Differentiation of clinical characteristics, mortality, healthcare utilization and costs among four subgroups in a population with heart failure

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Abstract:

Heart failure (HF) is associated with high mortality, decreased quality of life, and places a heavy burden on healthcare resources. Numerous HF patients are diagnosed without a conclusive echocardiogram and are lacking appropriate pharmacotherapy. The majority of HF studies in Sweden are based on hospital registries that may not represent the entirety of the HF patient population. This thesis examined HF patients in Region Halland (RH), Sweden, using on an unselected, community-based cohort, and determined factors associated with mortality, morbidity and healthcare costs.

Data regarding clinical characteristics and pharmacotherapy were retrieved from the Regional Healthcare Information Platform in Halland County. We applied a novel algorithm which extracted all available EF values for HF patients in RH, providing a real-world cohort for further study. Those without a conclusive echocardiogram, in which no defined phenotype could be deduced, were categorized as a fourth HF subgroup (HF-NDP).

A conclusive EF value was determined in 57% of cases and the distribution of HF phenotypes varied from those in registry-based studies. Of patients admitted to hospital due to HF symptoms, 1644 (33%) were readmitted with a CVD diagnosis within 100 days. Nearly half (43%) of the cohort was diagnosed clinically, the majority of these (58%) being diagnosed in hospital, which also carried a higher one-year mortality compared to those diagnosed in primary care. Healthcare encounters and costs were higher for all subgroups in the first year, decreasing in the second year to varying degrees.

These papers provide an in-depth examination of a real-world HF patient population. Mortality was highest among patients diagnosed clinically, while those with a combination of recommended medications, generally lacking in the cohort, showed a decreased risk of readmission. The results underline the importance of correct diagnostic procedure and treatment to reduce morbidity, mortality and healthcare costs.

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Abstract

Heart failure (HF) is associated with high mortality, decreased quality of life, and places a heavy burden on healthcare resources. Numerous HF patients are diagnosed without a conclusive echocardiogram and are lacking appropriate pharmacotherapy. The majority of HF studies in Sweden are based on hospital registries that may not represent the entirety of the HF patient population. This thesis examined HF patients in Region Halland (RH), Sweden, using on an unselected, community-based cohort, and determined factors associated with mortality, morbidity and healthcare costs.

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A conclusive EF value was determined in 57% of cases and the distribution of HF phenotypes varied from those in registry-based studies. Of patients admitted to hospital due to HF symptoms, 1644 (33%) were readmitted with a CVD diagnosis within 100 days. Nearly half (43%) of the cohort was diagnosed clinically, the majority of these (58%) being diagnosed in hospital, which also carried a higher one-year mortality compared to those diagnosed in primary care. Healthcare encounters and costs were higher for all subgroups in the first year, decreasing in the second year to varying degrees.

These papers provide an in-depth examination of a real-world HF patient population. Mortality was highest among patients diagnosed clinically, while those with a combination of recommended medications, generally lacking in the cohort, showed a decreased risk of readmission. The results underline the importance of correct diagnostic procedure and treatment to reduce morbidity, mortality and healthcare costs.

Abbreviations

ACEI	Angiotension-converting enzyme inhibitor
ARB	Angiotensin II receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
ASCVD	Atherosclerotic cardiovascular disease
BB	Beta blocker
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
EF	Ejection fraction
ED	Emergency department
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
HC	Hospital care
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HF-NDP	Heart failure with no defined phenotype
HR	Hazard ratio
IHD	Ischemic heart disease
IPC	Inpatient care
LoS	Length of stay
MRA	Mineralocorticoid receptor antagonist
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
OPC	Outpatient care
PC	Primary care
RAASI	Renin-angiotensin-aldosterone-system inhibitor
RH	Region Halland
RHIP	Regional Healthcare Information Platform

Chapter 1. Introduction

Chapter 1.1 Popular scientific summary of the thesis in Swedish (Populärvetenskaplig sammanfattning av avhandlingen på Svenska)

Denna avhandling omfattar fyra publicerade artiklar som behandlar hjärtsvikt, en kronisk sjukdom som uppstår när hjärtats pumpfunktion försämras. Hjärtsviktpatienter har en försämrad livskvalitet, högre dödlighet och ökad användning av sjukhusresurser, vilket har betydande ekonomisk påverkan inom sjukvårde. Individer med hjärtsvikt har en nedsatt livskvalitet, ökad dödlighet samt ökad sjukhusanvändning som medför betydande hälsoekonomisk påverkan. Vid hjärtsvikt har individen en nedsatt förmåga att pumpa ut blod i cirkulationen vilket kan te sig på olika sätt.

Den procentuella andel blod som pumpas ut vid varje sammandragning i vänster kammare kallas ejektionsfraktion. Ejektionsfraktionen undersöks oftast med ett ultraljud av hjärtat som kallas ekokardiografi. Hos en individ med normal hjärtfunktion uppskattas ejektionsfraktionen vara 50–70%. Vid hjärtsvikt har individen på något sätt en nedsatt pumpförmågan och ejektionsfraktionen kan antingen vara bevarad (≥50%) eller minskad (<50%). Hjärtsvikt har principiellt tre fenotyper varav den mest typiska är hjärtsvikt med reducerad ejektionsfraktion (HFrEF) med ejektionsfraktion <40%, hjärtsvikt med mild reducerad ejektionsfraktion (HFmrEF) med ejektionsfraktion 40–49% vilket var de riktlinjer som var aktuella vid studiens planerande och genomförande. När ejektionsfraktionen är bevarad (HFpEF) pumpar vänsterkammaren ut en normal andel blodvolym vid varje hjärtslag men däremot har hjärtat begränsningar att fylla på med tillräcklig blodmängd i vänsterkammaren.

Att fastställa ejektionsfraktionen är viktigt vid diagnostiken av hjärtsvikt för att kunna definiera hjärtsviktfenotyp som har olika terapeutiska riktlinjer. HFpEF har normal ejektionsfraktion men vid ekokardiografi påvisas fynd på

typiska strukturella, funktionella avvikelser i vänster kammare, förhöjt fyllnadstryck i vänster kammare samt förhöjda nivåer av natriuretiska peptider.

Det finns ett antal faktorer som potentiellt kan leda till hjärtsvikt varav vanligast är hjärt-kärlsjukdom samt högt blodtryck som orsakar ungefär 75% av fallen med hjärtsvikt. Därutöver förekommer ofta komorbiditeter så som diabetes, förmaksflimmer, njurfunktionsnedsättning och kronisk obstruktiv lungsjukdom som ytterligare försvårar behandlingen eftersom det är flera tillstånd att ta hänsyn till.

Den första studien undersöktes individer med hjärtsvikt i Region Halland i sydvästra Sverige. Tidigare studier som genomförts i Sverige med individer med hjärtsvikt har företrädelsevis baserats på nationella register som RiksSvikt eller sjukhusbaserade kohorter. En ny datoralgoritm har utvecklats för att extrahera ejektionsfraktioner från elektroniska sjukvårdsjournaler. Detta möjliggjorde en omfattande undersökning av alla hjärtsviktsfenotyper hos patienter med hjärtsvikt i en region, vilket skiljer sig från tidigare studier. Trots att algoritmen möjliggjorde insamling av ekokardiografier med mycket hög täckningsgrad, visade det sig att 43% av patienterna i kohorten hade en kliniskt baserad hjärtsviktsdiagnos utan användning av ekokardiografi. Dessa patienter kategoriserades i en fjärde undergrupp av hjärtsvikt utan definierad fenotyp (HF-NDP). Studien jämförde de kliniska egenskaperna, behandlingsstrategierna samt ettårs dödligheten fördelat på de fyra hjärtsvikts-subgrupperna.

