yes vs. No)	1.56 (1.49, 1.63)	<0.001
Valvular disease (Yes vs. No)	1.19 (1.13, 1.25)	<0.001
Malignant cancer (Yes vs. No)	1.13 (1.06, 1.20)	<0.001
Device therapy (Yes vs. No)	0.35 (0.30, 0.40)	<0.001
RAS-inhibitor use (Yes vs. No)	0.41 (0.39, 0.44)	<0.001
Beta-blocker use (Yes vs. No)	0.54 (0.51, 0.58)	<0.001
MRA use (Yes vs. No)	0.69 (0.65, 0.72)	<0.001
Digoxin use (Yes vs. No)	0.86 (0.81, 0.91)	<0.001
Diuretic use (Yes vs. No)	0.76 (0.72, 0.81)	<0.001

OR (95% CI) = Odds Ratio (95% Confidence Interval), NYHA Class = New York Heart Association Class, MAP = Mean arterial pressure, BMI = Body mass index, eGFR = estimated Glomerular filtration rate, COPD = Chronic obstructive pulmonary disease, RAS-inhibitor = renin-angiotensin system inhibitor, MRA = Mineralocorticoid receptor antagonist.

Table S11. Simplified multinomial model (i.e. not including NT-proBNP, NYHA class, mean arterial pressure, heart rate, BMI and eGFR)

	HFmrEF OR (95% CI)	p-value	HFpEF OR (95% CI)	p-value
Intercept	0.70 (0.62; 0.78)	< 0.001	0.60 (0.53; 0.67)	< 0.001
Age (> 75 years vs. < 75 years)	1.20 (1.14; 1.27)	< 0.001	1.47 (1.39; 1.56)	< 0.001
Sex (Female vs. Male)	1.54 (1.46; 1.63)	< 0.001	2.59 (2.45; 2.73)	< 0.001
Ischemic heart disease (Yes vs. No)	0.98 (0.93; 1.03)	0.448	0.61 (0.58; 0.64)	< 0.001
Anemia (Yes vs. No)	1.12 (1.06; 1.18)	< 0.001	1.36 (1.29; 1.44)	< 0.001
Atrial fibrillation (Yes vs. No)	1.46 (1.38; 1.54)	< 0.001	1.61 (1.52; 1.70)	< 0.001
COPD (Yes vs. No)	1.11 (1.04; 1.19)	0.002	1.36 (1.28; 1.45)	< 0.001
Diabetes (Yes vs. No)	1.03 (0.97; 1.09)	0.399	1.10 (1.04; 1.17)	0.001
Hypertension (Yes vs. No)	1.45 (1.38; 1.53)	< 0.001	2.03 (1.92; 2.15)	< 0.001
Valvular disease (Yes vs. No)	1.02 (0.96; 1.08)	0.603	1.26 (1.19; 1.33)	< 0.001
Malignant cancer (Yes vs. No)	1.04 (0.96; 1.12)	0.352	1.15 (1.07; 1.24)	< 0.001
Device therapy (Yes vs. No)	0.42 (0.36; 0.48)	< 0.001	0.24 (0.19; 0.30)	< 0.001
RAS-inhibitor use (Yes vs. No)	0.60 (0.56; 0.65)	< 0.001	0.36 (0.34; 0.39)	< 0.001
Beta-blocker use (Yes vs. No)	0.68 (0.63; 0.74)	< 0.001	0.45 (0.42; 0.49)	< 0.001
MRA use (Yes vs. No)	0.68 (0.64; 0.72)	< 0.001	0.70 (0.66; 0.74)	< 0.001
Digoxin use (Yes vs. No)	0.82 (0.76; 0.88)	< 0.001	0.83 (0.77; 0.89)	< 0.001
Diuretic use (Yes vs. No)	0.63 (0.59; 0.67)	< 0.001	0.96 (0.89; 1.03)	0.221

OR (95% CI) = Odds Ratio (95% Confidence Interval), HFmrEF = Heart failure with mid-range ejection fraction, HFpEF = Heart failure with preserved ejection fraction, COPD = Chronic obstructive pulmonary disease, RAS-inhibitor = renin-angiotensin system inhibitor, MRA = Mineralocorticoid receptor antagonist.

Table S12. Sensitivity analysis of the multinomial model without NT-proBNP

	HFmrEF OR (95% CI)	p-value	HFpEF OR (95% CI)	p-value
Intercept	0.73 (0.63; 0.84)	< 0.001	0.61 (0.52; 0.71)	< 0.001
Age (> 75 years vs. < 75 years)	1.41 (1.33; 1.49)	< 0.001	1.81 (1.70; 1.93)	< 0.001
Sex (Female vs. Male)	1.63 (1.54; 1.72)	< 0.001	2.76 (2.61; 2.93)	< 0.001
NYHA Class (III/IV vs. I/II)	0.52 (0.49; 0.56)	< 0.001	0.59 (0.54; 0.64)	< 0.001
MAP (≥ 90 vs. < 90 mmHg)	1.18 (1.12; 1.24)	< 0.001	1.24 (1.17; 1.31)	< 0.001
Heart rate (≥ 70 vs. < 70 BPM)	0.78 (0.74; 0.82)	< 0.001	0.74 (0.70; 0.78)	< 0.001
BMI				
(<18.5 vs. 18.5 - 24.9 kg/m2)	0.87 (0.71; 1.07)	0.18	0.84 (0.68; 1.03)	0.092
(25 - 29.9 vs. 18.5 - 24.9 kg/m2)	1.23 (1.14; 1.33)	< 0.001	1.38 (1.28; 1.49)	< 0.001
(≥30 vs. 18.5 - 24.9 kg/m2)	1.68 (1.53; 1.84)	< 0.001	2.13 (1.95; 2.32)	< 0.001
eGFR				
(60 - 89.9 vs. ≥ 90 mL/min/1.73m2)	0.94 (0.86; 1.02)	0.143	0.85 (0.78; 0.94)	0.001
(30 - 59.9 vs. ≥ 90 mL/min/1.73m2)	0.91 (0.83; 1.00)	0.043	0.81 (0.73; 0.89)	< 0.001
(<30 vs. ≥ 90 mL/min/1.73m2)	0.76 (0.67; 0.86)	< 0.001	0.57 (0.50; 0.65)	< 0.001
Ischemic heart disease (Yes vs. No)	1.02 (0.96; 1.07)	0.565	0.64 (0.60; 0.67)	< 0.001
Anemia (Yes vs. No)	1.26 (1.18; 1.33)	< 0.001	1.58 (1.49; 1.67)	< 0.001
Atrial fibrillation (Yes vs. No)	1.52 (1.44; 1.61)	< 0.001	1.68 (1.58; 1.78)	< 0.001
COPD (Yes vs. No)	1.21 (1.13; 1.30)	< 0.001	1.47 (1.37; 1.57)	< 0.001
Diabetes (Yes vs. No)	1.00 (0.94; 1.07)	0.946	1.03 (0.97; 1.10)	0.334
Hypertension (Yes vs. No)	1.36 (1.29; 1.44)	< 0.001	1.86 (1.76; 1.98)	< 0.001
Valvular disease (Yes vs. No)	1.11 (1.05; 1.18)	0.001	1.39 (1.31; 1.48)	< 0.001
Malignant cancer (Yes vs. No)	1.09 (1.01; 1.18)	0.028	1.22 (1.13; 1.32)	< 0.001
Device therapy (Yes vs. No)	0.44 (0.38; 0.52)	< 0.001	0.26 (0.21; 0.32)	< 0.001
RAS-inhibitor use (Yes vs. No)	0.54 (0.50; 0.59)	< 0.001	0.32 (0.29; 0.34)	< 0.001
Beta-blocker use (Yes vs. No)	0.66 (0.61; 0.71)	< 0.001	0.44 (0.41; 0.47)	< 0.001
MRA use (Yes vs. No)	0.70 (0.66; 0.75)	< 0.001	0.71 (0.67; 0.76)	< 0.001
Digoxin use (Yes vs. No)	0.86 (0.80; 0.92)	< 0.001	0.87 (0.81; 0.93)	< 0.001
Diuretic use (Yes vs. No)	0.70 (0.66; 0.75)	< 0.001	1.05 (0.98; 1.14)	0.171

OR (95% CI) = Odds Ratio (95% Confidence Interval), HFmrEF = Heart failure with mid-range ejection fraction, HFpEF = Heart failure with preserved ejection fraction, NYHA Class = New York Heart Association Class, MAP = Mean arterial pressure, BMI = Body mass index, eGFR = estimated Glomerular filtration rate, COPD = Chronic obstructive pulmonary disease, RAS-inhibitor = renin-angiotensin system inhibitor, MRA = Mineralocorticoid receptor antagonist

Table S13. Sensitivity analysis of the multinomial model without NT-proBNP and NYHA class

Multinomial	HFmrEF OR (95% CI)	p-value	HFpEF OR (95% CI)	p-value
Intercept	0.67 (0.58, 0.78)	<0.001	0.57 (0.49, 0.66)	<0.001
Age (> 75 years vs. < 75 years)	1.33 (1.26, 1.41)	<0.001	1.73 (1.63, 1.84)	<0.001
Sex (Female vs. Male)	1.62 (1.53, 1.71)	<0.001	2.75 (2.61, 2.91)	<0.001
MAP (≥ 90 vs. < 90 mmHg)	1.22 (1.16, 1.29)	<0.001	1.28 (1.21, 1.35)	<0.001
Heart rate (≥ 70 vs. < 70 BPM)	0.75 (0.71, 0.79)	<0.001	0.72 (0.68, 0.76)	<0.001
BMI				
(<18.5 vs. 18.5 - 24.9 kg/m2)	0.83 (0.69, 1.01)	0.06	0.81 (0.66, 0.99)	0.038
(25 - 29.9 vs. 18.5 - 24.9 kg/m2)	1.23 (1.13, 1.33)	<0.001	1.38 (1.28, 1.49)	<0.001
(≥30 vs. 18.5 - 24.9 kg/m2)	1.63 (1.49, 1.78)	<0.001	2.07 (1.90, 2.26)	<0.001
eGFR				
(60 - 89.9 vs. ≥ 90 mL/min/1.73m2)	0.94 (0.87, 1.03)	0.188	0.86 (0.78, 0.94)	0.001
(30 - 59.9 vs. ≥ 90 mL/min/1.73m2)	0.88 (0.80, 0.96)	0.005	0.79 (0.71, 0.87)	<0.001
(<30 vs. ≥ 90 mL/min/1.73m2)	0.69 (0.61, 0.79)	<0.001	0.53 (0.46, 0.60)	<0.001
Ischemic heart disease (Yes vs. No)	0.99 (0.94, 1.04)	0.68	0.62 (0.59, 0.66)	<0.001
Anemia (Yes vs. No)	1.22 (1.15, 1.29)	<0.001	1.54 (1.46, 1.63)	<0.001
Atrial fibrillation (Yes vs. No)	1.50 (1.42, 1.58)	<0.001	1.66 (1.56, 1.76)	<0.001
COPD (Yes vs. No)	1.14 (1.06, 1.22)	<0.001	1.40 (1.31, 1.49)	<0.001
Diabetes (Yes vs. No)	0.96 (0.91, 1.02)	0.235	1.00 (0.94, 1.06)	0.968
Hypertension (Yes vs. No)	1.35 (1.28, 1.43)	<0.001	1.86 (1.75, 1.97)	<0.001
Valvular disease (Yes vs. No)	1.06 (1.00, 1.12)	0.064	1.34 (1.26, 1.42)	<0.001
Malignant cancer (Yes vs. No)	1.07 (0.99, 1.15)	0.086	1.20 (1.12, 1.30)	<0.001
Device therapy (Yes vs. No)	0.42 (0.36, 0.49)	<0.001	0.25 (0.20, 0.31)	<0.001
RAS-inhibitor use (Yes vs. No)	0.55 (0.51, 0.60)	<0.001	0.32 (0.30, 0.34)	<0.001
Beta-blocker use (Yes vs. No)	0.67 (0.62, 0.72)	<0.001	0.44 (0.41, 0.48)	<0.001
MRA use (Yes vs. No)	0.68 (0.64, 0.72)	<0.001	0.69 (0.65, 0.73)	<0.001
Digoxin use (Yes vs. No)	0.85 (0.79, 0.91)	<0.001	0.86 (0.80, 0.93)	<0.001
Diuretic use (Yes vs. No)	0.64 (0.60, 0.69)	<0.001	0.98 (0.91, 1.06)	0.66

OR (95% CI) = Odds Ratio (95% Confidence Interval), HFmrEF = Heart failure with mid-range ejection fraction, HFpEF = Heart failure with preserved ejection fraction, NYHA Class = New York Heart Association Class, MAP = Mean arterial pressure, BMI = Body mass index, eGFR = estimated Glomerular filtration rate, COPD = Chronic obstructive pulmonary disease, RAS-inhibitor = renin-angiotensin system inhibitor, MRA = Mineralocorticoid receptor antagonist.

Figure S1a. Study flow SwedeHF

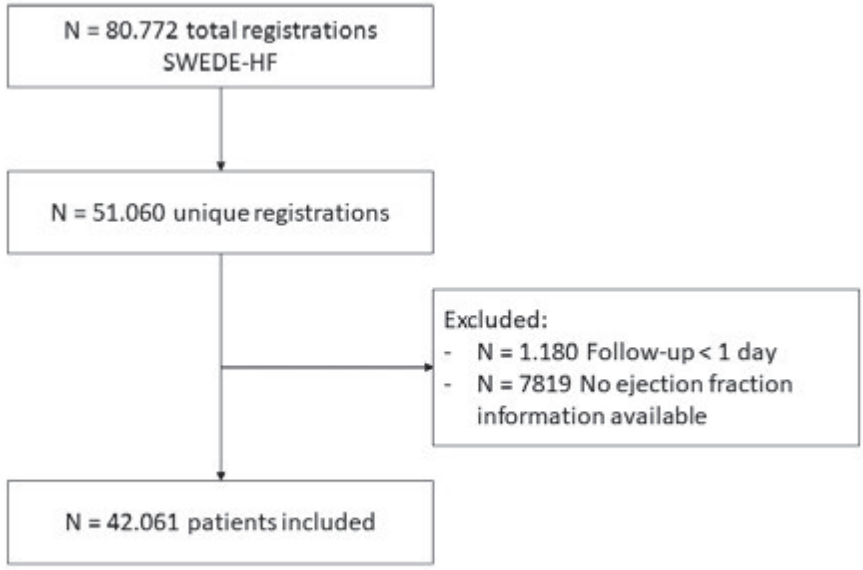


Figure S1b. Study flow CHECK-HF

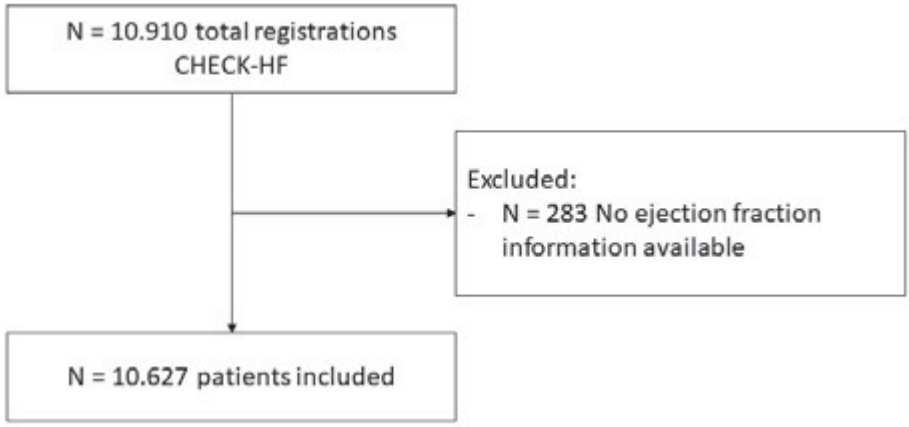
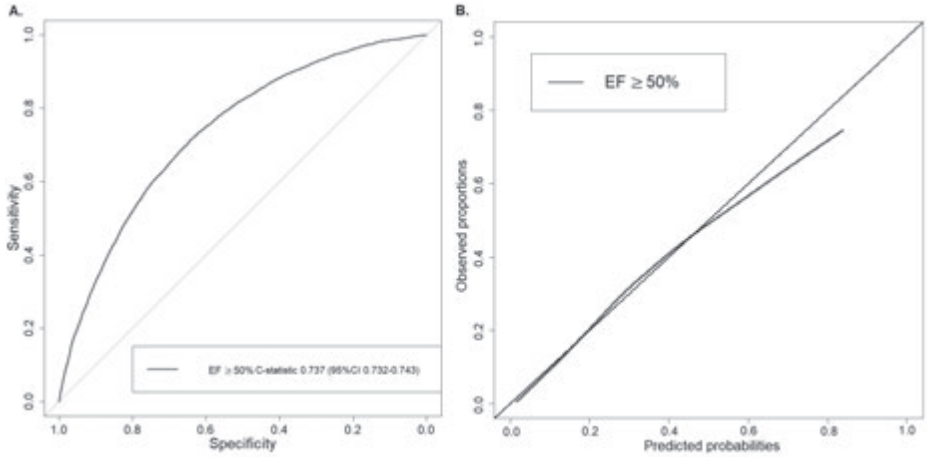
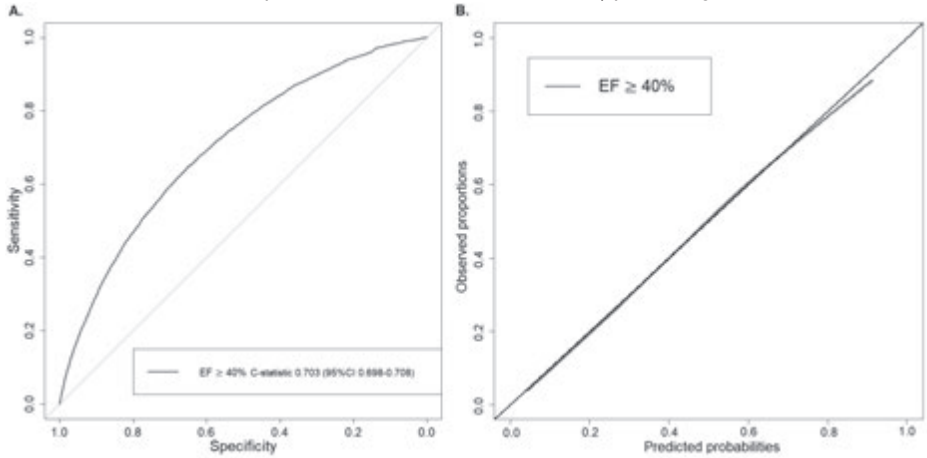