Den andra artikeln var en retrospektiv observationsstudie som inkluderade patienter som hade vårdats på sjukhus på grund av hjärtsvikt utifrån patient kohorten i den första studien. Deras kliniska egenskaper och medicinering dokumenterades, och patienterna observerades i 100 dagar efter utskrivning från sjukhuset. Patienter som återinlades med en kardiovaskulär diagnos under uppföljningsperioden analyserades för att identifiera riskfaktorer associerade med ökad risk för återinläggning.

Den tredje studien fokuserade mer ingående på HF-NDP-gruppen som identifierades i den första studien. Dessa patienter, som hade en kliniskt baserad hjärtsviktsdiagnos, delades in i två grupper beroende på om de diagnostiserats inom sekundär- eller primärvården. Därefter jämfördes de två grupperna ytterligare för att analysera dödlighetsfrekvenser vid olika intervaller under det första året efter diagnosen.

I den fjärde studien undersöktes sjukvårdsanvändning hos patienter med hjärtsvikt och de tillhörande kostnader. I denna kohort inkluderades patienter med två hjärtsviktsdiagnoser med minst 30 dagars mellanrum så att

hjärtsviktsdiagnosen var konfirmerad. Dessutom valdes en åldersbegränsning till 40–90 år. Detta för att mer tydligt undersöka sjukvårdsanvändning och kostnader associerade med diagnosen hjärtsvikt. Jämförelser gjordes mellan de fyra olika hjärtsvikts-subgrupper avseende sjukhusinläggningar, besök i sekundär och primärvård, uthämtade läkemedel. Patienternas sjukvårdsanvändning och kostnader samlades in och analyserades. Eftersom det är känt i andra studier att vårddagar på sjukhus genererar de största kostnaderna vid hjärtsvikt genomfördes analyser för att identifiera riskfaktorer associerade med längre sjukhusvistelser.

Sammantaget ger de fyra artiklarna i denna avhandling en djupare förståelse av hjärtsvikt när det gäller diagnostik, handläggning, behandling, behov av sjukhusvård och relaterade kostnader i en oselekterad hjärtsviktspatientpopulation i en svensk region. Studien beskriver fördelningen av hjärtsviktsfenotyper och förekomsten av subgruppen HF-NDP. I detta arbete har HF-NDP-gruppen utförligt karakteriserats, vilket tydliggör vikten av korrekt diagnostik för att kunna initiera rätt behandling. Studien identifierar även riskfaktorer för längre sjukhusinläggningar och återinläggningar inom 100 dagar efter utskrivning. Särskild uppmärksamhet bör ägnas dessa patientgrupper, både i primärvården och vid utskrivning från sekundärvården, för att minska dödlighet, sjuklighet och relaterade kostnader hos hjärtsviktspatienter.

Chapter 1.2 Etiology and epidemiology of heart failure

While atherosclerotic cardiovascular disease (ASCVD) is considered the most common etiology of HF, the myriad other potential causes can generally be separated in to two categories: those related to intrinsic heart disease, and those due to extrinsic factors [1-5]. Intrinsic heart disease includes IHD, valvular and rheumatic heart disease, hypertension, and cardiomyopathy[1-5]. Extrinsic pathologies are those that place the heart under duress due to high demand such as endocrine disorders, collagen vascular disease, or secondary to other comorbidities such as chronic obstructive pulmonary disease (COPD) [3, 6, 7]. Aging plays a significant role in the pathogenesis of HF, as the vast majority of HF patients are elderly while it remains relatively uncommon among younger patients [8-10]. In addition, obesity and unhealthy lifestyle choices

including poor nutrition, smoking, and excessive alcohol consumption are all believed to increase the risk of developing HF [1, 11].

The latter is thought to have contributed to the spike in new HF cases in the early 1990s [2-4, 10]. However, incidence of HF has since stabilised and, particularly in developed countries, has decreased considerably [1, 2, 12]. Although there are geographical variations, a study from 2013 showed that incidence rates in Sweden in 2010 were <4 per 1000 person years for both men and women, which is in accordance with those of North America and the rest of Western and Central Europe [8-10, 13]. A 2019 Swedish paper followed two separate HF cohorts, one based on national registers and one based on examination of electronic medical records, from 2010-2014. It was determined that incidence rates decreased over time, while prevalence increased in both cohorts [14]. While improved pharmacotherapy, and in particular treatment of IHD, has resulted in an observed reduction in incidence rates among HFrEF patients, the incidence rates of HFpEF patients remain largely unchanged, and in some studies have even shown an increased incidence [1, 2, 12, 15-17]. This, combined with an ever-aging population and improved diagnostics, means that the prevalence of HF has increased and will likely continue to do so over time [1, 15, 16].

At the time of publication, HF was considered a global pandemic with over 64 million people affected by the chronic, clinical syndrome [2, 18]. Data was not fully available for certain regions, but for the industrialized countries, the prevalence of HF was believed to be between 1-3%, due in large part to the growing number of HFpEF patients being diagnosed [2, 14, 18]. International therapeutic guidelines have traditionally been more clearly defined for patients with reduced EF [1, 2, 19]. The European Society of Cardiology (ESC) updated its guidelines in 2021 to include sodium-glucose cotransporter-2 inhibitors (SGLT2I) for all HF phenotypes [19]. However, prior to this, treatment of HFpEF was mainly focused on treatment of comorbidities such as hypertension [1, 19]. The most common comorbidities observed in HF patients is further discussed in chapter 1.3.

Chapter 1.3 Comorbidities common in heart failure

As has been previously established, HF often arises as a result of intrinsic or extrinsic factors that exert the heart to the point of affecting its pumping ability. It is therefore not uncommon that HF patients also suffer from other ailments

and are associated with multimorbidity [20-22]. Comorbidities common in HF patients are often referred to as cardiac and non-cardiac [23, 24]. Cardiac comorbidities involved the heart directly such as coronary artery disease, atrial fibrillation, cardiomyopathies, and valvular rheumatic heart disease. Frequently occurring non-cardiac comorbidities include diabetes, chronic kidney disease (CKD) and COPD. Some comorbidities are more common to a particular HF phenotype, while others affect all HF patients regardless of EF. For example, ischemic heart disease (IHD), preceded by ASCVD, is particularly common amongst HFrEF patients, while hypertension is more commonly seen among patients with HFpEF [20-25]. While the prognosis of HF has improved slightly since the turn of the millennium, it remains a syndrome associated with high mortality rates, high morbidity, and decreased quality of life, all of which become worse under the burden of comorbidity [26-30]. The following chapters will discuss some of the more common comorbidities seen in HF patients and their effect on patient outcomes.

Chapter 1.3.1 Atrial fibrillation

A commonly occurring comorbidity found in HF patients is atrial fibrillation. From a clinical standpoint, it can be challenging to discern one from the other as both present with similar symptoms and both may cause an increase in the biomarker n-terminal prohormone of brain natriuretic peptide (NT-proBNP) [1, 23]. A 2018 study examining the prognostic implications of atrial fibrillation in a large cohort of HF patients, found the prevalence to be between 27-39%, ranging from patients with reduced EF to those with HFpEF [23]. Additional studies have yielded similar results with the same distribution, i.e. atrial fibrillation appears to be more common among HF patients with preserved EF [16, 24]. In terms of outcomes, these same studies showed increased mortality and morbidity, measured as HF related hospitalization, in the HFpEF group but not in those with HFrEF.

Chapter 1.3.2 Diabetes

One of the more prevalent comorbidities found in HF patients is type 2 diabetes mellitus (T2DM). Previous studies have shown a drastic increase in the risk of cardiovascular morbidity and mortality in patients with both chronic ailments [31, 32]. In these studies, the prevalence was similar for all types of HF regardless of EF. Similarly, multivariate regression analyses predicted a 30-50% increased mortality risk in HF patients with T2DM, independent of EF.