Figure S2. Discrimination and calibration of the simplified logistic model (i.e. not including NT-proBNP, NYHA class, mean arterial pressure, heart rate, BMI and eGFR) predicting EF ≥50%



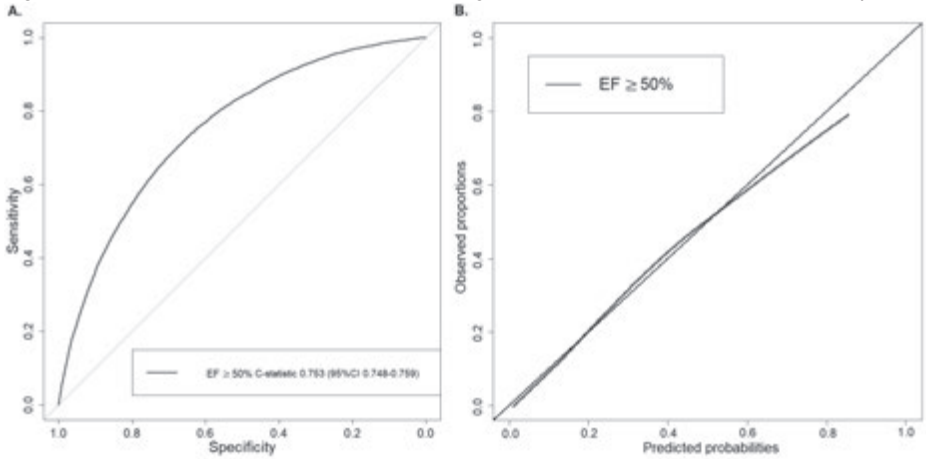
A. ROC curve, **B.** Calibration plot of observed proportions vs. predicted probabilities to assess the goodness-of-fit.

Figure S3. Discrimination and calibration simplified logistic model (i.e. not including NT-proBNP, NYHA class, mean arterial pressure, heart rate, BMI and eGFR) predicting EF cut-off ≥40%



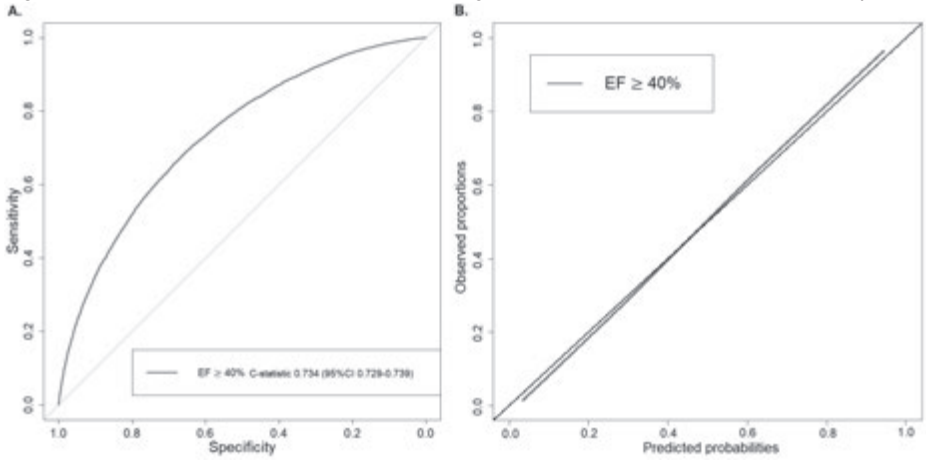
A. ROC curve, **B.** Calibration plot of observed proportions vs. predicted probabilities to assess the goodness-of-fit.

Figure S4. Discrimination and calibration of the logistic model EF cut-off ≥50% without NT-proBNP



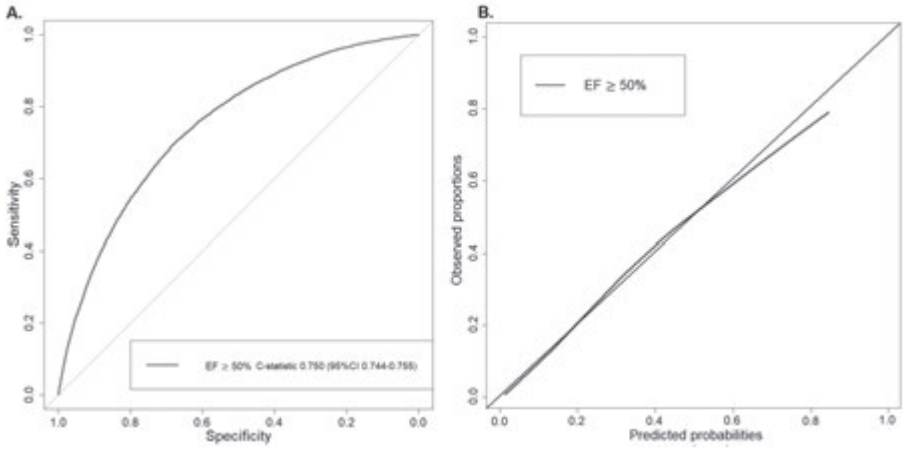
A. ROC curve, **B.** Calibration plot of observed proportions vs. predicted probabilities to assess the goodness-of-fit.

Figure S5. Discrimination and calibration of the logistic model EF cut-off ≥40% without NT-proBNP



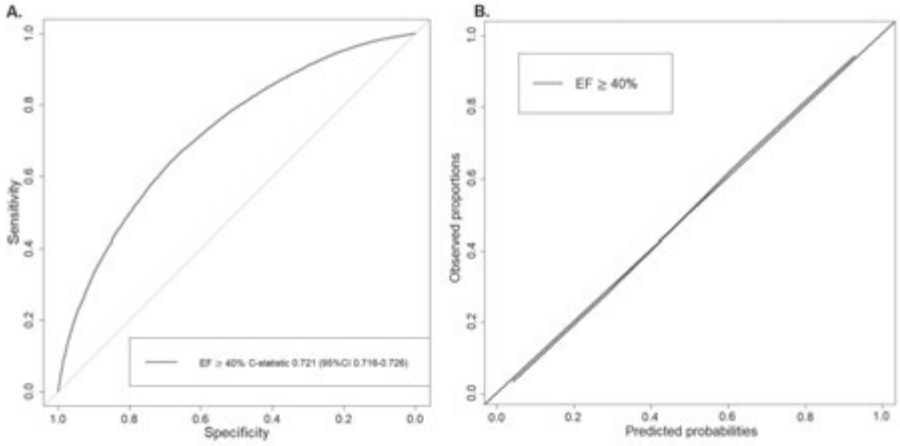
A. ROC curve, **B.** Calibration plot of observed proportions vs. predicted probabilities to assess the goodness-of-fit.

Figure S6. Discrimination and calibration of the logistic model EF cut-off ≥50% without NT-proBNP and NYHA class



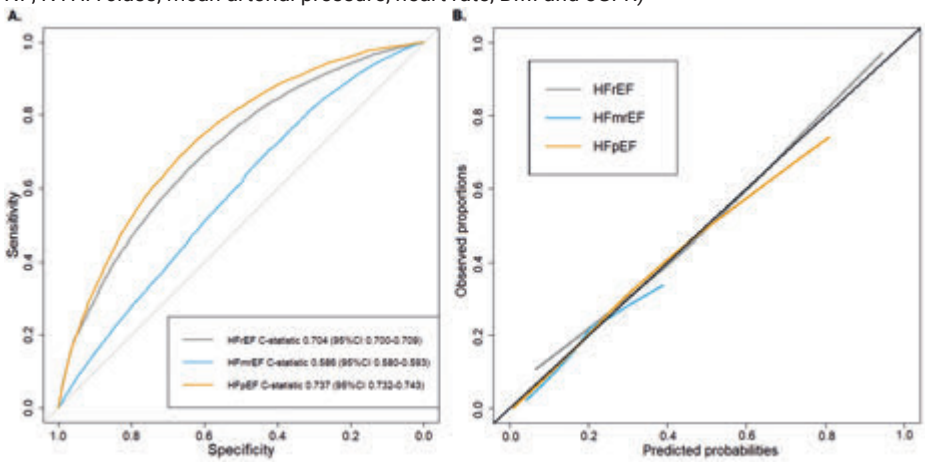
A. ROC curve, **B.** Calibration plot of observed proportions vs. predicted probabilities to assess the goodness-of-fit.

Figure S7. Discrimination and calibration of the logistic model EF cut-off ≥40% without NT-proBNP and NYHA class



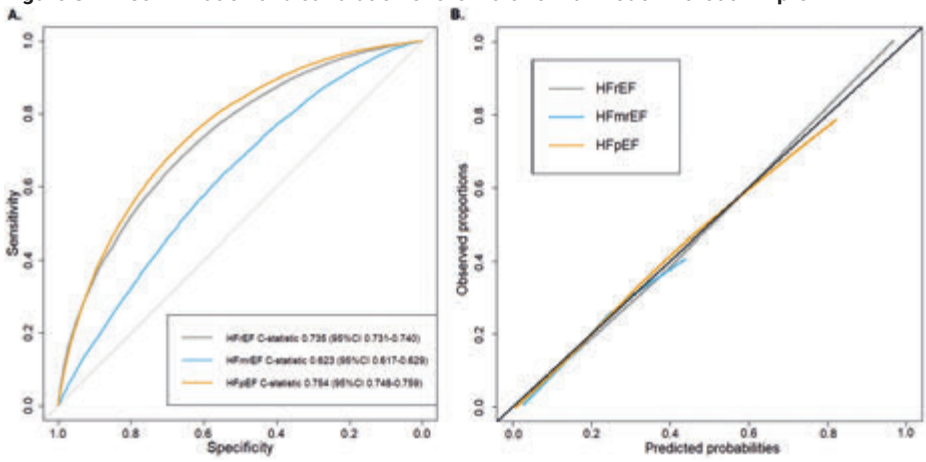
A. ROC curve, **B.** Calibration plot of observed proportions vs. predicted probabilities to assess the goodness-of-fit.

Figure S8. Simplified multinomial model discrimination and calibration (i.e. not including NT-proBNP, NYHA class, mean arterial pressure, heart rate, BMI and eGFR)



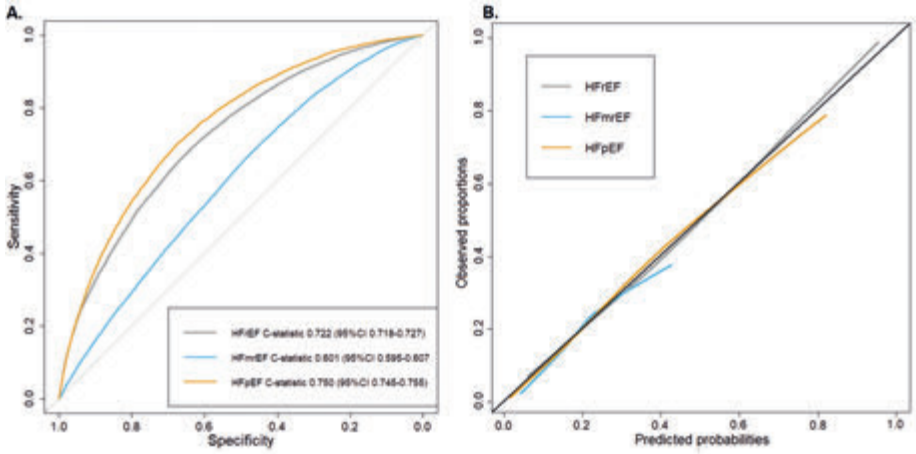
A. ROC curve **B.** Calibration plot of observed proportions vs. predicted probabilities to assess the goodness-of-fit. The plots are displaying one-vs-all approach, i.e. HFrEF vs HFmrEF + HFpEF, HFmrEF vs. HFrEF + HFpEF and HFpEF vs. HFmrEF + HFrEF.

Figure S9. Discrimination and calibration of the multinomial model without NT-proBNP



A. ROC curve **B.** Calibration plot of observed proportions vs. predicted probabilities to assess the goodness-of-fit. The plots are displaying one-vs-all approach, i.e. HFrEF vs HFmrEF + HFpEF, HFmrEF vs. HFrEF + HFpEF and HFpEF vs. HFmrEF + HFrEF.

Figure S10. Discrimination and calibration of the multinomial model without NT-proBNP and NYHA class



A. ROC curve **B.** Calibration plot of observed proportions vs. predicted probabilities to assess the goodness-of-fit. The plots are displaying one-vs-all approach, i.e. HFrEF vs HFmrEF + HFpEF, HFmrEF vs. HFrEF + HFpEF and HFpEF vs. HFmrEF + HFrEF.

CHAPTER 9

DERIVATION AND VALIDATION OF PHENOTYPIC CLUSTERS IN HEART FAILURE WITH PRESERVED EJECTION FRACTION

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Abstract

Aims. We aimed to derive and validate clinically useful clusters of patients with heart failure with preserved ejection fraction (HFpEF).

Methods and results. We derived a model from 2,153 HFpEF (defined as EF≥50%) patients from the Chronic Heart Failure ESC-guideline based Cardiology Practice Quality project (CHECK-HF) registry and externally validated in 6,770 patients from the Swedish Heart Failure Registry (SwedeHF). In CHECK-HF, median age was 77 [IQR 15] years, 54% were female and the most reported comorbidities were hypertension (50.7%), atrial fibrillation (38.4%), and diabetes (30.0%). Diuretics were most frequently prescribed (79.4%), followed by beta-blockers (78.3%), RAS-inhibitors (67.3%) and MRAs (38.5%). Latent class analysis identified four distinct HFpEF clusters: Class 1 (12.4% of patients) exhibited several characteristics similar to the HFrEF phenotype (notably history of ischaemic heart disease), class 2 (39.5%) were the oldest with concomitant atrial fibrillation, class 3 (21.7%) were the youngest with less comorbidities and medication use and lastly class 4 (26.4%) exhibited the 'classic HFpEF phenotype' (older age, hypertension, diabetes, female sex and diuretics use). These clusters were externally validated where, in addition, we observed differences in prognosis with cluster 3 having the best prognosis and cluster 2 the worst.

Conclusions. Four distinct clusters of HFpEF patients were identified that differed in clinical characteristics, HF drug therapy and prognosis. These results confirm the heterogeneity of HFpEF and form a basis for tailoring trial design to individualized drug therapy in HFpEF patients.

Introduction

Left ventricular ejection fraction (LVEF) is still the most commonly used marker to distinguish clinical sub-groups of heart failure (HF) but insufficiently reflects the heterogeneity of this chronic disease.[1,2] Based on LVEF, patients could be classified into HF with reduced ejection fraction (HFrEF; LVEF < 40%), mid-range ejection fraction (HFmrEF; LVEF 40 – 49%) or preserved ejection fraction (HFpEF; LVEF ≥ 50%).[3]

Due to the lack of evidence-based treatments, the European Society of Cardiology guidelines recommend treatment of HFpEF patients based on comorbidities and alleviating symptoms.[3] However, in the American College of Cardiology/American Heart Association focused update on HF management spironolactone (an mineralocorticoid receptor antagonist (MRA)) has a grade IIb recommendation and could be considered to treat selected HFpEF patients to decrease hospitalizations.[6] This recommendation was based on the post-hoc analysis on regional variation in the TOPCAT trial showing a beneficial effect of MRAs.[7–9]

The heterogeneity in HFpEF pathophysiology is proposed as one of the key arguments for the failure of clinical trials to establish clinically relevant effects of interventions. It is suggested that treatment in HFpEF patients should therefore be matched to distinct subsets of comorbidities, thus identifying patient groups most likely to benefit from targeted interventions. Possible effective HFpEF therapy could thus be determined by the identification of distinct HFpEF patient clusters.[10,11] Previous studies were conducted in smaller and selected HFpEF populations or included many characteristics that are often unavailable in commonly used registries.

The aim was to derive and validate clinically useful HFpEF clusters that distinguish clinical characteristics and outcomes based on easily accessible characteristics and thus creating HFpEF clusters that are widely applicable in different settings, including clinical trial design.

Methods

Derivation cohort

The Chronic Heart Failure ESC-guideline based Cardiology Practice Quality project registry (CHECK-HF) registry is a cross-sectional registration of unselected patients from 34 Dutch hospitals with the diagnosis of chronic HF treated at outpatient HF clinics (96%) or general cardiology outpatient clinics of the same hospitals (4%) in the period between September 2013 and September 2016. The registry contains 10,910 patients with chronic HF.[12]

Patients were included if they were 18 years or older and had a HF diagnosis based on the ESC guidelines: i.e. structural and/or functional cardiac abnormalities, signs and symptoms of HF.[3] Baseline ejection fraction was assessed by echocardiography and was available for the majority of the patients at inclusion (73%). HFpEF was classified as a LVEF $\geq$ 50% with no previously known reduced LVEF. In total, 2,267 (21.3%) patients in the registry were classified as HFpEF patients. From the patients classified as HFpEF, we included 2,153 patients for the analyses. We excluded 114 patients for whom information on HF drug treatment was lacking in the database.

This study was approved by the medical ethics committee 2017 at Maastricht University Medical Center (Maastricht, the Netherlands).

External validation cohort

The Swedish heart failure registry (SwedeHF) has been previously described in detail.[13] Briefly, SwedeHF was established in 2000 and broadly implemented throughout Sweden by 2003. The only inclusion criterion is clinician-judged HF. Patients are registered at discharge from hospital or after outpatient clinic visit on a web-based care report form and entered into the database (managed by Uppsala Clinical Research Center, Uppsala, Sweden). All permanent residents in Sweden have unique personal identification numbers that allows linking of disease-specific health registries and governmental health and statistical registries. For the current analysis, we linked SwedeHF to the National Patient Registry and the Cause of Death Registry, which provided additional data on baseline comorbidities, cause-specific outcomes and all-cause mortality.

In this study we included 8,555 patients with known LVEF > 50% and registered between 1 January 2012 and 31 December 2016. We excluded patients with in-

hospital death, i.e. follow-up > 1 day (n = 264) and only the first registration was considered (n = 3,372 multiple registrations excluded). This analysis received ethics committee approval. In SwedeHF, patients do not provide written informed consent, but are informed of entry into national quality registries and allowed to opt out.

Classification variables

We wielded a pragmatic approach to select the variables used for the analyses. We received clinician input and considered the presence of the variable in both registries. We selected 15 variables for the analyses: age, sex, body mass index (BMI), mean arterial pressure, heart rate, estimated glomerular filtration rate (eGFR), NYHA class, history of ischemic heart disease or valvular heart disease, presence of HF devices: no/yes (implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT)), comorbidities: atrial fibrillation (AF), diabetes mellitus (DM), hypertension, anemia, peripheral artery disease (PAD), and chronic obstructive pulmonary disease (COPD).

Outcomes

Information on current medication use was recorded for: beta-blockers, MRAs, diuretics and RAS-inhibitors: ACE-inhibitors and angiotensin II receptor blockers (ARB). In the validation cohort we furthermore assessed all-cause mortality and HF hospitalization.

Statistical analyses

Baseline continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR); categorical data is presented as counts and percentages (%).

Missing data in the baseline measurements (**Table S1**) was imputed, using multiple imputation, according to the mice algorithm in the statistical software package R. Analyses were performed on the 10 imputed datasets separately and results were pooled using Rubin's rules.

Independent predictors of use of diuretics, beta-blockers, RAS-inhibitors and MRAs were assessed using multivariable logistic regression analysis. All predictors of medication use in univariate analysis (data not shown) at p-value of <0.1 were included in the multivariable regression analysis. Results are presented as odds ratio (OR) and 95% confidence intervals.

Latent class analysis (LCA) was used to identify clusters of individuals with similar clinical profiles, using the *poLCA* package of R analysis. Latent class clusters of individuals were derived using maximum-likelihood estimation to identify the most common patterns of the predefined variables for a range of 2–10 subgroups. Informed by literature, the variables that were selected for the LCA were: age (<60 years, 60–75 years and >75 years), sex (male/female), NYHA class (I/II vs. III/IV), history of ischaemic heart disease (yes/no) and valvular disease (yes/no), BMI (<25 kg/m^2, 25-30 kg/m^2, >30 kg/m^2), eGFR (<30, 30-60 and >60 mL/min/1.73m^2), mean arterial pressure (<90 vs. >=90 mmHg), heart rate (<70 vs. >=70 bpm), HF devices (yes/no) and the comorbidities: AF, COPD, DM, hypertension, anemia, and PAD (yes/no). The optimal number of clusters of 4 was determined using the first minima of the Bayesian Information Criterion (BIC) and chi squared statistic (**Figure S1**). Patients were classified into latent classes (clusters), based on their probabilities of membership in each subgroup for every predefined categorical variable (**Table S2**). We investigated whether medication use differed between the latent classes of HFpEF patients created by LCA.

The clusters found in the CHECK-HF registry were validated in the SwedeHF registry by applying the subgroup probabilities (**Table S2**) to the validation cohort. Patients were classified according to the highest probability of cluster membership. We assessed whether the clusters were associated with all-cause mortality and HF hospitalization with a Cox proportional hazard model and visualization with Kaplan-Meier curves.

All analyses were performed using R version 3.2.3.

Results

Baseline characteristics

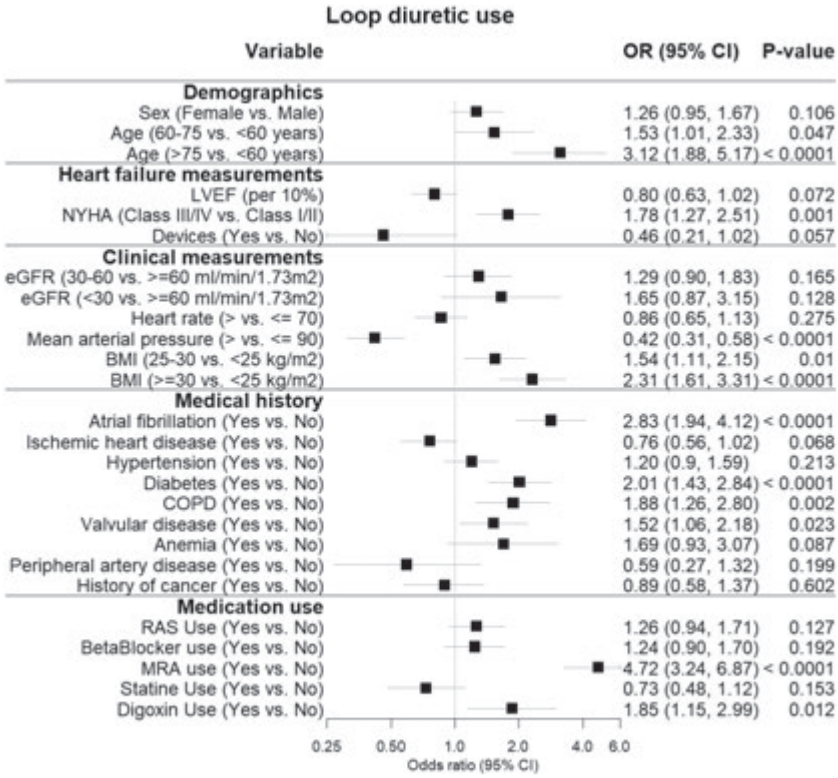
Baseline characteristics are shown in **Table 1**. Overall, in the CHECK-HF cohort, the median age was 77 years [IQR 69 – 84 years] and 54.5% were female. Comorbidities were common, of which hypertension, AF and DM were most prevalent. Diuretics were the most frequently prescribed type of HF medication, followed by beta-blockers, RAS-inhibitors and MRAs. (**Table 1**). In the SwedeHF registry, the median age was 80 years old [IQR 72 – 86 years] and 52.7% were female. Most prevalent comorbidities were similar to CHECK-HF, with the exception of anemia, which was more prevalent in SwedeHF. Medication use

was also similar, with beta-blockers and diuretics as most frequently prescribed medication (**Table 2**). Overall, comorbidities were more prevalent in SwedeHF, while device implantation, MRA, digoxin and statin use were more prevalent in CHECK-HF.

Determinants of drug therapy

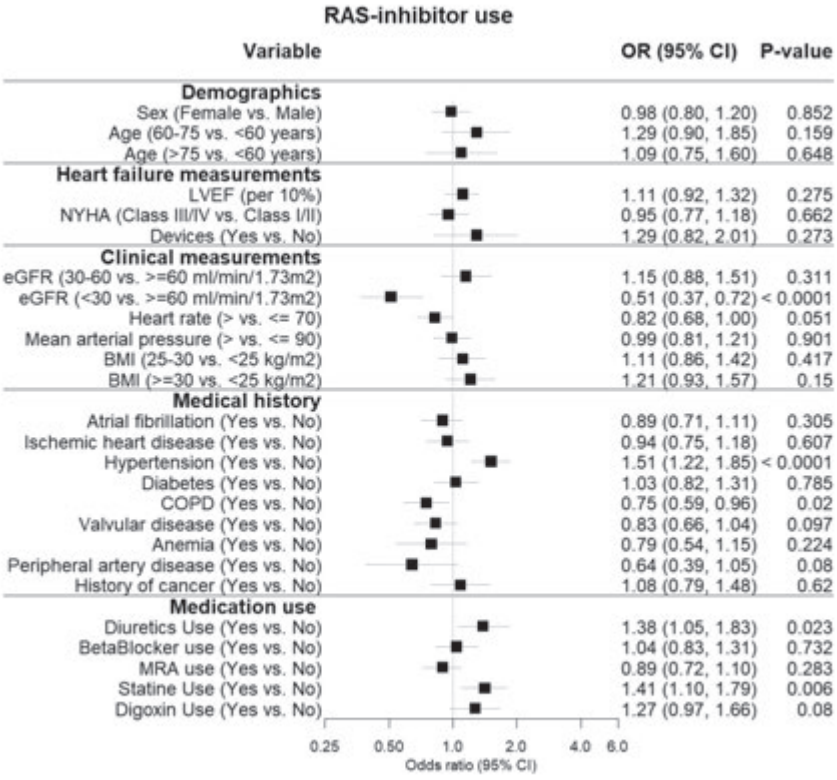
Multivariable predictors for drug therapy use of loop diuretics, RAS-inhibitors, beta-blockers and MRAs are shown in **Figure 1 - 4**. Older age, higher NYHA class, higher BMI, valvular disease, AF, COPD, DM and concomitant medication use of MRA and digoxin were all positively associated with loop diuretic use (**Figure 1**) with only higher mean arterial pressure negatively associated with loop diuretic use. In contrast, lower eGFR and COPD were negatively associated with RAS-inhibitor use (**Figure 2**), while hypertension, statin and diuretic use were statistically significant predictors for RAS-inhibitor use. Ischaemic heart disease, higher mean arterial pressure, BMI > 30 kg/m^2, digoxin and statin use were positively associated with beta-blocker use, while a higher heart rate was a negative predictor (**Figure 3**). Lastly, the statistically significant predictors for MRA use were: higher NYHA class, device therapy, lower eGFR, mean arterial pressure, AF, valvular disease, PAD, statin and diuretics use (**Figure 4**).

Figure 1. Determinants of diuretic use in HFpEF patients.



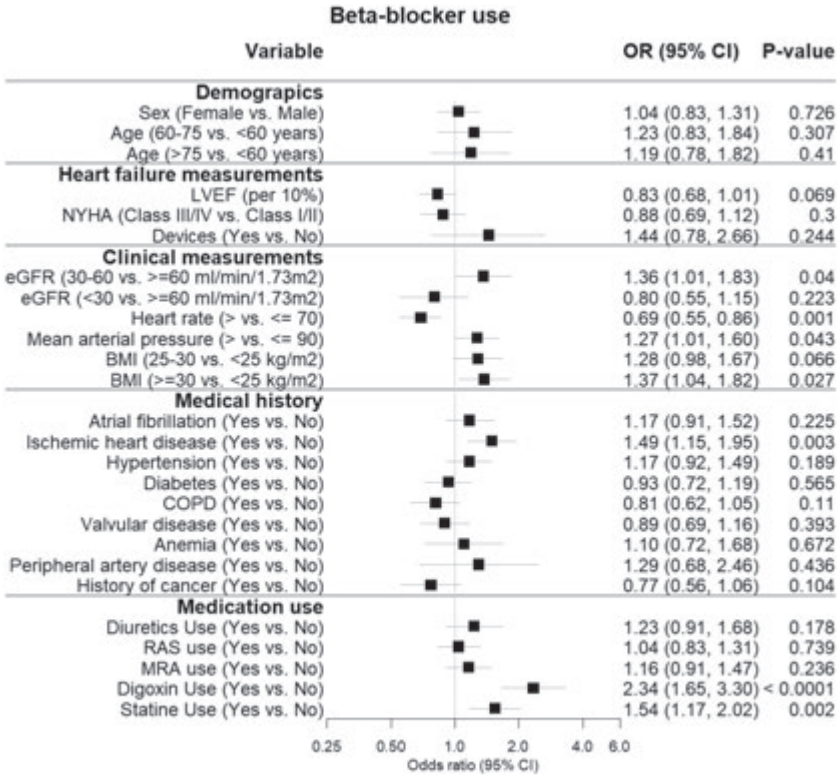
LVEF: Left Ventricular Ejection Fraction; NYHA class: New York Heart Association class; BMI: Body Mass Index; eGFR: estimated Glomerular Filtration Rate; COPD: Chronic Obstructive Pulmonary Disease; RAS-inhibitor: Renin-Angiotensin System Inhibitors; MRA: Mineralocorticoid Receptor Antagonists.

Figure 2. Determinants of RAS-inhibitor use in HFpEF patients.