Chapter 1.3.3 Chronic kidney disease

Chronic kidney disease is defined as having an estimated glomerular filtration (eGFR) rate of <60 mL/min/1.73 m^2 and is categorized into five stages based on the extent of kidney damage [33]. As CKD progresses, the eGFR worsens until the patient reaches stage five, also known as end-stage kidney disease, in which the kidneys are approaching failure or have already failed [33-35]. A lower eGFR is also associated with an increased risk of HF, which is not surprising consider the close interplay of the two [33]. In the presence of HF, there is poorer perfusion of the kidneys, which can lead to ischemic injury [36]. And, as the kidneys fail, the resulting fluid overload, uremia, anemia, and pro-inflammatory fibrosis of the myocardia, all contribute to left ventricular remodeling and cardiac dysfunction [36]. Studies have shown that CKD has a profound effect on HF patient outcomes, particularly in those with reduced EF. Both HFrEF and HFmrEF patients with CKD have a higher risk of cardiovascular and non-cardiovascular events, and a 20% increased risk of mortality compared to HFpEF [37].

Chapter 1.3.4 Chronic obstructive pulmonary disease

Similar to the interplay between HF and CKD, there appears to be a pathophysiological connection between HF and COPD. Decreased vital capacity, lung function and poorly saturated blood all increase cardiac demand, causing the heart to experience heavier than normal exertion for long periods of time, which can ultimately lead to cardiac dysfunction [6, 7]. In addition, HF can lead to fluid accumulation in the lungs, further worsening an already decreased lung function [23]. A 2017 study determined the prevalence of COPD to be 15 % in HFrEF, 12% in HFmrEF and 14 % in HFpEF [16]. A 2018 study of non-cardiac comorbidities in HF revealed that COPD was associated with increased all-cause mortality, increased morbidity (measured as need for hospitalization) and decreased quality of life [25].

Chapter 1.3.5 Iron deficiency

An additional comorbidity common to HF patients is anemia, and in particular, iron deficiency anemia [38]. Prevalence is higher among HFpEF patients compared to HF patients with reduced EF (approximately 40 % versus 30 %). Iron deficiency anemia in HF is negatively associated with survival, quality of life, and exercise capacity, and the administration at intravenous ferric carboxymaltose has been shown to reduce the risk of hospitalization in HF patients [38].

Chapter 1.3.6 Hypertension

Hypertension is a common affliction worldwide and may lead to the development of HF, particularly if left untreated. In the data underlying this thesis, hypertension was seen in over 6000 patients representing 71% of the total cohort. Hypertension was highest in the HFpEF group at 75% and these findings are in line with other publications. For example, in the Swedish HF registry, hypertension is seen in nearly 70% of patients and is highest among HFpEF patients at 72% [24]. The ASIAN-HF study showed a prevalence between 38-67% and was highest among HFpEF and HFrEF patients [39]. Data from the OPTIMIZE-HF registry determined that hypertension was the cause of HF in roughly one quarter of patients, ranging from 17% for HFrEF to 31% among HFpEF patients [40].

Chapter 1.4 Diagnostic principles of heart failure

The symptoms associated with HF are often diffuse and tend to overlap with many of the underlying issues that may cause HF in the first place, including fatigue, shortness of breath and peripheral edema [41]. As a result, numerous efforts have been made to define diagnostic criteria.

Chapter 1.4.1 Brief history of heart failure

The first documented case of HF is generally believed to have been identified in the well-preserved remains of an Egyptian dignitary known as Nebiri some 3,500 years ago [42]. A modern-day pathologist examining the remains concluded that fluid in the lungs was likely due to HF as the histopathology could not be better explain by any other cause. The Egyptians were aware of other HF features as well, including left ventricular hypertrophy and coronary atherosclerosis, which were also identified in mummies. Ancient Chinese, as well as Greek and Roman texts, also describe symptoms such as edema and dyspnea, but it is not certain that the symptoms were caused by HF. Egyptian scientists Erophilus, Erasistratus and Galen performed human dissections, and the medieval Arab scholar Ibn al-Nafi theorized as to the function of the heart with various theories. While some maintain that it was Ibn al-Nafi who first postulated a right-to-left blood flow via the lungs [43], the majority accredit this ground-breaking discovery to the 17th English physician William Harvey, who even went on to describe some of the hemodynamic anomalies seen in HF [42,43].

Work continued through the 18th century when Lancisi discovered that valvular regurgitation could lead to ventricular dilatation, and in the 19th century, physicians deepened their understanding of the effects of cardiac hypertrophy in HF, the discovery of HF as both acute and chronic, and gained knowledge regarding adaptation and maladaptation in the failing heart [42]. The advent of cardiac catheterization and cardiac surgery in the 20th century offered a wealth of knowledge on heart disease and cardiac structure but added little in terms of the pathophysiological processes involved in HF [42]. Building on Starling's 1918 publication "Law of the Heart", physiologist Stanley Sarnoff described 'Families of Starling Curves' in the mid-1950s, which put cardiac contractility, or inotropy, at the forefront of HF research [44]. With a greater understanding of the pathophysiology of HF, there was renewed focus on developing pharmacological treatments, and improving diagnostic criteria to more effectively identify HF in the early stages.

Chapter 1.4.2 Diagnostic criteria of heart failure

Perhaps the most well-known cardiovascular cohort study is the Framingham Heart Study of 1971 [45]. Subjects involved in this long-term, multigenerational study underwent physical examinations, the results of which were studied and evaluated by medical doctors in a process known as physician adjudication. Researchers then categorized the diagnostic parameters into major or minor criteria to determine the likelihood that the presenting symptoms were the result of HF. Some fourteen years later in 1985, Carlson et al., devised the Carlson criteria, a points-based system that attempted to ascertain the certainty of a HF diagnosis [46, 47]. In addition to patient history and physical examination, chest X-rays were also considered when determining the likelihood of a HF diagnosis. Beginning in the late 1980s, the Cardiovascular Health Study aimed to identify risk factors associated with coronary heart disease and stroke [48]. Researchers included the use of electrocardiograms (ECG) and echocardiograms in determining a diagnosis of HF. While the Carlson criteria have mainly been applied in HF research, both the Framingham and Cardiovascular Health Study criteria have been used in the clinical setting [47,49]. A 2004 study comparing the two showed that the Framingham criteria was more effective in identifying HF but that mortality rates were similar in both [49].

Many of the diagnostic criteria outlined in these previous studies are still applied in clinical practice today. Improved radiological- and echocardiographic techniques, magnetic imaging, as well as the addition of the

cardiac biomarker NT-proBNP have been added to international guidelines to aid in the effectiveness and accuracy of HF diagnosis [1, 50]. The following chapters will discuss diagnostic tools outside of the physical examination that increased the likelihood of a correct HF diagnosis.

Chapter 1.4.3 Echocardiography

There have been many advances in echocardiography since it was first introduced into clinical practiced as a diagnostic modality some fifty years ago [51]. Technological improvements have allowed for better anatomical imaging, and Doppler techniques provide insight into cardiac blood flow and contractility. Since HF is defined as a syndrome caused by structural and/or functional cardiac dysfunction, echocardiography is an ideal investigative and diagnostic tool [52]. Compared to cardiac magnetic imaging, echocardiography is ambulatory, non-invasive, and cost-effective, and as such continues to be the gold standard in HF diagnostic imaging modalities [51.52]. Echocardiography is regularly used to determine the size of the ventricles, measure ventricular wall thickness, and examine potential valvular pathologies. It is therefore a useful instrument in determining the type of HF (systolic vs. diastolic vs. mixed; left vs. right vs. mixed), as well as potential underlying causes (valvular disease, cardiomyopathies etc.) [52]. By measuring left ventricular ejection fraction, echocardiography is also useful in identifying HF phenotypes (HFrEF, HFmrEF and HFpEF). Progress in patients with reduced EF can be objectively measured as improvements in EF percentages. However, the same cannot be said HFpEF patients, in which the EF is already preserved within a “normal” range. New advancements in echocardiographic and Doppler techniques enable assessment of left atrial and left ventricular filling pressures, as well as left ventricular wall contractility, and thus provide a deeper understanding of this ever-growing subset of HF patients [51-57].

Chapter 1.4.4 Laboratory assessment of heart failure

Laboratory testing can be used to rule out HF as part of a differential diagnosis, as much as can be used to strengthen a suspicion of HF. In addition, laboratory testing is used to help identify potential underlying causes of HF as well as the severity of comorbidity burden [30]. The biomarkers most closely associated with HF diagnosis are B-type natriuretic peptide (BNP) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP). While both have been used in the investigation of cardiovascular disease, NT-proBNP has a longer half-life,

resulting in higher plasma levels, and thereby a higher sensitivity [55, 56]. Furthermore, unlike its counterpart BNP, NT-proBNP does not degrade either *in vivo* or *in vitro*. NT-proBNP is particularly useful in the detection of early onset HF, is generally considered to have greater diagnostic value and is therefore considered the gold standard [55-58]. Numerous studies have been put forth in an attempt to distinguish normal values from pathological values. The classification system applied in this thesis is that proposed by James Januzzi et al., in 2018 (Figure 1). In this paper, positive and negative predictive values of age-stratified cut-offs were tested to either confirm the likelihood of an acute HF diagnosis or to exclude it with convincing results [59].

Figure 1: Recommended N-terminal prohormone of brain natriuretic peptide (NT-proBNP) cut-offs for suspected acute heart failure diagnosis.

	Cut-off levels (pg/mL)		
	Age < 50	**Age 50–75**	**Age > 75**
HF unlikely	<300		
"Grey zone"	300–450	300–900	300–1800
HF likely	>450	>900	>1800

Note: HF=heart failure; NT-proBNP=N-terminal prohormone of brain natriuretic peptide.

While NT-proBNP is the chief biomarker used to diagnose acute onset HF, a number of other laboratory values can be applied to determine the underlying cause and assess the extent of comorbidity. In the more acute setting, a troponin series and creatine kinase-MB levels are used to investigate potential myocardial infarction, a common cause of HF (particularly HFrEF). Arterial blood gases are used to investigate hypoxia and underlying pulmonary pathology, and blood cultures are taken when the suspected HF is believed to be caused by endocarditis or some other systemic infection [39]. Estimated glomerular filtration rate and urinalysis are used to determine renal function and possible kidney damage related to, or caused by, HF. Serum sodium, potassium as well as calcium and magnesium are used to determine electrolyte imbalance, which are especially valuable when the HF is treated with diuretics [35]. A complete blood count with serum iron transferring saturation and ferritin

are used to investigate anaemia/iron deficiency anaemia, and liver function tests can be used to detect hepatic congestion and/or volume overload [39]. Lyme serology, human immunodeficiency virus and thiamine may also be ordered to determine more uncommon causes of HF. In terms of comorbidities and risk management, a lipid profile can be used to determine potential hyperlipidaemia, and serum glucose and haemoglobin A1C levels can detect an underlying diabetes mellitus.

Chapter 1.5 Regional Healthcare Information Platform

Halland, a county in the southwest of Sweden, has a population of approximately 330,000 people. The healthcare system, known as Region Halland (RH) is comprised of three hospitals with forty inpatient wards and two emergency departments, thirty outpatient clinics, and forty-eight primary care (PC) facilities, of which nearly half are considered private or semi-private. As the Swedish healthcare system is decentralized, each county is able to invest in its own information technology platform to store its pertinent healthcare data, so long as it meets national standards. In 2016, RH built a data management and analysis platform that includes information from both the primary- and secondary care levels, as well as care resources both independent and at assisted living residences [60]. The Regional Healthcare Information Platform (RHIP) receives patient data from a multitude of sources including national registers such as the Swedish Prescribed Drugs Register and Apotekets Dosdispensering (Apodos), which offer an in-depth look at pharmacotherapy. In addition, organisational data and data concerning healthcare economics as determined by the Patient Encounter Costing (PEC) method are available in RHIP. The largest data source in terms of direct patient care comes from the electronic medical records (EMR) system, VAS. VAS has been in use in RH since 2009 and is routinely used by healthcare providers to record patient data including: physical examination findings, clinical data such as blood pressure and heartrate, and clinical investigation results including laboratory results and assessment of radiological examinations [60]. The data are stored in the RH data warehouse and linked to RHIP where they are housed in an SQL server [60]. Once on the platform, the patient data are easily accessible and can be structured and filtered to aid in further analysis. Since the data are based on individual patient social security numbers, they are assigned a pseudonymized platform ID number for added security. The information in

RHIP is visit- and patient-centred and categorized into so-called data tables. The five data tables include:

1. Visit tables: the total number of healthcare encounters with primary- and secondary care (including inpatient, outpatient, ambulance, and emergency department) as well as pharmacy visits.
2. Detail visit tables: detailed information from these healthcare encounters including medical and procedural notes, diagnoses, and medications.
3. Detail patient tables: patient demographics including age, gender and geographical IDs as recorded in national registers.
4. Resource tables: based on human resource data, this is information related to the utilization of medical personnel per hour per day, and also includes data for medical secretaries, care delivery units and care providers other than physicians, nurses and nursing assistants.
5. Cost tables: based on the PEC method, this table concerns cost data and includes resource capacity and utilization [60].

For research purposes, a data set is generated using a key limited to authorized IT personnel working in RH. The key is not available to the researcher. New platform IDs are generated to represent the target population and the key is then deleted. For added security, the data may only be accessed by authorized researchers and are protected behind regional IT firewalls [60].

Chapter 1.6 Extraction of ejection fraction values

Since EF values were not part of the structured electronic medical record (EMR) data, they were instead retrieved from the free text notes of any given echocardiographic investigation. Most EF values within these notes are described with a defined grammatical structure, which lends itself to an analysis based on a restricted set of rules. As such, it was concluded that developing an algorithm based on regular expression (RE) and keyword search would be more than sufficient to complete the task of EF extraction. The RE method was developed using the Python programming language (version 3.8). A machine learning approach was briefly considered. However, it would require numerous examples of previously labelled echocardiography notes for the training process, which simply did not exist, and as such, machine learning was not possible in this study.

Ejection fraction values were most commonly expressed in the free text notes as: **“<keyword> <a variable amount of characters or word> <numbers or limited set of statements>”**

Keywords were either simple, such as ‘EF’ or ‘Ejection fraction’, or could consist of multiple words, such as ‘Systolic left ventricular function’. As EF is the percentage of blood pumped from the left ventricle with each heartbeat, its values, in this context known as ‘statements’, were typically represented as a number followed by a percent sign, for example 40%. However, EF values could also be expressed as less than or greater than a value, such as >55%, or describing a range of values, such as 40-50%. In many cases, EF values were expressed using words, like ‘normal’, ‘moderate’ or ‘severe’. The above construction is ideal for an RE approach. Search patterns were created to find combinations of words that fit the above structure and identified the intended statements. Based on the retrieved statements of both numerical values and verbal descriptions, EF was categorized as HFrEF, with an EF <40%, HFmrEF, in which the EF is between 40-49%, and HFpEF, where the EF is preserved at ≥50%. HF patients diagnosed without echocardiography had no defined phenotype and were categorized as HF-NDP in these studies.

With the parameters set, validation of the RE-based method for extracting EF values was determined in two independent steps. Upon development, the algorithm was run on a limited set of echocardiography notes. From these, 100 notes were randomly selected from manual processing by two independent physicians. The manually extracted EF categories were compared with the results automatically generated by the RE method. The initial validation step revealed a degree of discrepancy, and the errors made by the RE method were then used to identify new rules and keywords to improve the search parameters. Performance of the refined RE method was then tested against an additional set of 100 randomly selected notes and exceeded the threshold for accuracy set by the researchers. Finally, the RE method determined HF phenotypes in one of two ways: either by extracting a numeric EF value when available, or phenotype specific keywords. Therefore, a stratified random sampling was applied to evaluate the effectiveness of the RE method with an equally distributed proportion of notes collected for the different phenotypes and the HF-NDP subgroup. In the event that multiple EF values were available for the same patient, the lowest conclusive EF was applied as it best represented the patient’s heart function at onset and was used to determine the HF phenotype.