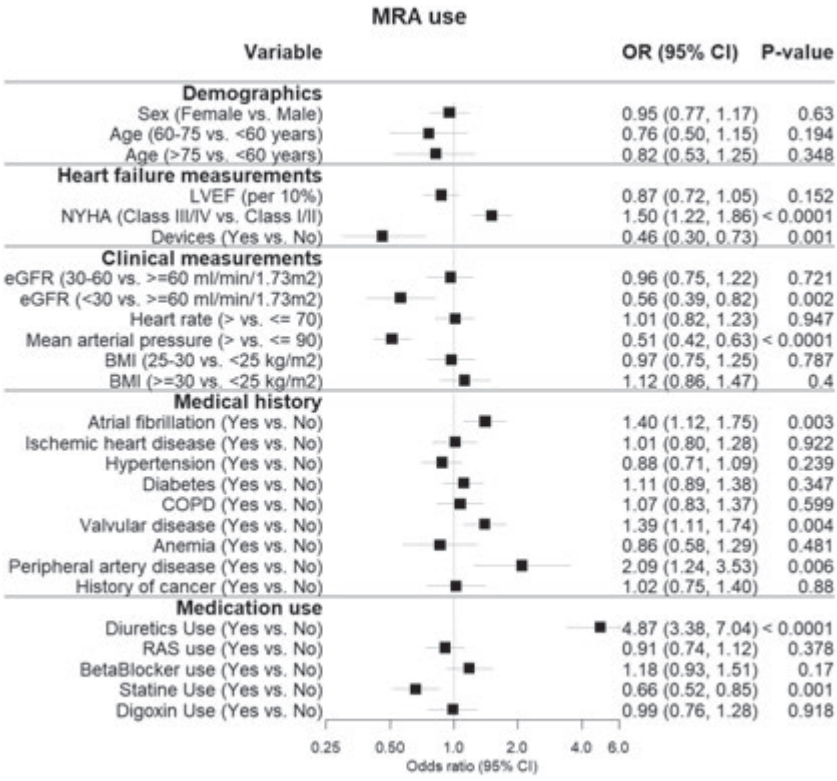
LVEF: Left Ventricular Ejection Fraction; NYHA class: New York Heart Association class; BMI: Body Mass Index; eGFR: estimated Glomerular Filtration Rate; COPD: Chronic Obstructive Pulmonary Disease; RAS-inhibitor: Renin-Angiotensin System Inhibitors; MRA: Mineralocorticoid Receptor Antagonists.

Figure 3. Determinants of Beta-blocker use in HFpEF patients.



LVEF: Left Ventricular Ejection Fraction; NYHA class: New York Heart Association class; BMI: Body Mass Index; eGFR: estimated Glomerular Filtration Rate; COPD: Chronic Obstructive Pulmonary Disease; RAS-inhibitor: Renin-Angiotensin System Inhibitors; MRA: Mineralocorticoid Receptor Antagonists.

Figure 4. Determinants of MRA use in HFpEF patients.



LVEF: Left Ventricular Ejection Fraction; NYHA class: New York Heart Association class; BMI: Body Mass Index; eGFR: estimated Glomerular Filtration Rate; COPD: Chronic Obstructive Pulmonary Disease; RAS-inhibitor: Renin-Angiotensin System Inhibitors; MRA: Mineralocorticoid Receptor Antagonists.

Cluster analysis

A total of 266 patients (12.4%) were assigned to latent class 1, 851 patients (39.5%) to class 2, 468 patients to class 3 (21.7%) and 568 patients to class 4 (26.4%). The patient characteristics per latent class classification are shown in **Table 1**. All variables used in the LCA showed high distinctive discrimination between latent classes (p value < 0.001). Class 1 was characterized by male dominance, almost all patients had history of ischemic heart disease, high NYHA classification, high prevalence of DM and COPD but low eGFR values. Class 2

was a female dominant cluster with the oldest patients, high prevalence of AF and valvular disease. Patients in class 3 were the youngest and most likely male patients. These patients had less comorbidities compared to the other clusters, lowest NYHA class, no renal disease, however 40% of the patients had history of ischemic heart disease and 15% had an implantable device. Patients in class 4 were mostly female and older. This cluster was characterized by obesity, DM, hypertension and AF.

The percentage medication use per latent class classification are shown in **Table 1**. Latent class 1 and latent class 3 showed a similar profile in medication use, with high loop diuretic and MRA use. RAS-inhibitors were used more often in latent class 1 and 2 compared to latent class 3. We observed no statistically significant differences in beta-blockers use between the latent classes.

External validation

In SwedeHF there were 2,080 patients (24.3%) assigned to class 1, 3,513 patients (41.1%) to class 2, 961 patients (11.2%) to class 3 and 2,001 patients (23.4%) to class 4. Compared to CHECK-HF there were more patients included in class 1 and less patients in class 3. There were more patients with AF, hypertension, PAD and anaemia in class 1, while there were less patients with diabetes (**Table 1**). In class 2 there were more patients with hypertension, PAD and anemia, while there were less COPD patients. In class 3, there were less patients with a HF device and more patients with AF, hypertension and valvular disease. Lastly, in class 4 there were more patients with ischemic heart disease, valvular disease, anaemia and hypertension while less patients with AF (**Table 2**).

Table 1. CHECK-HF Baseline patient characteristics for the overall cohort and per latent class.

CHECK-HF	Overall N = 2153 (100%)	Class 1 N = 266 (12.4%)	Class 2 N = 851 (39.5%)	Class 3 N = 468 (21.7%)	Class 4 N = 568 (26.4%)	p-value
Demographics						
Age (Years, median [IQR])	77.0 [69.0, 84.0]	75.0 [68.0, 81.0]	82.0 [78.0, 86.0]	65.0 [56.0, 72.0]	77.0 [70.0, 82.0]	<0.001
Sex (Female, %)	54.5	30.8	61.6	31.2	74.2	<0.001
Heart failure measurements						
LVEF (%, median [IQR])	59.0 [53.0, 61.0]	58.0 [52.0, 61.0]	59.0 [53.0, 60.0]	58.0 [54.0, 62.0]	59.0 [53.0, 61.0]	0.991
NYHA (Class III/IV, %)	31.1	45.2	34.6	3.0	42.8	<0.001
Edema (%)	17.8	19.6	14.9	11.1	27.0	<0.001
Devices (%)	4.8	4.9	0.9	15.6	1.8	<0.001
Clinical measurements						
SBP (mmHg, mean (sd))	134.8 (22.9)	135.4 (23.8)	128.1 (21.2)	142.0 (21.5)	138.6 (23.3)	<0.001
DBP (mmHg, mean (sd))	72.7 (12.2)	69.8 (11.6)	69.0 (11.2)	78.0 (11.7)	75.2 (12.3)	<0.001
MAP (mmHg, mean (sd))	93.4 (13.9)	91.6 (13.7)	88.7 (12.4)	99.3 (13.3)	96.3 (13.9)	<0.001
MAP (>= 90 mmHg, %)	59.0	48.9	42.4	80.1	71.2	<0.001
Heart rate (bpm, mean (sd))	72.8 (14.9)	70.4 (13.0)	74.0 (15.4)	68.1 (12.6)	76.1 (15.5)	<0.001
Heart rate (>= 70 bpm, %)	55.0	45.8	59.1	39.7	65.7	<0.001
BMI (kg/m2, mean (sd))	28.5 (5.9)	29.8 (5.1)	25.1 (3.9)	28.1 (5.5)	33.2 (5.7)	<0.001
<25	30.2	13.2	52.9	27.8	6.6	<0.001
25-29.9	35.6	42.8	41.5	45.2	15.0	
>=30	34.2	44.0	5.6	27.1	78.4	
Creatinine (umol/L, median [IQR])	99.0 [73.0, 132.0]	124.0 [96.0, 184.5]	101.0 [75.0, 130.0]	78.0 [61.0, 92.5]	105.5 [76.8, 140.0]	<0.001
eGFR (ml/min/1.73m2, median [IQR])	53.6 [36.2, 77.0]	43.1 [28.3, 62.6]	50.4 [35.7, 69.7]	82.7 [66.1, 96.8]	48.5 [33.9, 67.7]	<0.001
>=60	42.4	28.9	35.2	89.0	34.7	<0.001
30-59.9	42.7	40.3	51.4	11.0	46.9	
<30	14.9	30.8	13.4	0.0	18.4	

Table 1. Continued

CHECK-HF	Overall N = 2153 (100%)	Class 1 N = 266 (12.4%)	Class 2 N = 851 (39.5%)	Class 3 N = 468 (21.7%)	Class 4 N = 568 (26.4%)	p-value
Medical history (%)						
Ischaemic heart disease	28.6	97.7	16.2	40.0	5.5	<0.001
Atrial fibrillation	38.2	18.0	52.1	9.2	50.7	<0.001
Hypertension	50.7	51.1	40.2	39.3	75.7	<0.001
Valvular disease	24.7	4.5	44.1	3.8	22.4	<0.001
COPD	19.1	27.8	23.3	7.1	18.8	<0.001
Diabetes	30.0	68.0	9.5	9.2	59.9	<0.001
Peripheral artery disease	3.3	6.0	4.5	0.0	3.0	<0.001
Anemia	6.6	8.3	9.2	0.4	7.2	<0.001
History of cancer	14.0	12.3	16.3	13.1	12.3	0.192
Medication use (%)						
Diuretics	79.4	82.3	89.0	49.1	88.7	<0.001
RAS-inhibitor	67.3	72.9	62.6	71.2	68.7	0.002
Beta-blocker	78.3	81.6	74.0	81.4	80.5	0.001
MRA	38.5	38.7	46.2	20.9	41.2	<0.001
Digoxin	18.0	8.3	23.6	7.9	22.5	<0.001
Statins	81.5	94.4	73.4	91.2	79.4	<0.001

LVEF: Left Ventricular Ejection Fraction; NYHA class: New York Heart Association class; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure; BMI: Body Mass Index; eGFR: estimated Glomerular Filtration Rate; COPD: Chronic Obstructive Pulmonary Disease; RAS-inhibitor: Renin-Angiotensin System Inhibitors; MRA = Mineralocorticoid Receptor Antagonists; median [IQR]: median [Interquartile range]; mean (SD): mean (Standard Deviation).

Table 2. SwedeHF baseline patient characteristics for the overall cohort and per latent class

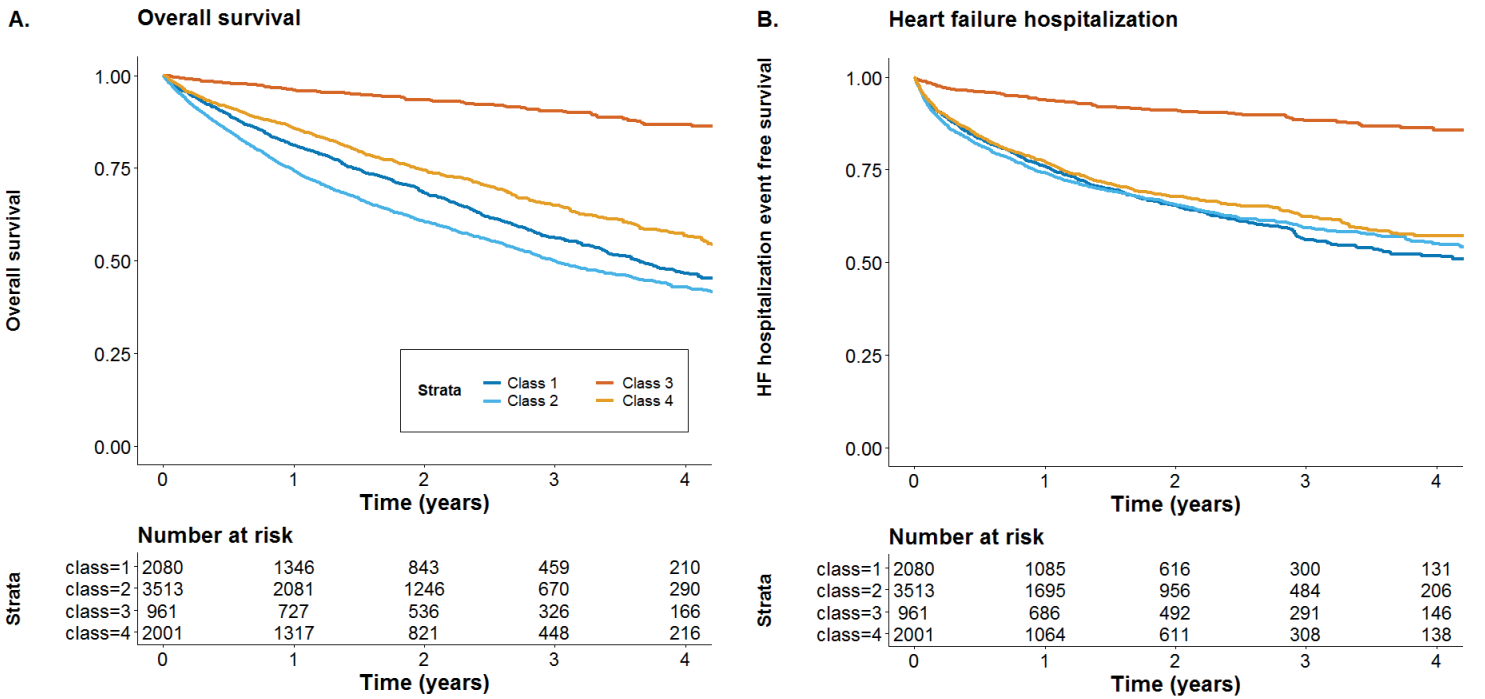
SwedeHF	Overall N = 8555 (100%)	Class 1 N = 2080 (24.3%)	Class 2 N = 3513 (41.1%)	Class 3 N = 961 (11.2%)	Class 4 N = 2001 (23.4%)	p-value
Demographics						
Age (Years, median [IQR])	80.0 [72.0, 86.0]	78.00 [71.0, 84.0]	84.00 [79.0, 88.0]	65.00 [54.0, 72.0]	78.0 [71.0, 84.0]	<0.001
Sex (Female, %)	52.7	33.6	60.5	33.0	68.2	<0.001
Location (Out-patient, %)	44.6	41.9	38.3	73.8	44.4	<0.001
Heart failure measurements						
NYHA (Class III/IV, %)	36.9	47.3	38.3	4.7	44.5	<0.001
NT-proBNP (median [IQR])	2090.0 [929.0, 4370.0]	2050.0 [883.5, 4579.5]	2835.0 [1506.0, 5410.5]	553.5 [187.5, 1461.0]	1800.0 [882.5, 3714.5]	<0.001
NT-proBNP (≥ median, %)	43.3	42.6	55.3	12.7	38.1	<0.001
Follow-Up location (Specialty, %)	48.3	49.1	44.7	66.7	44.7	<0.001
Devices (%)	1.9	3.3	0.7	5.7	0.7	<0.001
Clinical measurements						
SBP (mmHg, mean (sd))	131.6 (21.4)	132.7 (21.2)	128.6 (21.6)	130.9 (19.95)	136.1 (21.0)	<0.001
DBP (mmHg, mean (sd))	72.6 (12.0)	71.4 (11.6)	70.8 (12.0)	77.0 (10.9)	75.1 (11.9)	<0.001
MAP (mmHg, mean (sd))	92.3 (13.0)	91.8 (12.6)	90.1 (13.2)	94.9 (12.3)	95.4 (12.7)	<0.001
MAP (>= 90 mmHg, %)	58.1	56.3	48.9	69.8	70.8	<0.001
Heart rate (bpm, mean (sd))	74.4 (16.3)	71.8 (15.2)	76.1 (16.4)	68.4 (14.8)	77.1 (16.8)	<0.001
Heart rate (>= 70 bpm, %)	58.0	49.6	63.6	38.7	66.2	<0.001
BMI (kg/m2, mean (sd))	28.1 (6.2)	29.7 (5.9)	24.1 (3.6)	28.5 (6.2)	32.9 (5.8)	<0.001
<25	33.2	16.8	60.5	28.5	6.6	
25-29.9	34.7	43.0	37.0	40.1	19.9	
>=30	32.1	40.2	2.5	31.5	73.4	
Creatinine (umol/L, median [IQR])	95.00 [77.0, 124.0]	109.00 [84.00, 143.00]	95.00 [77.00, 122.00]	79.0 [68.0, 91.0]	98.0 [77.0, 127.0]	<0.001
eGFR (ml/min/1.73m2, median [IQR])	56.0 [40.5, 74.3]	51.4 [36.6, 70.8]	53.3 [40.4, 68.9]	82.5 [70.4, 94.0]	53.45 [38.3, 70.1]	<0.001
>=60	43.5	37.1	36.7	94.6	38.0	
30-59.9	45.7	46.7	54.3	5.4	48.7	
<30	10.8	16.2	9.1	0.0	13.3	

Table 2. Continued

SwedeHF	Overall N = 8555 (100%)	Class 1 N = 2080 (24.3%)	Class 2 N = 3513 (41.1%)	Class 3 N = 961 (11.2%)	Class 4 N = 2001 (23.4%)	p-value
Medical history (%)						
Ischaemic heart disease	48.6	98.5	40.6	36.0	16.9	<0.001
Atrial fibrillation	67.3	55.3	79.1	32.3	75.8	<0.001
Hypertension	81.8	90.6	75.5	57.1	95.8	<0.001
Valvular disease	37.1	19.4	57.6	13.7	30.9	<0.001
COPD	17.8	26.6	16.5	5.5	17.1	<0.001
Diabetes	31.2	60.0	5.8	6.1	58.1	<0.001
Peripheral artery disease	11.9	22.6	11.9	0.6	6.3	<0.001
Anemia	41.9	52.2	47.9	5.8	37.2	<0.001
History of cancer	12.5	14.8	13.4	7.8	10.7	<0.001
Medication use (%)						
Diuretics	81.6	85.8	85.1	48.7	87.3	<0.001
RAS-inhibitor	73.1	73.9	68.4	84.5	74.8	<0.001
Beta-blocker	82.7	85.5	80.7	82.8	83.1	<0.001
MRA	30.1	29.3	29.6	24.1	34.9	<0.001
Digoxin	12.9	7.9	15.6	7.9	15.7	<0.001
Statins	44.1	68.0	31.6	40.2	43.0	<0.001

NYHA class: New York Heart Association class; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure; BMI: Body Mass Index; eGFR: estimated Glomerular Filtration Rate; COPD: Chronic Obstructive Pulmonary Disease; RAS-inhibitor: Renin Angiotensin System Inhibitors; MRA = Mineralocorticoid Receptor Antagonists; median [IQR]: median [Interquartile range]; mean (SD): mean (Standard Deviation).