Chapter 1.7 Classification of heart failure and recommended pharmacotherapy

The syndrome of HF is associated with high mortality, decreased quality of life, high morbidity with frequent hospitalizations and a heavy economic burden on healthcare systems worldwide [1-4, 13-19, 27-29]. With an increasing prevalence affecting a predominantly aging population, HF has garnered much attention within the medical community as healthcare providers attempt to find tenable solutions to curb this global pandemic. Over the past decades, several classification systems have been adopted to better understand HF. The American College of Cardiology, together with the American Heart Association Task Force, have described the development of HF as four stages [61]. The first stage, A, defines patients who have not yet developed HF but have underlying conditions such as hypertension, coronary artery disease, obesity and cardiomyopathies, which place them in a higher risk group. Stage B describes patients with structural damage to the heart muscle but who have yet to exhibit HF symptoms. Patients who have or have had symptoms consistent with HF are in stage C, while stage D refers to patients with more advanced HF symptoms which either impact their daily activities or require hospitalization. In practice, until the patient develops HF, treatment should be focused on reducing risk factors. For example, medications to reduce hypertension and hyperlipidemia, and nutrition and exercise plans. However, once a HF diagnosis has been confirmed, the treatment protocol is extended depending on the type of HF the patient has. As such, HF classification systems have also been implemented to determine the type of HF and the extent to which the symptoms affect the patient's daily life. The two classification systems discussed in the following chapters are based on 1) pathophysiology, and 2) subjective symptom evaluation.

Chapter 1.7.1 Heart failure classification based on pathophysiology

Historically, HF has been a purely clinical diagnosis [41-43, 45-49]. Patients would present with symptoms that physicians would investigate based on established criteria and, if the patient fulfilled said criteria, they would be diagnosed with HF [41-43]. The introduction of echocardiography into clinical practice some 50 years ago added a whole new dimension to the diagnosis of HF [51-54]. The evolution of imaging techniques and Doppler allow for an accurate appreciation of cardiac anatomy and function. Perhaps most important to HF

is the determination of an ejection fraction, the percentage of blood pumped from the left ventricle with each heartbeat [15, 16, 23-29]. A normal, rhythmic heartbeat has two phases: the systolic phase, in which the heart muscles contract, and the diastolic phase, when they relax allowing the chambers to fill with blood.

In systolic HF, some sort of dysfunction is preventing the left ventricle from contracting as normal. The origin may be muscular (myocardial infarction, cardiomyopathy etc), vascular (coronary artery disease, hypertension etc), or valvular (aortic stenosis, mitral regurgitation) in nature. The extent of damage is often reflected in the EF. Based on guidelines current during the study period, a normal EF wass estimated to be between 50-70%, an EF <40% was considered as HF with reduced EF, or HFrEF, and an EF in between was known either as mildly reduced or mid-range, HFmrEF [19, 50].

Figure 2: Definition of HF-phenotypes based on the 2016 ESC therapeutic guidelines.

Type of HF		HFrEF	HFmrEF	HFpEF
Criteria	1	Symptoms ± signs[a]	Symptoms ± signs[a]	Symptoms ± signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

In diastolic HF, the muscles of the left ventricle are unable to relax as normal, which impedes the chamber's ability to fully fill [62]. Contractility may be impaired but not to the same extent as in systolic HF. As a result, the EF is often preserved and as such, diastolic HF is synonymous with HFpEF. The underlying etiology of diastolic HF is similar to that of systolic HF but is more frequently associated with comorbidities such as hypertension. Since both conditions affect the left ventricle, systolic and diastolic HF are known together as left-sided heart failure and share similar signs and symptoms [62].

Less commonly, a patient may present with signs and symptoms suggestive of right-sided HF. In this condition, a dysfunction in the pumping ability of the right ventricle leads to volume and pressure overload, resulting in a backward flow of blood into the venous system [63-64]. Depending on the extent of the HF, symptoms may include shortness of breath and abdominal distention [64]. While

right-sided HF may occur on its own, it is often secondary to a pre-existing, left-sided HF [63-64].

Chapter 1.7.2 Heart failure classification based on symptoms

The most commonly applied HF classification system to describe patient symptoms and prognosis was developed in 1928 by the New York Heart Association (NYHA) [65]. While it has gone through several iterations since its inception, the fundamental theme remains the same – a staged system defining the progression of HF severity based on patient-reported symptoms [66]. The NYHA classification system is the gold standard for grading the more subjective side of HF and has been cited in numerous studies since it was first published nearly a century ago [66-72]. According to NYHA, patients with Class I HF have no apparent symptoms and the syndrome does not limit them in their daily lives [66]. Class II patients exhibit mild symptoms that limit them slightly in their day-to-day lives. Compared to Class I, these patients may, for example, feel slightly short of breath upon exertion such as walking or climbing stairs [66]. In Class III, symptoms have worsened such that they impact daily activities to a larger extent. Patients in Class III may only be able to walk shorter distances of 20-100 meters and described themselves as most comfortable at rest [67]. Finally, HF patients in Class IV of the NYHA classification system have rather sever symptoms and are often bed-ridden [66]. In many instances, particularly when HF is quickly diagnosed and appropriate pharmacotherapy is implemented relative to the onset of symptoms, the NYHA class remains stable for long periods of time. In other cases, an acute HF can improve after medical intervention resulting in a lower NYHA class over time. However, in most cases, the patient's condition worsens, and the NYHA class trajectory reflects this deterioration over time.

Chapter 1.7.3 Heart failure pharmacotherapy

The articles comprising this thesis are based on data available until the year 2019. The most current guidelines pertaining to HF treatment at that time in Europe were released in 2016 by the ESC Task Force [1]. These guidelines have since been amended in 2021 and again in 2023 [19, 50]. The guidelines from 2016 focused chiefly on patients with reduced EF, particularly those with HFrEF. Adequate pharmacotherapy for these patients consisted primarily of two medications: a betablocker (BB) and a renin-angiotensin-aldosterone-system inhibitor (RAASI), either an angiotensin-converting enzyme inhibitor (ACEI),

an angiotensin II receptor blocker (ARB) or an angiotensin receptor neprilysin inhibitor (ARNI) [1]. In more advanced HF, the addition of a mineralocorticoid receptor blocker (MRA) was recommended, and diuretics were used to alleviate symptoms of congestion [1]. For patients with HFmrEF, both BB and RAASI were recommended in certain instances, as well as diuretics, while the focus of treatment for HFpEF patients was to improve underlying conditions such as hypertension with the administration of diuretics as needed [1]. In the articles of this thesis, many HFpEF patients were already prescribed either a BB, a RAASI or both as part of their hypertension treatment. The addition of sodium-glucose co-transporter 2 (SGLT2) inhibitors, dapagliflozin and empagliflozin, to a treatment regimen including ACE inhibitors, ARNIs, beta-blockers, and MRAs has been shown to reduce the risk of cardiovascular death and worsening heart failure in patients with HFrEF. More recently, two clinical trials involving these SGLT2 inhibitors have demonstrated their benefits in patients with HF and an LVEF >40%, prompting an update in the recommendations for treating both HFmrEF and HFpEF as well [73-76].

Previous publications have shown that adequate pharmacotherapy not only has a positive effect on mortality but also reduces the need for hospitalization [77-78]. Despite the established guidelines and well-documented outcomes in terms of mortality and morbidity, numerous HF patients at the time of these studies were either missing adequate pharmacotherapy or prescribed suboptimal doses [79-83].

Chapter 1.8 Healthcare resource utilization and cost of heart failure

The syndrome of HF carries with it high rates of mortality and morbidity [84-85]. European studies based on secondary care patients, considered to be more unstable, show one-year mortality rates between 21-36% [78, 83-85]. PC-based studies, which include more stable, chronic HF patients, show one-year mortality rates between 7-16% [81, 82]. Patients with new onset HF, or those who experience an acute worsening of their symptoms, are often quite unwell and require a great deal of medical attention until they are stable enough to be discharged from hospital. It is estimated that 44% of HF patients are admitted to an internal medicine department at least once per year [82] with an average of 6-7 days spent in hospital annually [83, 86, 87]. Readmissions due to HF complications are common and almost half of hospitalized HF patients are readmitted within 6 months [86, 87]. This high demand on healthcare resource

utilization inevitably places a high financial burden on healthcare systems worldwide [2, 86-92]. It is understood that inpatient care accounts for the greatest cost share, representing approximately 75-80% [78, 90, 93-95]. Over the past decades, the incidence of HF has stabilized in most developed countries [1, 2, 12]. However, advancements in life-saving cardiovascular interventions and an ever-aging population means that the prevalence is expected to rise over time [1, 15, 16]. Add to this, the fact that most HF patients have one or more chronic comorbidities and one can quickly foresee an increasingly demanding situation for healthcare providers and policy makers.

A 2014 study examined healthcare costs, both direct and indirect, attributed to HF from 197 countries worldwide [91]. Direct costs accounted for 60% of the total $108 billion, while the remaining $43 billion were attributed to indirect costs to society including early death and lost productivity [91]. Another review of sixteen international studies, determined the lifetime cost of care for the average HF patient to be $126,819 [96]. Costs varied greatly among countries with Germany shouldering the heaviest economic burden. A German study from 2011 found the cost of HF-related care to be €3150 per patient per year, with hospitalization accounting for 74% of the total [92]. In addition, there was a significant increase in the cost of care from HF patients NYHA Class II-IV. In Sweden, the cost of HF care has been studied for a number of years with great variability in the results over time. A 1999 study found the average yearly cost of HF-related hospital care to be between 1.3-1.6 billion Swedish kronor (SEK), approximately 75% of the total cost of 2-2.6 billion SEK [97]. While this was a lofty sum at the time, accounting for almost 2% of the annual Swedish healthcare budget, it dwarfs in comparison to a more recent study that showed annual hospital care costs related to HF ranging from 6.23-8.86 billion SEK from 2005 to 2014 [98]. Consistent with previous findings, the latter study found that hospital admissions were the largest cost driver, with an annual all-cause secondary care cost of 122,758 SEK per patient. The study revealed a decrease in hospital admissions after the first year, post-diagnosis and found no significant difference in hospital resource utilization between HFrEF and HFpEF patients [98].

Chapter 1.9 Aims

The aim of this project is to describe the HF patient population in RH using a community-based approach, and to identify potential differences compared to previous registry-based studies. Furthermore, the project aims to examine

factors associated with one-year all-cause mortality, increased risk of cardiovascular readmission within 100 days of discharge, healthcare utilization in the two years following diagnosis, and associated healthcare costs. Lastly, this project aims to compare patients diagnosed with and without the use of echocardiography in terms of clinical characteristics and mortality.

Chapter 1.10 Original papers and author contributions

This thesis is based on the following four papers:

I. Clinical characteristics and mortality of patients with heart failure in Southern Sweden from 2013 to 2019: a population-based cohort study. Davidge J, Ashfaq A, Ødegaard KM, Olsson M, Costa-Scharplatz M, Agvall B. BMJ Open 2022:12(12):e064997.

II. Clinical characteristics at hospital discharge that predict cardiovascular readmission within 100 days in heart failure patients - An observational study. Davidge J, Halling A, Ashfaq A, Etminani K, Agvall B. Int J Cardiol Cardiovasc Risk Prev 2023:16:200176.

III. Heart failure patients without echocardiography are more commonly diagnosed in hospital care and are associated with higher mortality compared to primary care. Samskog V, Davidge J, Halling A, Agvall B. Scand J Prim Health Care 2023:1-9.

IV. Healthcare utilization and costs associated with heart failure during the first two years after diagnosis – an observational study from Region Halland, Sweden. Davidge J, Halling A, Agvall B. (Unpublished manuscript)

The author of this thesis was involved in the conceptualization of all studies as well as formal analysis and data interpretation. Furthermore, the author contributed to the writing, reviewing and editing of the above manuscripts for important intellectual content and final approval of the versions to be published.

Chapter 2. Methods

Chapter 2.1 Ethical considerations

Chapter 2.1.1 Ethical approval statement

An informed consent was waived, and the study procedures were approved by the Swedish Ethical Review Authority with reference number 2020-00455. As the studies were retrospectively designed and based on pseudonymized data from the Region Healthcare Information Platform, individual patient consent was not required in accordance with the approval. All methods in these studies were carried out in accordance with relevant guidelines and regulations.

Chapter 2.1.2 Data availability

The data underlying the articles presented in this thesis cannot be shared publicly as the data was retrieved from patient medical records which are protected under the Swedish Health and Medical Services Act and the Secrecy Act in accordance with Swedish legislation.

Chapter 2.1.3 Personal reflections

Upon reflection, these is an issue regarding co-authorship which may pose an ethical dilemma. As primary author, I signed a disclosure taking responsibility for all aspects of the research. The colleagues who designed the algorithm also described it in the methods section of the manuscript. Although I did read through it prior to submission, my knowledge of applied intelligent systems is admittedly limited. It is possible that my colleagues may have mistakenly written something inaccurate which I was unable to detect.

Chapter 2.2 HF diagnostic codes

Diagnostic data used in the articles of this thesis were retrieved from the electronic medical record system VAS which is the current system used in RH, Sweden. The diagnoses are coded based on the tenth revision of the International Classification of Diseases and Related Health Problems (ICD-10). ICD-10 is used throughout Scandinavia and in many countries around the world. Although these diagnostic data have yet to be validated nationally in Sweden, a study from Sahlgrenska University in Gothenburg showed an overall high validity of HF diagnosis for patients admitted 2000-2012 [99]. This, in turn, suggests that the diagnostic validity in the Swedish patient register may also be high. Furthermore, validation studies in other Scandinavian countries show a high specificity and positive predictive value for HF, although the sensitivity was lower when compared to published validation studies [100, 101]. The ICD-10 codes used in the articles of this thesis can be found in the Table I.

Table I: Heart failure codes considered in the study based in ICD-10 coding.

Description	ICD-10 Code
Hypertensive heart disease with heart failure	I110
Dilated cardiomyopathy	I420
Endomyocardial (eosinophilic) disease	I423
Endocardial fibroelastosis	I424
Other restrictive cardiomyopathy	I425
Alcoholic cardiomyopathy	I426
Cardiomyopathy due to drug and external agent	I427
Other cardiomyopathies	I428
Cardiomyopathy, unspecified	I429
Cardiomyopathy in infectious and parasitic diseases classifed elsewhere	I430
Cardiomyopathy in metabolic diseases	I431
Cardiomyopathy in nutritional diseases	I432
Cardiomyopathy in other diseases classified elsewhere	I438
Congestive heart failure	I500
Left ventricular heart failure	I501
Heart failure, unspecified	I509

Chapter 2.3 Summary of study populations, study procedures and statistical analyses applied

Paper I

Study population

The study included all individuals 18 years of age or older, who were clinically assessed and diagnosed with HF (ICD-10 diagnoses: I110, I420, I423, I424, I425, I426, I427, I428, I429, I430, I431, I432, I438, I500, I501, and I509) between 2013-2019. The patients included were residents of RH at the time of diagnosis according to the Swedish National Population Registry. To ensure the HF patient cohort was incidental, a lookback period from 2008-2012 was implemented. The patients were followed until the end of the study period or, in instances of mortality, until the date of death. A total of 8775 patients were included in the study (Figure 3).