Figure 5. Kaplan Meier curves for the association between latent classes and A) all-cause mortality, B) HF hospitalization.



We assessed the association between latent classes and all-cause mortality and HF hospitalization in the external validation cohort (**Figure 5**). There were marked differences between the clusters. Latent class 3 had the highest survival and was the reference category for both outcomes. For all-cause mortality, the hazard ratio (HR) for class 1 was 5.41 (95% CI 4.29 – 6.82, p-value < 0.001), patients in class 2 had the worst survival with a HR of 6.71 (95% CI 5.35 – 8.42, p-value <0.001) and the HR for class 4 was 4.13 (95% CI 3.27 – 5.23, p-value <0.001). For HF hospitalization prognosis was similar among class 1, 2 and 4, with a HR for class 2 = 4.41 (95% CI 3.60 – 5.50, p-value <0.001), HR for class 3 = 4.40 (95% CI 3.55 – 5.46, p-value < 0.001) and the HR for class 4 = 3.95 (95% CI 3.16 – 4.93, p-value <0.001).

Discussion

The HFpEF patients enrolled in the CHECK-HF and SwedeHF are comparable to other HFpEF Western populations, with a large proportion of elderly, females and many comorbidities.[14–17] Many HFpEF patients received drug therapy similar to HFrEF potentially based on their concomitant diseases. We applied a novel classification technique to cluster HFpEF patients providing more insight in underlying phenotypes of HFpEF. This technique was able to derive and externally validate four distinct clusters of patients with related characteristics and significant differences in medication use and prognosis.

Cluster analysis

The current analysis has clustered a large real-world HFpEF population, compared to previous analyses, in which we found four distinct clusters. Patients from latent class 1 shared several characteristics similar to the HFrEF phenotype, notably history of ischaemic heart disease and male dominance. However, these patients also exhibited classic HFpEF characteristics, with multiple cardio-metabolic comorbidities, many patients with hypertension, DM and obesity.[20] Yet, due to the history of ischaemic heart disease, these patients might be candidates for drug therapies proven to be effective in HFrEF patients. Indeed, many of these patients received drug therapy recommended for the HFrEF phenotype, including RAS inhibitors, beta-blockers and MRAs. We were able to validate the clusters in an external cohort and in addition found that these patients had poor prognoses for all-cause mortality and HF hospitalization.

Patients from latent class 2 had the most AF and valvular disease. However, other characteristics which are traditionally associated with HFpEF, such as diabetes, obesity and hypertension, were remarkably infrequent.[21,22] These patients also had the worst survival in the external validation cohort. Diagnosing and treating HFpEF patients with AF is challenging, as both diseases independently increase left atrial size and cause dyspnea. However, diuretic therapy was prescribed in almost 90% of patients in latent class 2, suggesting at least to some extent congestion based on increased filling pressure associated with HFpEF.

Patients classified to latent class 3 were the youngest and had the fewest comorbidities compared to the other latent classes. This is reflected in drug therapy prescription, i.e. less prescription of diuretics or MRAs compared to the other latent classes, which could be related to fewer signs of HF (less edema and lower NYHA class). Furthermore, the best prognosis in terms of all-cause mortality and HF hospitalization was seen in patients from latent class 3. It could be that these patients were misclassified as HFpEF due to their characteristics, i.e. HF device implantation and ischemic heart disease, but not actually had HFpEF.

Patients in latent class 4 appear the most similar to the "classic HFpEF" phenotype: older age, female sex, obesity, hypertension and diabetes. Most prescribed medication were diuretics, however beta-blockers were also prescribed in more than 80% of patients. In the external validation cohort these patients had the second best survival for all-cause mortality.

Several studies have investigated clusters of HF, either over the whole range of ejection fraction,[18] or specifically for HFpEF.[10,11] Shah et al (2015) describe three clusters within HFpEF patients: an obesity cardio-metabolic cluster with high obesity, hypertension and diabetes, a cluster with low BNP and high obesity and a cardio-renal phenotype with chronic kidney disease (CKD).[10,19] The best prognosis for the composite outcome of CV hospitalisation and death was seen in the youngest, low BNP cluster, while the worst prognosis was seen in the oldest cluster with CKD. In contrast, Kao et al (2015) found six clusters, among others cardio-metabolic and cardio-renal phenotypes, as well as additional phenotypes.[11] The primary outcome of all-cause mortality or CV hospitalization occurred most often in the cluster with high obesity and worse renal function as well as the eldest female cluster with high rates of AF, while the youngest clusters with few comorbidities had the best prognosis. These studies share the

same conclusion: HF is a heterogeneous syndrome and different risk groups can be identified through clustering analysis.

Our clusters were similar to those found in these previous studies. We found similarities in the prognosis of the clusters, with the AF dominant cluster showing the worst survival in all three studies, while the best prognosis was observed in the youngest cluster. However, we also observed several differences, mainly in the build-up of the clusters. Compared to Shah et al (2015) we found a young, male dominant cluster, while they observed a low NT-proBNP cluster.[9] We did not take NT-proBNP into account in these analyses due to the high rate of missing information in both registries. In addition, we found a 4th phenotype that was dominated by AF and valvular disease. Medication prescription differed considerably between studies which made it difficult to compare studies directly. However, of note, diuretics were equally little prescribed in latent class 3 in our analyses and the low BNP cluster described by Shah et al. [10,19] Even though different approaches and different variables were used to cluster HFpEF patients, there were several clusters that were strikingly similar between studies, which verifies the result that we can define clinically relevant clusters within the HFpEF patient group. These results could form a basis for tailoring trial design to discern potential cluster specific interventions.

Drug therapy use in HFpEF patients

Medication use in CHECK-HF and SwedeHF HFpEF patients was similar to other European and Asian registries, with high prescription rates of diuretics, as well as beta-blockers and RAS-inhibitors.[23–25] We hypothesize that Dutch and Swedish physicians may conceive positive, beneficial effects of aforementioned drugs, despite the lack of recommendations for their use.[3] However, it seems also the result of treating comorbidities such as AF or hypertension, which are prevalent comorbidities.[26,27] Almost 40% of CHECK-HF patients and 30% of SwedeHF received MRAs. Higher NYHA class was one of the strongest predictors for MRA use, indicating that patients with more severe HF would receive more often MRAs than other patients. This is not surprising, since, based on previous guidelines for HFrEF patients, MRAs were only recommended to the most severe patients, i.e. NYHA class III/IV.[28]

Strengths and limitations

This study has several strengths. First, the CHECK-HF registry is one of the largest and contemporary European HF registries (data up to 2016).[12] Another

strength is the detailed information on medication use, and comorbidities. Third, we used a pragmatic and highly feasible approach by choosing to use easily obtainable clinical information to improve the applicability of the model. Lastly, one of the strengths of this study is the validation of the identified clusters in an external cohort. Limitations of this study include the missing indication for medication prescription and the lack of follow-up data in the development cohort. However, we were able to report associations between latent classes and relevant patient outcomes in the external validation cohort. Another limitation is the data driven approach of phenotypic clustering, this is highly influenced by the cohort. Yet, we were able to discern clusters of patients comparable to previous studies. Future studies should focus on prospectively testing the potential therapeutic impact of clustering to improve hard clinical endpoints.

Conclusion

This study demonstrates that phenotype clustering may result in clinically meaningful classes of HFpEF patients. Clinical characteristics of patients between classes varied considerably, notably regarding age, sex, ischaemic aetiology, comorbidity distribution, drug therapy and prognosis. These results signify the heterogeneity in the HFpEF population and form a basis for tailoring trial design.

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Supplemental material

Figure S1. Determining number of subgroups based on AIC, BIC, likelihood ratio and chi2.

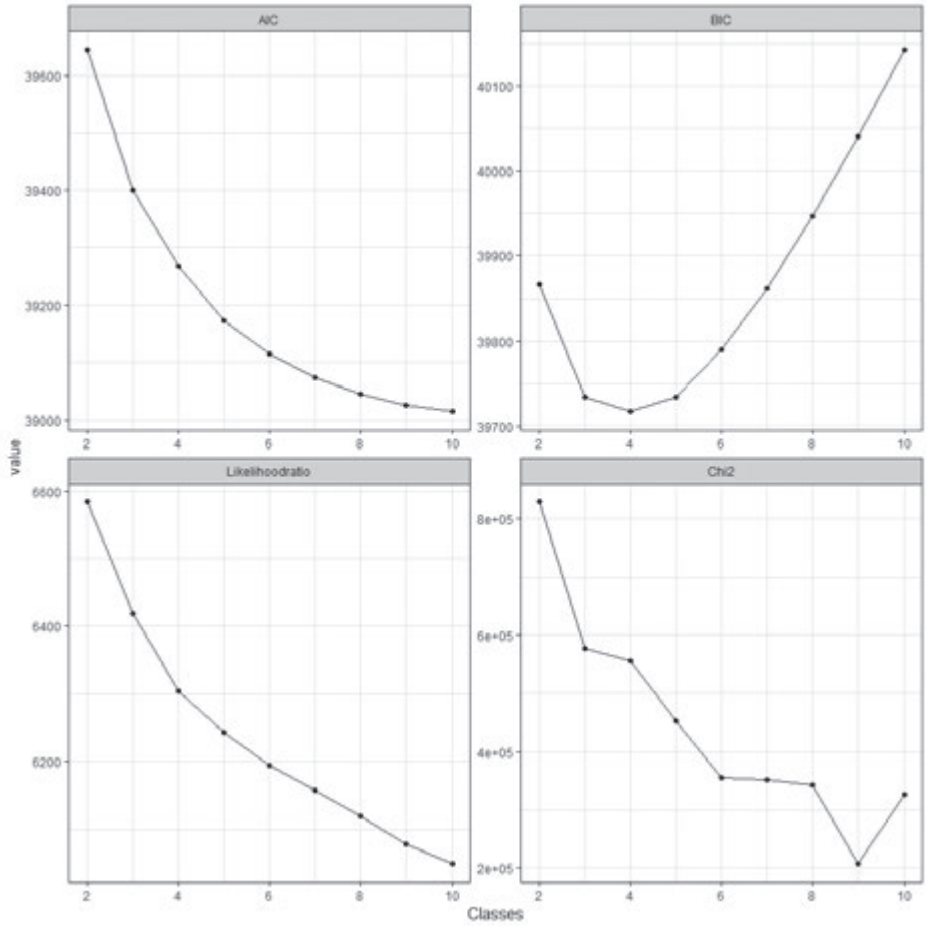

Table S1. Missing baseline patient characteristics

	CHECK-HF		SwedeHF	
	N missing	**% Missing**	**N missing**	**% Missing**
Demographics				
Age	2	0.09	0	0
Sex	6	0.3	0	0
Heart failure measures				
NYHA	34	1.6	3734	43.6
Devices	0	0	0	0
Clinical measurements				
BMI	167	7.8	2619	30.6
Heart rate	18	0.8	156	1.8
MAP	13	0.6	139	1.6
eGFR	892	41.4	193	2.3
Comorbidities				
Ischaemic heart disease	0	0	0	0
Valvular disease	0	0	0	0
Hypertension	0	0	0	0
Diabetes	0	0	0	0
COPD	0	0	0	0
Atrial fibrillation	0	0	0	0
Peripheral artery disease	0	0	0	0
Anemia	0	0	310	3.6
Medication use				
Loop diuretics	0	0	178	2.1
RAS-inhibitors	0	0	39	0.5
Beta-blockers	0	0	32	0.4
MRA	0	0	85	1.0

NYHA: New York Heart Association; BMI: Body Mass Index; MAP: Mean Arterial Pressure; eGFR: estimated Glomerular Filtration Rate; COPD: Chronic Obstructive Pulmonary Disease; RAS-inhibitors: Renin-Angiotensin System Inhibitors; MRA: Mineralocorticoid Receptor Antagonists.

Table S2. Probabilities for each predefined variable per LCA class

Variable	Categories	Class 1	Class 2	Class 3	Class 4
Sex	Male	0.682	0.389	0.6733	0.2685
	Female	0.318	0.611	0.3267	0.7315
Age	< 60 years	0.0532	0.0199	0.3268	0.0453
	60 - 75 years	0.426	0.1381	0.4903	0.3677
	> 75 years	0.5207	0.8419	0.1829	0.5871
NYHA	NYHA I/II	0.5681	0.6604	0.9493	0.5787
	NYHA III/IV	0.4319	0.3396	0.0507	0.4213
Devices	No	0.944	0.988	0.8532	0.9826
	Yes	0.056	0.012	0.1468	0.0174
MAP	< 90 mmHg	0.4866	0.5618	0.2216	0.3149
	> 90 mmHg	0.5134	0.4382	0.7784	0.6851
Heart rate	< 70 bpm	0.5253	0.4122	0.5851	0.3619
	> 70 bpm	0.4747	0.5878	0.4149	0.6381
BMI	< 25 kg/m^2	0.1688	0.5048	0.281	0.1085
	25 - 30 kg/m^2	0.4196	0.3915	0.4357	0.2127
	> 30 kg/m^2	0.4116	0.1037	0.2833	0.6788
eGFR	> 60	0.3175	0.351	0.8459	0.3545
	30 - 60	0.3874	0.5094	0.1541	0.4697
	< 30	0.2951	0.1396	0.000	0.1759
Ischaemic heart disease	No	0.1052	0.8334	0.6154	0.3545
	Yes	0.8948	0.1666	0.3846	0.0892
Atrial fibrillation	No	0.7885	0.4828	0.8917	0.5102
	Yes	0.2115	0.5172	0.1083	0.4898
Hypertension	No	0.5085	0.5932	0.6018	0.2645
	Yes	0.4915	0.4068	0.3982	0.7355
Valvular disease	No	0.9338	0.5732	0.9427	0.7651
	Yes	0.0662	0.4268	0.0573	0.2349
COPD	No	0.7378	0.7709	0.9195	0.8065
	Yes	0.2622	0.2291	0.0805	0.1935
Diabetes	No	0.4119	0.8664	0.8758	0.4729
	Yes	0.5881	0.1336	0.1242	0.5271
Peripheral artery disease	No	0.9378	0.9558	0.9982	0.9715
	Yes	0.0622	0.0442	0.0018	0.0285
Anemia	No	0.916	0.9088	0.992	0.9299
	Yes	0.084	0.0912	0.008	0.0701

NYHA: New York Heart Association; MAP: Mean Arterial Pressure; BMI: Body Mass Index; eGFR: estimated Glomerular Filtration Rate; COPD: Chronic Obstructive Pulmonary Disease.

CHAPTER 10

GENERAL DISCUSSION

Real-world evidence (RWE) has rapidly expanded over the last decade with the promise of improved patient care and precision medicine. However, the sheer increase of healthcare data collected cannot automatically be translated to improvements in clinical practice. Real-world data (RWD) has a great potential to contribute to enhancements in healthcare. To accomplish this, several hurdles and challenges that researchers might face have to be overcome when using RWD. The aim of this thesis was to assess the potential of RWD in heart failure research. This chapter will describe the key findings from the studies in the thesis, their interpretation and future perspectives related to challenges and opportunities in RWD in heart failure.

Key findings

I. *Risk factors*: Through a large population-based study we were able to identify differences in risk factors between men and women: smoking, atrial fibrillation and diabetes showed stronger associations with incident heart failure in women compared to men (**Chapter 1**). We also expanded our knowledge on healthy lifestyle factors in the general population. Our analyses suggest that combinations with specific LS7 components, notably glucose, body mass index, smoking or blood pressure, were associated with decreased incidence of heart failure (**Chapter 2**).

II. *Treatment*: Trends for heart failure medication over 15 years of follow-up were investigated for over 85,000 heart failure patients, we found that little change in medication prescription rates occurred after 6 months of heart failure diagnosis, these findings suggest heart failure management can be improved in the general population (**Chapter 4**). We additionally showed that beta-blockers were associated with improved all-cause and cardiovascular mortality in heart failure with reduced ejection fraction (HFrEF) patients aged 80 years or older (**Chapter 5**).

III. *Prognosis*: Big data on change in biomarkers could be used to pursue surrogate endpoints in HFrEF trials. We found that reductions in ANP, NT-proBNP, CRP, sST2 and WAP4C levels were associated with improved mortality/morbidity over clinical characteristics and biomarker baseline values alone (**Chapter 6**). Additionally, we showed that data could be harmonised between different European countries, there were distinct

differences in patient case mix and crude survival was highest in Sweden, followed by the UK and Spain. (**Chapter 7**).

IV. *Phenotyping*: We created an algorithm to predict subphenotypes of heart failure and validated these results in an independent cohort. Accuracy was good for the prediction of heart failure with preserved ejection fraction (HFpEF) and HFrEF but lower for heart failure with mid-range ejection fraction (HFmrEF), indicating that routine clinical characteristics could be used to identify different ejection fraction phenotypes in datasets where ejection fraction is not documented (**Chapter 8**). With a machine learning model we identified distinct HFpEF clusters: a cluster with similar HFrEF characteristics, a traditional HFpEF cluster, a "healthy" cluster with low comorbidities and an old atrial fibrillation ridden cluster. These clusters could form a basis for tailoring trial design to individualised drug therapy in HFpEF patients (**Chapter 9**).

Opportunities of real-world data

In recent years the use and potential of RWD has expanded tremendously seeing that RWD studies have the unique opportunity to study patients in normal clinical practice. More and more information is collected from a patient, ranging from hospital and GP records, but also information from wearables and –omics data is increasingly exploited. All this information could be used for clinical decision making, assessing temporal changes over time or disease epidemiology. Several opportunities of RWD will be discussed, as well as the opportunities we have seized from RWD in this thesis.

Linkage of electronic health records

To manage and support a patient's healthcare, medical information on the patient is digitally stored in electronic health records (EHR). However, EHRs are more than just storing patient information. In addition, it has improved communication between healthcare providers, with faster access to the data and increasing the efficiency of the workflow.[1] EHRs facilitated this by collecting a wide variety of data, from basic demographics to clinical, lab, diagnosis, procedural and prescription data.

EHRs have further potential outside of this clinical/administrative function, it is also a rich data source that could be used to study a disease in the general

population.[2] Many GP practices and hospitals work with an EHR system, all these single sources of data collection could be linked, most often via a personal number or identifying information such as name, address and date of birth.[1,3] Via the linkage of data sources, patients follow-up can be enriched through data from GP, hospital admissions and death registries over their lifetime, allowing researchers to study the natural history of a disease, including risk, prognosis and epidemiology.[2,3]

In the UK, the CALIBER resource with linked EHRs has proven to be representative of the general population and allows the study of a disease spanning decades of data.[4–7] This resource contains data on more than 10 million individuals with linked data across GP, hospital and mortality data sources. Patients have been followed-up since 1998, with the potential for some patients to have 20 years of follow-up.

CALIBER provided the opportunity for us to examine the consistency of risk factors for heart failure across age and sex specific subgroups from the general population.[8] Mainly modifiable risk factors and comorbidities showed strong associations with incident heart failure. Moreover, smoking, atrial fibrillation and diabetes showed stronger associations with incident heart failure in women compared to men (**Chapter 1**). Secondly, we studied temporal trends of medication prescription in heart failure patients. We found increased beta-blocker prescriptions over time, yet not for mineralocorticoid receptor-antagonists (MRA). We found higher prescription rates of loop diuretics in women and elderly patients together with lower prescription rates of RAS-inhibitors, beta-blockers, or MRA in these patients. Lastly, little change in medication prescription rates occurred after 6 months of heart failure diagnosis, these findings suggest that the management of heart failure patients could be improved in the general population (**Chapter 4**).

The real-world patient

Real-world patients seen in clinical practice are a more diverse group of patients than those participating in RCTs. Patients in RCTs are a homogenous selection from real-world patients, generally younger, more often male and with less comorbidities. That is a result of the research question that trialist aspire to answer: What is the efficacy of a new drug? Nonetheless, there are many other research questions that could not be answered through a RCT. We can learn different things from real world-patients that we cannot learn from a trial patient.

In real-world studies we can include those patients that are underrepresented in RCTs, including elderly, women, patients with chronic kidney disease and other comorbidities, and those that may have less severe heart failure.[9] Moreover, patients can be studied during a longer follow-up time, and RWD can therefore assess also safety outcomes such as rare adverse events. Furthermore, RWD reflects a setting of typical clinical practice so it reflects how interventions would be used in routine healthcare. Based on this temporal changes over time can be studied as well as the economic burden of diseases over time.

One of the cornerstones of heart failure treatment since the successful trials from the late nineties are beta-blockers.[10–12] However, the RCTs had not included representative samples of elderly patients.[13] Even though the European Society of Cardiology (ESC) guidelines for heart failure do not have an age limit on the recommendation for beta-blocker treatment, it has been reported that beta-blocker use in elderly patients are more frequently discontinued and less likely up-titrated due to concerns regarding tolerance and efficacy.[14] In our study we showed that in elderly patients (aged ≥80 years old) with HFrEF the use of beta-blockers was associated with reduced all-cause and cardiovascular mortality, suggesting that the survival benefit from this treatment is not impaired by older age (**Chapter 5**).[15]

It is important to stress that analyses in real world patients should not replace RCTs, however it can add valuable information and can complement results obtained from RCTs. The Food and Drug Administration (FDA) acknowledges the fact that RWE could fulfil an important role in improving health care and uses RWD to make regulatory decisions since the 21st Century Cures Act in 2016.[16]

One opportunity that is emerging with the more frequent use and availability of RWD: the registry based RCT (RRCT).[17,18] To overcome a lack of generalisability, but also complex designs and extensive costs of RCTs, a novel way to analyse RWD can reduce these limitations. RRCTs can combine trial recruitment, randomisation and outcome assessment with routine clinical care and can be seen as a simplified, pragmatic approach of conducting an RCT. In heart failure, the Spironolactone Initiation Registry Randomized Interventional Trial in HFpEF (SPIRRIT-HFpEF) has been initiated to test the efficacy of spironolactone + usual care versus usual care alone in real-world HFpEF patients. Spironolactone, a MRA, has shown efficacy in HFrEF, but trials in HFpEF have failed.[19] If the RRCT outcome is to be positive, it may deliver substantial impact to HFpEF patients

around the world. This approach could be seen as an efficient use of existing resources and provides a much needed bridge between RCT evidence-based medicine and RWD.

Techniques to analyse large quantities of big data

Due to the need to answer research questions that cannot be answered in a RCT or conventional research, such as generalisability, heterogeneity, health technology assessment or temporal patterns over time, more attention has been focussed on RWD. Currently, many researchers are interested in machine learning techniques to analyse large quantities of data, such as routine healthcare data. When data is analysed through a machine learning model, the model learns from the data and is then able to apply what it has learned to make an informed decision.[20] The learning part can either be supervised or unsupervised, which means that the data is either labelled or unlabelled with the correct outcome. Supervised machine learning examples are classification or regression analysis to predict the outcome based on variables. A good example of unsupervised machine learning is clustering. What this technique does, is to find a structure or pattern within the data and have like objects grouped together.

Clustering is especially of interest in heart failure research. As a result of the heterogeneity in HFpEF pathophysiology, it is suggested that treatment in HFpEF patients should potentially be matched to distinct subsets of comorbidities, identifying patient groups most likely to benefit from targeted interventions. Possible effective HFpEF therapy could thus be determined by the identification of distinct HFpEF patient clusters.[21,22] Consequently, we derived a cluster model with latent class analysis from almost 2,200 HFpEF patients from the CHECK-HF registry and validated the clusters in 6,800 patients from the Swedish heart failure registry. This analysis identified four distinct HFpEF clusters: a cluster with similar HFrEF characteristics, a traditional HFpEF clusters, a “healthy” cluster with low comorbidities and an old AF ridden cluster. We observed differences in prognosis with the healthy cluster having the best prognosis and the old AF cluster the worst (**Chapter 9**). The results of this analysis could be widely applicable in different settings, including clinical trial design, as a result of the easily accessible variables selected to identify the clusters.

Challenges of real-world data

In this thesis we sought to address several challenges that researchers might come across using RWD in their studies. Many of these challenges involved with RWD have been incorporated in the FAIR Guiding Principles for scientific data management and stewardship. Several stakeholders, ranging from academia and industry to funding agencies and publishers, have come together in 2016 to create measurable principles, called the FAIR Principles to give more attention to good data management.[23,24] FAIR stands for Findable, Accessible, Interoperable and Reusable. Especially RWD can be difficult to find and access or to integrate the data with other datasets, however with good data management and adopting the FAIR Principles the full potential of RWD could be achieved. Here we want to show examples of our studies, what can or should be achieved to overcome challenges of RWD.

Data quality in routine healthcare data

Despite the promise of RWD, many researchers still do not, or do not understand how to, utilise its full potential. This is due to the complexity of the data and the sheer amount of data processing that needs to be completed before the data, specifically routine healthcare data such as EHRs, can be analysed.[25] Data of this volume that is delivered in an unstructured format can be quite a challenge. It takes time and experience to transform RWD into a structured database. In order to achieve an infrastructure that allows for the facilitation of research in an efficient, sustainable and qualitative manner, data needs to be harmonised and standardised.

Phenotyping in guidelines

Before we can standardise and harmonise data in a structured format, we need to reach consensus on the phenotyping of diseases in EHRs. As data contained in routine care databases are generated for healthcare, not research, the dataset is not optimised for secondary uses. Many RWD sources use the International Classification of Diseases and Related Health Problems (ICD) revision 9 or 10, which classifies diseases based on standard diagnostic terms. However, researchers could have different opinions on which diagnostic codes should be included to capture a disease. In the case of heart failure, multiple diagnostic codes are indicating heart failure, however some researchers also include dilated cardiomyopathy when defining heart failure in ICD codes, reasoning that it is in the HFrEF aetiology.[26] Recently, in the CALIBER resource a framework has been

implemented in 15 million UK individuals to create algorithms for 51 diseases spanning three sources of linked EHRs.[6] This facilitates reproducibility, data quality and translational research in this resource.[27] In the case of heart failure, there are many examples of EHRs based algorithms to define this disease that are all slightly differ.[26,28] We should move forward from standardised algorithms for each resource separately to a set of standardised algorithms in all routine data resources.[29] If all phenotypes were captured in a set of guidelines for RWD use, this would considerably increase the reliability and reproducibility of RWD. The phenotype definitions in such a guideline would need to have monitoring and updating as disease coding practice might change over time, however this would greatly improve the quality of future RWD research.

Harmonising and standardising data

Besides phenotype definition, different systems use various ways to structure and format their data. If all systems would be standardised in the same way it would promote the use of these databases by making it more accessible and stimulate (international) collaboration and comparison of RWD.[30] Standardisation and harmonisation could be done manually. To compare heart failure mortality across European countries we standardised the UK, Swedish and Spanish data by mapping the data into a common format (**Chapter 7**). Another approach is with the common data model (CMD) from the Observational Medical Outcomes Partnership (OMOP).[31] This is a process in which data from the individual data sources is converted to a CDM and the clinical terminologies are mapped using standard SNOMED (Systematised Nomenclature of Medicine) vocabularies, all clinical, procedural and medical codes can be mapped to the SNOMED vocabularies. The CDM preserves all data and codes from the original data source, but adds the standardised vocabulary. The CDM is a labour intensive process to start with, since all codes have to be mapped to a new standard SNOMED vocabulary. However, in the end, it might be more efficient and worthwhile, especially if the comparison between resources mapped to the CDM will be used for many studies to come or new comparisons with resources already mapped to the CDM can be established. Another opportunity with the CDM approach is standardised phenotyping of diseases could be implemented efficiently across a span of data resources. There is no right or wrong way in choosing which approach to use, what is important is that data harmonisation and standardisation are a key step in data processing that needs ample preparation and joint effort from clinicians, epidemiologists and data

scientists to facilitate collaborative research across data platforms, resources and countries.

Incomplete information collection in routine healthcare data

The next step after disease phenotyping definitions and data harmonisation is data analysis and also here there are challenges to be identified. One of the challenges is that EHRs are more likely to have incomplete data collection, since the aim is not medical research.[1,32,33] For example, if a patient does not go to the GP for a check-up for various reasons, such as restriction by insurance or finances or getting care elsewhere, you as a researcher will not have an opportunity to complete follow-up.[34] This creates a gap in the information collection during follow-up or might lead to misclassification of a patient, i.e. a patient quit smoking in between GP visits but is still recorded as smoker from the previous visit. Analysing only those patients with complete follow-up is common practice in traditional research methods. However, in the case of EHRs, we would rather apply methods for missing data handling. Hereby we assume that missing data is missing at random (MAR), i.e. the missing value is not related to the missing data, if we condition for other measured covariates. If we take into account the measured covariates, we could impute those variables with missing values. Missing at random cannot be tested, so we take into account that this is an assumption and that there is a level of uncertainty associated with imputation.[33] Other scenario's encompass patients where values are completely missing at random (MCAR) or missing not at random (MNAR). When data is MCAR, the data is considered a random sample of the population, however this is rarely seen in clinical practice. MNAR arises when the probability of the variables measured is dependent on the value of that variable. [35] For example, in heart failure natriuretic peptides (NT-proBNP) are measured as it indicates severity or worsening of the disease, this hormone will be more often measured if the clinician suspects heart failure. MAR and MNAR conditions cannot be distinguished from one another. If we would apply the wrong imputation techniques on MNAR variables we could actually introduce bias in our analyses. However, when we are investigating multiple variables, we could condition the MNAR variable on multiple additional variables and the MNAR variable could thus be considered MAR in certain situations.[35,36] Currently several missing data simulation studies are investigating the best methods to address missing data, because with the proper techniques missing data can be taken into account and lead to unbiased results.[37,38]

In the case of heart failure, left ventricular ejection fraction (EF) is often missing or not documented.[39,40] The current ICD-10 classification includes codes for systolic and diastolic heart failure, however most cases are identified with the code for heart failure unspecified. The new ICD-11 revision, which will take effect in 2022, does allow for classification in heart failure with reduced, mid-range and preserved ejection fraction. However, before this new ICD-11 revision is fully integrated and applicable, it will be many years. Therefore, to be able to investigate EF phenotypes in EHRs right now, we created an algorithm that identifies EF phenotypes based on routinely collected baseline characteristics (**Chapter 8**). In over 40,000 patients from the Swedish Heart Failure Registry we performed multivariable logistic regression models and multinomial models to predict 1) EF ≥ vs. <50%; and 2) EF ≥ vs. <40% and 3) HFrEF vs. HFmrEF vs. HFpEF. The models were validated in the database from the CHECK-HF study, a cross-sectional registry of over 10,000 patients from the Netherlands. Accuracy was good for the prediction of HFpEF and HFrEF but lower for HFmrEF. This might be explained by the heterogeneity that characterises HFmrEF, with a large proportion of patients having transitioning EF for different reasons (e.g. atrial fibrillation and ischemic heart disease) which may make EF prediction more challenging.[41–44] This models shows that routine clinical characteristics can be used to identify the EF subphenotypes, which could be used in datasets where EF is not documented.