Study procedure

The date of HF diagnoses, hereafter referred to as index, as registered for each patient. Age and sex were recorded at index. The lookback period was used to attain information regarding concomitant diseases up until index and the diagnoses, based on ICD-10 classification, are displayed in Table II. Charlson Comorbidity Index (CCI) was evaluated for all patients for with one or more chronic comorbidity [102, 103]. All-cause mortality was observed until one year post-index and the number of days after index were recorded.

The NT-proBNP values registered were those available closest to index and were described as either normal or elevated. A NT-proBNP value <125 ng/l was considered normal [104]. Kidney function was determined based on p-creatinine and eGFR (ml/min/1,73 m^2) values available at index and defined as follows: eGFR $\geq$60 ml/min was considered normal; eGFR 30-59 ml/min was considered lowered; and eGFR <30 ml/min was considered as impaired [105]. The clinical parameters of heart rate, systolic and diastolic blood pressure were also collected at index.

Figure 3: Flow chart describing the exclusion criteria of the cohort and the distribution of HF subgroups.

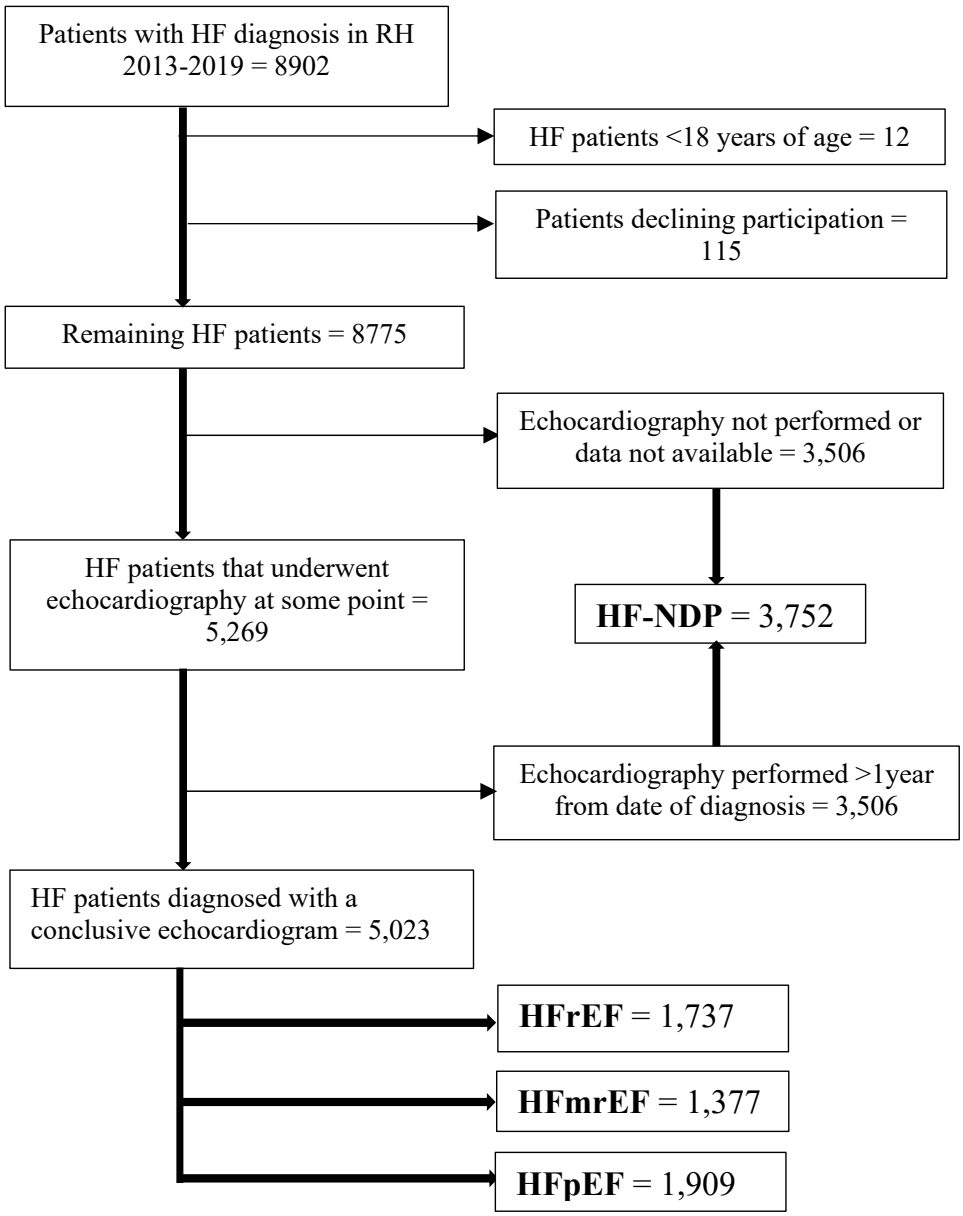


Table II: ICD-10 codes for the comorbidities registered in the studies.

Disease	ICD-10 codes
Heart failure	I110, I420, I423-I432, I438, I500, I501, I509
Hypertension	I10-I15
Ischemic heart disease	I20-I25
Cerebrovascular insult	I60-I69
Atrial fibrillation	I48
Diabetes mellitus	E10-E14
Chronic obstructive pulmonary disease	J44

Medications registered were those recommended by the 2016 ESC guidelines for HF treatment and included BB (C07), RAASI (C09), MRA (C03DA) and loop-diuretics (C03C). The drugs registered in this study are listed in Table III). When treatment data were analysed, ARNI was incorporated into the RAASI treatment group, as the number of patients prescribed an ARNI was relatively small during the study period. As many of the patients were prescribed BB and/or RAASI to lower blood pressure, data regarding HF medications dispensed at the pharmacy were extracted both prior to and after index. Dosage or the amount of drug were not considered. Based on post-index therapeutic strategies, four separate treatment groups were created: Single therapy with either a BB or a RAASI; double therapy with both BB and RAASI, triple therapy with BB, RAASI and MRA; and no therapy, describing those patients who were not prescribed BB or RAASi, or were only prescribed loop-diuretics or MRA.

Table III: Evidence-based pharmacotherapy recommended for treatment of heart failure with reduced left ventricular function according to ESC guidelines current during the study period. Target doses listed as mg/day.

Medication (ATC-code)	Target dose/day
ACE-I (C09)	
Captopril	150 mg
Enalapril	20 mg
Lisinopril	20 mg
Ramipril	10 mg
Trandolapril	4 mg
Beta-blockers (C07)	
Bisoprolol	10 mg
Carvedilol	50 mg
Metoprolol	200 mg
Nebivolol	10 mg
ARB (C09)	
Candesartan	32 mg
Valsartan	320 mg
Losartan	150 mg
MRA (C03DA)	
Eplerenone	50 mg
Spironolactone	50 mg
ARNI (C09DX04)	
Sacubitril/valsartan	194/206 mg

Note: ACEI= Angiotensin-converting enzyme inhibitor; ARB=Angiotensin II receptor blocker; MRA=Mineralocorticoid receptor antagonist; ARNI=Angiotensin receptor neprilysin inhibitor

The methods applied to extract ejection fraction values and subsequent validation testing is described in chapter 1.6.

Statistical analysis

Descriptive statistics were applied for age, sex, concomitant diseases, laboratory parameters and HF treatment. Categorical variables were analysed using Chi-2-Square tests and displayed as frequencies and percentages. Continuous variables were described as means ± standard deviation (SD) or, when applicable, median, and interquartile range (IQR). Comparison of groups was accomplished using Kruskal-Wallis tests. Missing baseline or follow-up covariate values were identified for both continuous and categorical variables and were considered as randomly missing in both groups. The number of missing values noted for both eGFR and NT-proBNP were considered nominal and, as the latter was not used in comparing HF phenotypes, it was determined that imputation was not necessary. Cox regression models were applied to examine all-cause mortality, firstly comparing those with echocardiography and those with no defined phenotype, and second to compare the different HF-phenotypes. The models were adjusted for age, sex, kidney function, NT-proBNP, comorbidities and treatment strategies, with each covariate showing statistical significance in univariable analyses with a p-value of <0.10 and having data available for at least 80% of the patient cohort. A two-sided P-value <0.05 was considered as statistically significant. All analyses were performed with IBM SPSS Statistics 27.0.