Implications for future research

Based on the opportunities and challenges, reinforced by the findings of the studies in this thesis, there are several conditions that warrant our attention in future research. It is important to focus on the foundation of the underlying structures of RWD to keep it successful in the future and seize the opportunities that RWD provide.

The future of EHRs

EHRs have undergone many changes in the past years with new features discovered and added at a quick pace. Now is the time to zoom out and reflect on the recent technological enhancements to improve EHRs in the coming years. For EHRs to keep playing an important role in RWD studies and for RWD studies to play a key role in EHRs there are few key elements that attention should be focussed on. Enhancing the current state of EHRs and RWD will achieve higher quality data, improve efficiency and increase interoperability.

One of the most important features that is a necessity for high quality research is an improvement in data quality. To be able to perform a secondary analysis of routine clinical data the data completeness would ideally need to improve. This means that the records need to be kept up to date and the correct clinical codes need to be associated with the patient. RWD analysis could help in this step. Machine learning models that use natural language processing could be incorporated in the digital hospital system suggesting ICD codes when a clinician makes an entry, reducing administrative time for the clinician, increasing efficiency and complementing EHR quality. EHRs have the potential to become useful clinical tools for the clinician, if and when more information about a patient is complete, with integrated clinical decision support systems.[45] With these systems algorithms for risk prediction could be implemented in the EHRs, and form recommendations for treatment decisions based on medical guidelines. Clinicians could get real-time updates on the patient risk with each new visit and updated records.

It is important to not forget that EHRs and RWD research are a revolving door and both can profit from each other. They fuel back into each other. EHRs can provide the RWD that researchers need to answers scientific questions related to the real-world patient, to for example, improve risk prediction models. On the other hand, RWD research can provide a better quality of healthcare with techniques such as natural language processing, but also implementing guidelines or risk models created in big data back in EHR systems.

The last feature of RWD, and thus EHRs, discussed here is the interoperability, one of the pillars of the FAIR Guiding Principles.[23,24] Interoperability would ideally need to increase to ensure that patient information can be shared between healthcare providers to assure the best care.[46] One of the new ways that could increase interoperability is with data accessibility via servers in a cloud, which can reduce costs and increase scalability.[47–49] More data could be stored in a cloud than some local servers are equipped to handle. Furthermore, to manage these massive amounts of data, cloud computing can integrate advanced techniques such as machine learning. However, several concerns are associated with cloud computing, such as security and privacy.[47–49]

Privacy in routine healthcare data

Access to patient data for scientific purposes might be challenging, as privacy concerns are increasing.[50] The implementation of the recent General Data

Protection Regulation (GDPR) in 2018 meant that the regulations concerning privacy have been modernised and harmonised across Europe. It allows for better protection and rights to individuals. Specifically, in the scientific field, this has influenced patient consent, data access and data sharing.[51] In a time where routine healthcare data has many different secondary uses, besides the initial administrative purpose, it can now be linked and compared to different datasets, new data keeps getting added such as –omics and wearable data, new techniques are applied to make steps towards precision medicine or patients are participating in an RRCT and many more, there is a need for support from patients providing consent for sharing their health information.[52]

Without proper information provided, patients could fear misuse of data, as it is unknown to them what will happen to their data when they consent to sharing health information, or they therefore might decide not to consent at all. The most well-known type of consent is consent for one particular study. However, this is not feasible for RWD studies, because of data re-use, this would mean a patient would be asked over and over again if they would consent. Broad consent is a far better option for RWD studies, in which consent is given for future research with some specified limitations. This limits the burden on healthcare staff to obtain consent for each patient and each study and also provides some limitations to what the data could be used for. Several sources of RWD also use opt out as a form of consent, if a patient does not opt out their data might be used for future studies. A recent study showed that patients might have a preference for an online e-consent application with the option to show more information if needed.[52] To realise such a structure, discussion between stakeholders, policy makers and lawyers needs to take place to create a consent policy that is in line with patient wishes and regulations. It would be advisable that patients become more engaged in their own healthcare and medical research.[52]

Black box phenomenon

The future of EHRs could move forward with machine learning with the potential of natural language processing and integrating machine learning prediction models in EHRs and many other applications not mentioned here. However, a recent paper compared logistic regression with machine learning techniques for prediction modelling and found that there was no superior performance of the machine learning models over logistic regression when the machine learning models had low risk of bias. Furthermore, they show that there is worse reporting in machine learning papers and model validation is often not performed.[53] The

lack of guidelines for reporting machine learning models is hampering the next step beyond creating prediction models: the implementation into clinical practice – potentially via clinical decision support systems. It is important to question whether those that are supposed to use these models and algorithms actually use them or are machine learning techniques just a black box.[50] To achieve a future EHR system that is functional for all users, whether that is a clinician treating a patient, a researcher performing an RRCT or data scientist creating a new risk prediction model, a multidisciplinary approach is necessary.

Role of the epidemiologist in RWD research

An important concept that needs to be discussed is the role of the epidemiologist in a research climate with more and more interest in using RWD. One has to wonder if we should all become data scientists now. Perhaps a better idea would be to make use of the strengths of an epidemiologist. Epidemiologists have extensive training in design and analysis of studies, therefore we could play a leading role to guard methodological quality in an era in which research is increasingly become more of a black box. We can, together with clinicians, formulate relevant and answerable research questions to reduce research waste.[54] Especially in the era of RWD and the challenges associated with it, it is of utmost importance that there are epidemiologists that can give insights in how routine clinical data can be used in research in a reliable way.

We, as epidemiologists, should come forward as gatekeepers, ensuring that the quality and validity is maintained within RWD research. There should be close collaboration between data scientists, epidemiologists and clinicians as part of multidisciplinary teams to make the implementation of RWD research into clinical practice a success and to develop clinically relevant knowledge. We should stand up as mediators, translating what are clinically relevant questions for the clinician, design a study and assess fitting data to then helping data scientists execute the right methods to answer the question. This is how we could bridge the gap between endless data and making use of the opportunities RWD provides, overcome the challenges associated with RWD and achieve successful RWE from RWD.

Epidemiologists could play a key role in improving the current constraints of RWD: 1) data accessibility, quality and standardisation, 2) interoperability of EHR systems, and 3) improve methodological quality of RWD studies. The potential impact of RWD could be increased by epidemiologists and contribute to improve a new era of healthcare based on RWE from RWD.

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APPENDICES

Summary

The rapid increase of real-world data (RWD) has led to a great potential benefit to contribute to improvements in healthcare. However, the sheer increase of healthcare data collected cannot automatically be translated to clinical practice. The aim of this thesis was to assess the potential of RWD in heart failure by investigating the opportunities RWD provides, but also what the challenges are within RWD. We identified linkage of electronic health records (EHRs), the ability to study patients in a real-world setting and techniques to analyse large quantities of data as opportunities in heart failure. Challenges we came across were quality of routine healthcare data, a lack of consensus on phenotyping diseases in RWD, harmonising and standardising data and incomplete data collection. Here we summarize the chapters of this thesis that are underlying the opportunities and challenges of RWD in heart failure.

In part 1 risk factors for heart failure were discussed. In **chapter 2** we investigated risk factors for heart failure in a large population-based study in the UK. Within the linked EHR resource CALIBER, we conducted a study in almost 900,000 individuals aged 55 years and older without heart failure at the start of the study. The aim of the study was to verify associations of (un)known risk factors for heart failure. We had the opportunity to examine the consistency of risk factors across different age and sex subgroups from the general population. In CALIBER we had linked EHRs available for patients between 2000 and 2010 from GP records, hospital discharges and the national death registry. Almost 50,000 individuals developed incident heart failure during follow-up. Incidence was highest in patients older than 75 years and across all ages higher for men than for women. By using large volumes of data we were able to show differences in the association of risk factors with heart failure between men and women; atrial fibrillation, COPD and diabetes had stronger associations with incident heart failure in women compared to men. Mainly modifiable risk factors had a substantial population attributed risk. This study highlighted the importance of preventive strategies targeting modifiable lifestyle risk factors for heart failure, besides blood pressure management, in the general population.

We continued our research on modifiable lifestyle factors in **chapter 3** of this thesis where we studied the American Heart Association Life's Simple 7 (LS7) and the risk of heart failure in a general Dutch population. LS7 is a concept in which healthy behaviours that could reduce the burden of cardiovascular disease

(CVD) are recommended, and consists of known CVD risk factors: smoking, physical activity, body mass index, diet, blood pressure, total cholesterol, and glucose. The aim of this study was to provide insight in combinations of specific LS7 components that could reduce the risk of heart failure. This study included almost 40,000 participants from the European Prospective Investigation into Cancer and Nutrition-Netherlands (EPIC-NL) cohort and almost 700 participants developed heart failure during follow-up. Both an ideal and intermediate score for LS7 were associated with a 50% or more decrease in risk for heart failure. Our analyses furthermore showed that combinations with specific LS7 components, notably glucose, BMI, smoking or blood pressure, were also associated with a lower incidence of heart failure. Given the robust associations between a healthy lifestyle and reduced incidence of heart failure, this study provided evidence that prevention of incident heart failure could be accomplished by implementing healthy lifestyle patterns. The American Heart Association LS7 could be seen as a way to improve cardiovascular health and to reduce morbidity and mortality from CVDs, and in particular heart failure.

In the second part of the thesis we studied heart failure treatment. In **chapter 4** we described several trends in pharmacological treatment for 85,000 heart failure patients in the CALIBER resource over almost 15 years' follow-up (2002 – 2015) in the UK. Several trends were seen in this time frame, including increased beta-blocker prescriptions over time (29% in 2002-2005 and 54% in 2013-2015), which was not observed for mineralocorticoid receptor-antagonists (MR-antagonists) (18% in 2002-2005 and 18% in 2013-2015); higher prescription rates of loop diuretics in women and elderly patients together with lower prescription rates of RAS-inhibitors, beta-blockers, or MR-antagonists in these patients; little change in medication prescription rates before and after 6 months of heart failure diagnosis; and lastly, patients hospitalised for heart failure who had no follow-up in primary care had considerably lower prescription rates compared to patients with a heart failure diagnosis in primary care with or without heart failure hospitalisation. These findings suggest heart failure management can be improved in the general population. This chapter shows that linkage of EHRs is a key component for following patients over time.

In **chapter 5** we assessed the association between beta-blocker use and outcomes in heart failure with reduced ejection fraction (HFrEF) patients ≥80 years. Based on randomized controlled trials (RCTs) it is known that beta-blockers reduce mortality and morbidity in HFrEF. However, patients older than

80 years are poorly represented in RCTs. Therefore, we performed a study in patients with ejection fraction (EF) <40% and age ≥80 years from the Swedish heart failure Registry. The association between beta-blocker use, all-cause mortality and cardiovascular (CV) mortality/heart failure hospitalization was assessed with a propensity score matched analysis. Of 6,562 patients age ≥80 years, 86% received beta-blockers. In the matched cohort including 1,732 patients, beta-blocker use was associated with a significant reduction in risk of all-cause mortality. Reduction in CV mortality/heart failure hospitalization was not significant due to the lack of association with heart failure hospitalization, whereas CV death was significantly reduced. This study shows that in HFrEF patients ≥80 years of age, i.e. those patients underrepresented in RCTs, use of beta-blockers was high and was associated with improved all-cause and CV survival.

In the third part of this thesis we investigated prognosis within heart failure patients. In **chapter 6** we assessed whether and to what extent changes over time in multiple circulating biomarkers were associated with subsequent mortality/morbidity in HFrEF. Among 1,327 patients from BIOSTAT-CHF, we assessed associations between 9-month changes in 30 biomarkers and all-cause death/heart failure hospitalization. This was done by adding the changes in biomarkers, modelled as splines, together with the baseline biomarker value, to the BIOSTAT-CHF risk score. Of 30 biomarkers tested, 9-month reductions in concentrations for the following biomarkers were separately associated with reduced risk of outcome after adjustments for baseline biomarker levels and the BIOSTAT-CHF risk score: ANP, BNP, CRP, GDF-15, NT-proCNP, Neuropilin, Osteopontin, Procalcitonin, Pentraxin-3, Polymeric immunoglobulin receptor, Pro-adrenomedulin, RAGE, sST2, Syndecan-1, TNF-1α, VEGFR-1 WAP-4C. Of these biomarkers, changes in ANP, sST2, CRP and WAP-4C were independently associated with the risk of outcome on top of all the other biomarkers tested. For early phase heart failure trials, there is a lack of suitable surrogate endpoints. This study shows that changes in biomarker levels may be used as surrogate endpoints for early phase HFrEF trials.

In **chapter 7** we compared the case mix, medication use and survival of heart failure patients across three different countries in Europe: UK, Spain and Sweden. In this study 13,334 patients from the CALIBER resource in the UK, 18,862 patients from ABUCASIS in Spain and 11,050 patients from the Swedish heart failure registry were included. The UK, Swedish and Spanish data sources

differ with regard to logical organization, terminologies, vocabularies and coding schemes and their systematic analysis in a comparable manner was therefore challenging. To be able to compare patients from these different data sources the data was mapped into a common format. Data was harmonised between the countries with the ICD classification (International Statistical Classification of Diseases). Medication use was not consistent across the countries, with more RAS-inhibitors and beta-blockers prescribed in Sweden and more MR-antagonists and diuretics prescribed in Spain. We found a higher all-cause mortality in Spain compared to Sweden and the UK, which might be related to case-mix of baseline characteristics, with Spanish patients more frequently having hypertension, COPD, diabetes, chronic renal disease, valvular disease and cancer. International data harmonisation is needed to be able to assess the quality of care and outcomes across Europe. Implementation of a common data model is key to achieve this goal. This study might stimulate an initiative to improve interoperability of databases across Europe.

The last part of this thesis included phenotyping. In **chapter 8** the aim of the study was to create an algorithm that identifies ejection fraction (EF) phenotypes for research purposes. This was done since EHRs frequently lack phenotypic information that is needed to discern relevant sub-phenotypes, thereby preventing analyses focusing on specific EF phenotypes and limiting EHRs use in heart failure research. We included 42,061 heart failure patients from the Swedish heart failure Registry and created a prediction model including 22 variables to predict 1) EF≥ vs. <50%; and 2) EF≥ vs. <40%, 3) heart failure with preserved EF (HFpEF) vs. heart failure with mid-range EF (HFmrEF) vs. HFrEF. The model was validated in the database from the Chronic Heart Failure ESC-guideline based Cardiology Practice Quality project (CHECK-HF) study, a cross-sectional survey of 10,627 patients from the Netherlands. Accuracy was good for the prediction of HFpEF and HFrEF but lower for HFmrEF, indicating that routine clinical characteristics could be used to identify different EF phenotypes. The external validation showed similar discriminative ability to the development cohort. The proposed algorithm thus could enable more effective research on heart failure in a big data setting where EF status is unknown.

In **chapter 9** we aimed to derive and validate clinically useful clusters of patients with HFpEF. The reason to conduct this study was as a result of the heterogeneity in HFpEF pathophysiology being proposed as one of the key arguments for the failure of RCTs to establish clinically relevant effects of interventions in these

patients. It is suggested that treatment in HFpEF patients should therefore be matched to distinct subsets of comorbidities, thus identifying patient groups most likely to benefit from targeted interventions. We derived a clustering model from 2,153 HFpEF (defined as EF≥50%) patients from the CHECK-HF registry and externally validated this model in 6,770 patients from the Swedish heart failure Registry. Latent class analysis identified four distinct HFpEF clusters: Cluster 1 (12.4% of patients) exhibited several characteristics similar to the HFrEF phenotype (notably history of ischaemic heart disease), cluster 2 (39.5%) were the oldest with concomitant atrial fibrillation, cluster 3 (21.7%) were the youngest with less comorbidities and medication use and lastly cluster 4 (26.4%) exhibited the 'classic HFpEF phenotype' (older age, hypertension, diabetes, female sex and diuretics use). These clusters were externally validated where, in addition, we observed differences in prognosis with the healthy cluster having the best prognosis and the older atrial fibrillation cluster the worst. These results confirm the heterogeneity of HFpEF and form a basis for tailoring trial design to individualized drug therapy in HFpEF patients.

Nederlandse samenvatting

De snelle toename van real-world data (RWD) kan potentieel een grote bijdrage leveren aan verbeteringen in de gezondheidszorg. De enorme toename van de verzamelde gegevens in de gezondheidszorg kan echter niet automatisch worden vertaald naar de klinische praktijk. Het doel van dit proefschrift was om het potentieel gebruik van RWD op het gebied van hartfalen in kaart te brengen door te onderzoeken welke mogelijkheden RWD biedt, maar ook wat de uitdagingen zijn binnen RWD. We identificeerden een aantal onderwerpen, zoals de koppeling van elektronische patiëntendossiers (EPD's), de mogelijkheid om patiënten in een reële omgeving te bestuderen en technieken om grote hoeveelheden gegevens te analyseren als kansen op hartfalen. Uitdagingen die we tegenkwamen waren de kwaliteit van de routinematige gegevens in de gezondheidszorg, een gebrek aan consensus over de fenotypering van ziekten in RWD, het harmoniseren en standaardiseren van gegevens, en het onvolledig verzamelen van gegevens. We vatten hier de hoofdstukken van dit proefschrift samen die te maken hebben met de kansen en uitdagingen van RWD bij hartfalen.

In deel 1 zijn risicofactoren voor hartfalen besproken. In **hoofdstuk 2** hebben we de risicofactoren voor hartfalen onderzocht in een groot bevolkingsonderzoek in het Verenigd Koninkrijk. Binnen de gekoppelde EPD-bron CALIBER hebben we een onderzoek uitgevoerd bij bijna 900,000 personen van 55 jaar en ouder zonder hartfalen bij de start van het onderzoek. Het doel van het onderzoek was het verifiëren van associaties van (on)bekende risicofactoren voor hartfalen. We hadden de gelegenheid om de consistentie van risicofactoren in verschillende leeftijds- en geslachtssubgroepen uit de algemene bevolking te onderzoeken. In CALIBER hadden we voor patiënten tussen 2000 en 2010 gekoppelde EPD's ter beschikking met huisartsendossiers, ziekenhuisontslagen en het nationale overlijdensregister. Bijna 50,000 personen ontwikkelden hartfalen tijdens de follow-up. De incidentie was het hoogst bij patiënten ouder dan 75 jaar en voor alle leeftijden hoger voor mannen dan voor vrouwen. Door gebruik te maken van grote hoeveelheden gegevens konden we verschillen aantonen in de associatie van risicofactoren met hartfalen tussen mannen en vrouwen; atriumfibrillatie, COPD en diabetes hadden sterkere associaties met het ontwikkelen van hartfalen bij vrouwen dan bij mannen. Voornamelijk modificeerbare risicofactoren hadden een aanzienlijk risico dat aan de bevolking werd toegeschreven. Deze studie benadrukte het belang van preventieve strategieën die zich richten op

modificeerbare leefstijl risicofactoren voor hartfalen, naast het beheer van de bloeddruk in de algemene bevolking.

In **hoofdstuk 3** van dit proefschrift hebben we ons onderzoek naar modificeerbare leefstijlfactoren voortgezet, waarbij we de American Heart Association Life's Simple 7 (LS7) en het risico op hartfalen in een algemene Nederlandse populatie onder de loep hebben genomen. LS7 is een concept waarin gezond gedrag wordt aanbevolen dat de last van hart- en vaatziekten (HVZ) zou kunnen verminderen, en bestaat uit bekende risicofactoren voor HVZ: roken, verminderde lichaamsbeweging, hoge body mass index (BMI), ongezond dieet, hoge bloeddruk, hoog totaal cholesterol en glucose. Het doel van deze studie was om inzicht te geven in combinaties van specifieke LS7-componenten die het risico op hartfalen zouden kunnen verminderen. Deze studie omvatte bijna 40,000 deelnemers van het EPIC-NL (European Prospective Investigation in Cancer and Nutrition-Netherlands) cohort en bijna 700 deelnemers ontwikkelden hartfalen tijdens de follow-up. Zowel een ideale als een middenmaatse score voor LS7 werden geassocieerd met 50% of meer afname van het risico op hartfalen. Onze analyses toonden verder aan dat combinaties met specifieke LS7-componenten, met name glucose, BMI, roken of bloeddruk, ook geassocieerd werden met een lagere incidentie van hartfalen. Gezien de sterke associaties tussen een gezonde leefstijl en een verminderd risico op hartfalen, leverde deze studie bewijs dat het voorkomen van incidenteel hartfalen kan worden bereikt door het implementeren van gezonde leefstijlpatronen. De American Heart Association LS7 kan worden gezien als een manier om de cardiovasculaire gezondheid te verbeteren en de morbiditeit en mortaliteit als gevolg van HVZ, en in het bijzonder hartfalen, te verminderen.

In het tweede deel van het proefschrift hebben we de behandeling van hartfalen bestudeerd. In **hoofdstuk 4** hebben we verschillende trends beschreven in de farmacologische behandeling van 85,000 hartfalenpatiënten in de CALIBER-middelen gedurende bijna 15 jaar follow-up (2002-2015) in het Verenigd Koninkrijk. In dit tijdsbestek werden verschillende trends gezien, waaronder een toename van het aantal voorschriften voor bètablokkers in de loop der tijd (29% in 2002-2005 en 54% in 2013-2015), die niet werd waargenomen bij mineralocorticoïde receptor-antagonisten (MR-antagonisten) (18% in 2002-2005 en 18% in 2013-2015); hogere voorschrijfpercentages van lisdiuretica bij vrouwen en oudere patiënten, samen met lagere voorschrijfpercentages van RAS-remmers, bètablokkers, of MR-antagonisten bij deze patiënten; weinig verandering in het

aantal voorgeschreven medicijnen voor en na 6 maanden diagnose van hartfalen; en tot slot hadden patiënten die voor hartfalen in het ziekenhuis werden opgenomen en die geen follow-up hadden in de eerstelijnsgezondheidszorg, aanzienlijk lagere percentages medicatie voorschrijving dan patiënten met een diagnose van hartfalen in de eerstelijnsgezondheidszorg met of zonder opname in het ziekenhuis. Deze bevindingen suggereren dat de behandeling van hartfalen in de algemene populatie kan worden verbeterd. Dit hoofdstuk laat zien dat het linken van EPD's een belangrijk component is voor het volgen van patienten door de tijd.

In **hoofdstuk 5** bekeken we het verband tussen het gebruik van bètablokkers en de uitkomsten bij hartfalen met verminderde ejectiefractie (HFrEF) patiënten ≥80 jaar. Op basis van gerandomiseerde gecontroleerde studies (RCT's) is bekend dat bètablokkers de mortaliteit en morbiditeit in HFrEF verminderen. Echter, patiënten ouder dan 80 jaar zijn slecht vertegenwoordigd in RCT's. Daarom hebben we een studie uitgevoerd bij patiënten met ejectiefractie (EF) <40% en leeftijd ≥80 jaar uit de Zweedse hartfalenregistratie (SwedeHF). De associatie tussen bètablokkergebruik, algemene mortaliteit en cardiovasculaire (CV) mortaliteit/ hartfalenhospitalisatie werd beoordeeld met een propensityscore gematchte analyse. Van de 6,562 patiënten in de leeftijd van ≥80 jaar kreeg 86% bètablokkers. In het gematchte cohort, met in totaal 1,732 patiënten, werd het gebruik van bètablokkers geassocieerd met een significante vermindering van het risico op algemene sterfte. De vermindering van de CV-sterfte/ hartfalenhospitalisatie was niet significant vanwege het gebrek aan associatie met hartfalenhospitalisatie, terwijl de CV-sterfte aanzienlijk werd verminderd. Deze studie toont aan dat bij HFrEF-patiënten ≥80 jaar, d.w.z. patiënten die ondervertegenwoordigd zijn in RCT's, het gebruik van bètablokkers hoog was en geassocieerd werd met een verbeterde algemene en CV-overleving.

In het derde deel van dit proefschrift hebben we de prognose binnen hartfalenpatiënten onderzocht. In **hoofdstuk 6** bekeken we of en in hoeverre veranderingen in de loop van de tijd in meerdere circulerende biomarkers geassocieerd werden met latere mortaliteit/morbiditeit in HFrEF. Bij 1,327 patiënten van BIOSTAT-CHF beoordeelden we associaties tussen 9-maanden veranderingen in 30 biomarkers en algemene sterfte/ hartfalen hospitalisatie. Dit werd gedaan door de veranderingen in biomarkers, gemodelleerd als splines, samen met de baseline biomarkerwaarde toe te voegen aan het BIOSTAT-CHF risicomodel. Van de 30 geteste biomarkers werden 9-maanden verminderingen

in concentraties voor de volgende biomarkers afzonderlijk geassocieerd met een verminderd risico op uitkomst na aanpassingen voor de baseline biomarkeringsniveaus en de BIOSTAT-CHF-risicoscore: ANP, BNP, CRP, GDF-15, NT-proCNP, Neuropilin, Osteopontin, Procalcitonin, Pentraxin-3, Polymere immunoglobuline receptor, Pro-adrenomedulin, RAGE, sST2, Syndecan-1, TNF-1α, VEGFR-1 WAP-4C. Van deze biomarkers werden veranderingen in ANP, sST2, CRP en WAP-4C onafhankelijk van elkaar in verband gebracht met het risico op een resultaat boven op alle andere geteste biomarkers. Voor de vroege fase van de hartfalen RCT's is er een gebrek aan geschikte surrogaat-eindpunten. Deze studie toont aan dat veranderingen in biomarkeringsniveaus kunnen worden gebruikt als surrogaat-eindpunt voor vroege fase HFrEF-RCT's.

In **hoofdstuk 7** hebben we de casemix, het medicijngebruik en de overleving van hartfalenpatiënten in drie verschillende landen in Europa vergeleken: Verenigd Koninkrijk, Spanje en Zweden. In deze studie werden 13,334 patiënten uit CALIBER in het Verenigd Koninkrijk, 18,862 patiënten uit ABUCASIS in Spanje en 11,050 patiënten uit SwedeHF opgenomen. De Britse, Zweedse en Spaanse databronnen verschillen van elkaar op het gebied van logistieke organisatie, terminologie, vocabulaires en coderingsschema's en hun systematische analyse op een vergelijkbare manier was daarom een uitdaging. Om patiënten uit deze verschillende databronnen te kunnen vergelijken werden de gegevens in een gemeenschappelijk structuur in kaart gebracht. De gegevens werden geharmoniseerd tussen de landen met de ICD-classificatie (International Statistical Classification of Diseases). Het medicijngebruik was niet in alle landen consistent, met meer RAS-remmers en bètablokkers die in Zweden werden voorgeschreven en meer MR-antagonisten en diuretica die in Spanje werden voorgeschreven. We vonden een hogere algemene mortaliteit in Spanje in vergelijking met Zweden en het Verenigd Koninkrijk, die mogelijk verband houdt met een casemix van basiskenmerken, waarbij Spaanse patiënten vaker hypertensie, COPD, diabetes, chronische nieraandoeningen, valvulaire aandoeningen en kanker hebben. Er is behoefte aan internationale gegevensharmonisatie om de kwaliteit van de zorg en de resultaten in heel Europa te kunnen beoordelen. De implementatie van een gemeenschappelijk gegevensmodel is essentieel om dit doel te bereiken. Deze studie zou een initiatief kunnen stimuleren om de interoperabiliteit van databanken in heel Europa te verbeteren.

Het laatste deel van dit proefschrift beschrijft de fenotypering van hartfalen. In **hoofdstuk 8** was het doel van het onderzoek het creëren van een algoritme dat ejectiefractie (EF) kan fenotypen voor onderzoeksdoeleinden. Dit werd gedaan omdat fenotypische informatie vaak ontbreekt bij EPD's. Deze informatie is nodig om relevante subfenotypen te onderscheiden. Door het missen van deze informatie zijn analyses gericht op specifieke EF-fenotypen en het gebruik van EPD's beperkt. We hebben 42,061 hartfalenpatiënten uit SwedeHF geanalyseerd en een voorspellingsmodel opgesteld met 22 variabelen om 1) EF≥ vs. <50%; en 2) EF≥ vs. <40%, 3) hartfalen met behouden EF (HFpEF) vs. hartfalen met mid-range EF (HFmrEF) vs. HFrEF te voorspellen. Het model is gevalideerd in de CHECK-HF database (Chronic Heart Failure ESC-guideline based Cardiology Practice Quality project), een cross-sectioneel onderzoek van 10,627 patiënten uit Nederland. De nauwkeurigheid was goed voor de voorspelling van HFpEF en HFrEF, maar lager voor HFmrEF, wat aangeeft dat routinematige klinische kenmerken kunnen worden gebruikt om verschillende EF-fenotypen te identificeren. De externe validatie toonde een vergelijkbaar discriminerend vermogen als in het ontwikkelingscohort. Het voorgestelde algoritme zou dus effectiever onderzoek naar hartfalen mogelijk kunnen maken in een big data setting waar de EF-status onbekend is.

In **hoofdstuk 9** hebben we klinisch bruikbare clusters van patiënten met HFpEF geïdentificeerd en gevalideerd. De reden om dit onderzoek uit te voeren was dat de heterogeniteit in de HFpEF pathofysiologie een van de belangrijkste argumenten is voor het falen van RCT's om klinisch relevante effecten van interventies bij deze patiënten vast te stellen. Er wordt gesuggereerd dat de behandeling van HFpEF-patiënten daarom moet worden afgestemd op verschillende subsets van comorbiditeiten, zodat de patiëntengroepen kunnen worden geïdentificeerd die het meest gebaat zijn bij gerichte interventies. We hebben een clustermodel gecreeërd van 2,153 HFpEF-patiënten (gedefinieerd als EF≥50%) uit de CHECK-HF-registratie en hebben dit model extern gevalideerd bij 6,770 patiënten uit SwedeHF. Bij de analyse werden vier verschillende HFpEF-clusters geïdentificeerd: Cluster 1 (12.4% van de patiënten) vertoonde verschillende kenmerken die vergelijkbaar zijn met het HFrEF-fenotype (met name de geschiedenis van ischemische hartziekte), cluster 2 (39.5%) waren de oudste patiënten met atrium fibrilleren, cluster 3 (21.7%) waren de jongste patiënten met minder comorbiditeiten en medicijngebruik en tot slot cluster 4 (26.4%) vertoonde het 'klassieke HFpEF-fenotype' (oudere leeftijd, hypertensie, diabetes, vrouwelijk geslacht en gebruik van diuretica). Deze clusters werden

extern gevalideerd, waarbij we bovendien verschillen in prognose zagen met het gezonde cluster met de beste prognose en het oudere atrium fibrilleren-cluster de slechtste prognose. Deze resultaten bevestigen de heterogeniteit van HFpEF en vormen een basis voor het op maat maken van een RCT voor geïndividualiseerde geneesmiddelentherapie bij HFpEF-patiënten.

Dankwoord

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About the author

Alicia Uijl was born on 3 September 1991, in Zwijndrecht, the Netherlands. After graduation from her secondary school Develstein college in 2009, she studied Biomedical Sciences at Leiden University. Here, she obtained her Bachelor's degree in 2012 and her Master's degree in 2015. During her Master's she specialised in Epidemiology. She did a research project during her Master's on the relative contributions of visceral fat and liver fat to insulin resistance in the general population with the Epidemiology department at Leiden University Medical Center. In 2016 she started her PhD project at the Julius Center for Primary Care and Health Sciences, University Medical Center Utrecht, leading to this thesis. She was under supervision of prof. dr. F.W. Asselbergs, prof. dr. A.W. Hoes, dr. S. Koudstaal and dr. I. Vaartjes. She spent a research period abroad from September 2016 – September 2017, where she worked at the Institute for Health Informatics at University College London, United Kingdom, under supervision of dr. R.H.H. Groenwold. She then spent a second research period abroad, at Karolinska Institutet, Sweden, where she worked from September 2018 – June 2019. During her PhD trajectory she obtained her post-graduate Master's degree in Clinical Epidemiology online in 2019. Currently, she participates in the BigData@Heart project of the Innovative Medicines Initiative at the Julius Center.

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