Paper II

Study population

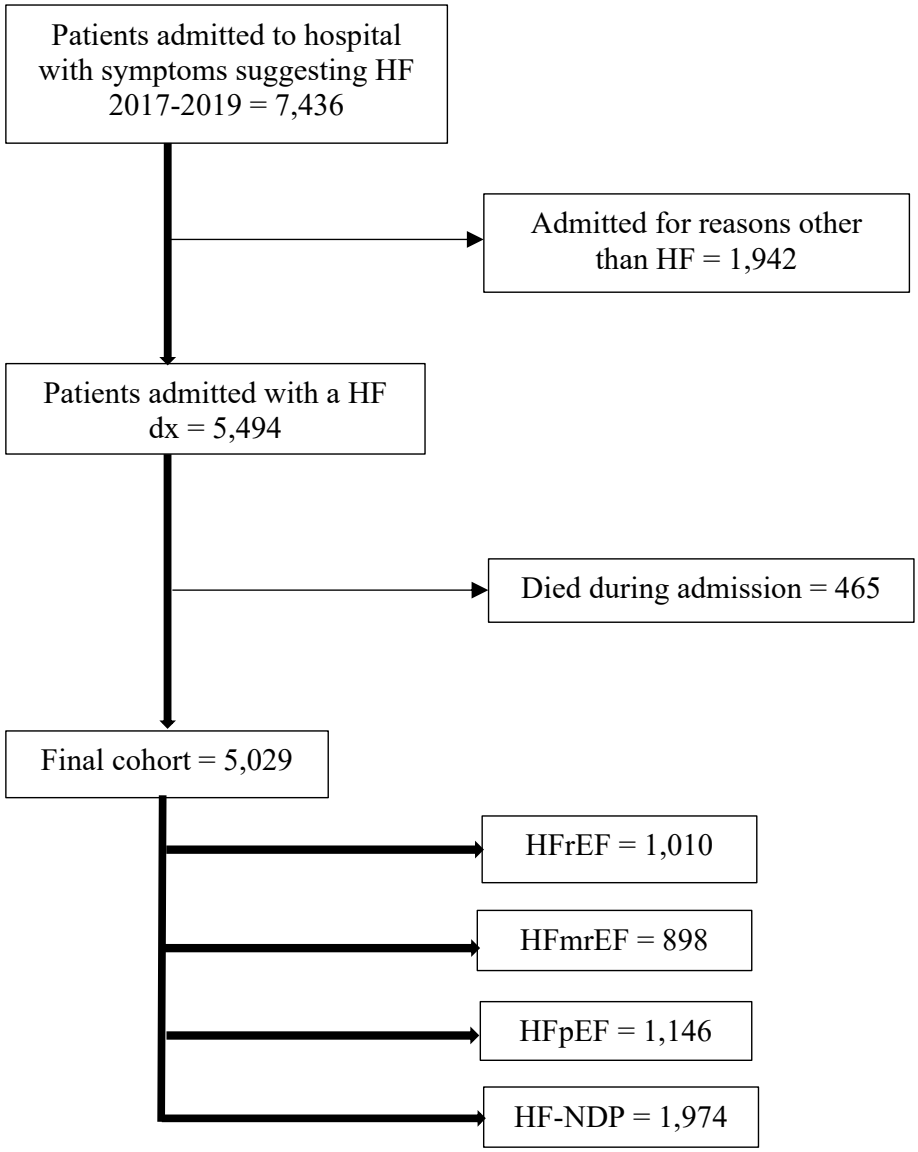
All adult HF patients admitted to hospital in RH from 2017 to 2019 were initially considered for the study (Figure 4). The patients must have received an ICD-10 diagnosis of HF (Table I) at some point during the period between 2013 and 2019. The patients must have been listed as residing in RH according to the Swedish National Population Registry at the time of hospital admission. A total of 7436 patients were hospitalized during the study period, 5494 of which were admitted with a HF diagnosis, suggesting that the reason for admission was most likely due to HF related complications. A total of 465 patients died while in hospital. As the study focused on readmission, these patients were excluded from the final cohort. A patient could only be included once in the study. In instances where patients were admitted to hospital more than once occasion, only the first hospitalization was included. In all, 5029 patients were admitted to hospital due to HF and subsequently discharged.

Study procedure

Data regarding NT-proBNP values were collected from 7 days before index until discharge and the highest values were recorded. The NT-proBNP levels were divided into three groups to determine the likeliness that they were associated with HF based on age with values <300 ng/l considered normal and defined as 'HF unlikely' [59, 104]. Elevated values were evaluated in terms of the patient's age and defined as either 'grey-zone' or 'HF likely' as stated in Figure 1. Available eGFR (ml/min/1.73 m^2) and p-creatinine values were used to assess kidney function [105]. The values recorded were those closest to index. An eGFR ≥60 ml/min was considered as normal kidney function, while a value between 30-59 ml/min was considered as lowered, and <30 ml/min was recorded as impaired kidney function. Heart rates were collected at index and grouped as either ≥70 or <70 beats per minute.

Pharmacotherapeutic data was obtained through the Swedish Prescribed Drugs Register and the pharmacy's dose dispensing unit (Apodos) via RHIP. Treatments registered were those recommended by the 2016 ESC guidelines and included BB (C07), RAASI (ACEI, ARB and ARNI) (C09), MRA (C03DA) and loop-diuretics (C03C). All registered drugs are listed in the Table III. The data recorded was based on medications dispensed at the pharmacy from 120 days prior to index and at the time of readmission. Dosages were not considered.

Figure 4: Flow chart describing the exclusion criteria and distribution of the study cohort.



Statistical analysis

Categorical variables were analysed using Chi-squared tests and summarized as frequencies and percentages. Continuous variables were described as means ± SD or median, where applicable. Comparison of groups was accomplished using Kruskal-Wallis tests. A two-sided P-value <0.05 was considered as statistically significant. Patient age was grouped as either >75 or ≤75 years of age. Length of stay (LoS) was grouped as > 6 or ≤ 5 bed days. There were missing values in the data regarding kidney function. However, as the number was less than 10%, imputation was not performed. Imputation was performed on NT-proBNP data, which showed missing values of 16%, but was not presented in the article as it had no effect on the outcome in the Cox regression model for readmission. A Spearman rank correlation analysis was performed to examine the relationship between NT-proBNP and kidney function based on eGFR levels of >60 ml/min, 30-60 ml/min and <30 ml/min.

To examine the time to readmission within 100 days of discharge, a Cox regression model was applied and adjusted for HF phenotype, age, LoS, heart rate, NT-proBNP level and recommended HF pharmacotherapy. Analysis of pharmacotherapy was based on the presence or absence of recommended therapy with BB and RAASI in combination. All other analyses were performed with IBM SPSS Statistics 27.0.

Paper III

Study population

A retrospective, population-based study examining patients newly diagnosed with HF without the use of diagnostic echocardiography from 2013-2019. Patients included were those age ≥18, residing in RH, in which a first-time HF diagnosis according to ICD-10 (Table I) appeared in the electronic medical records. The patients were followed for one year from the date of diagnosis (Figure 5).

The primary inclusion criterion was a first-time HF diagnosis, known henceforth as index, in which echocardiography was not used to determine the ejection fraction at index. Patients who had undergone echocardiography greater than one year from index were excluded, is the results were considered

clinically irrelevant to the HF diagnosis. The waiting time for echocardiography in RH was 1-3 months during the study period.

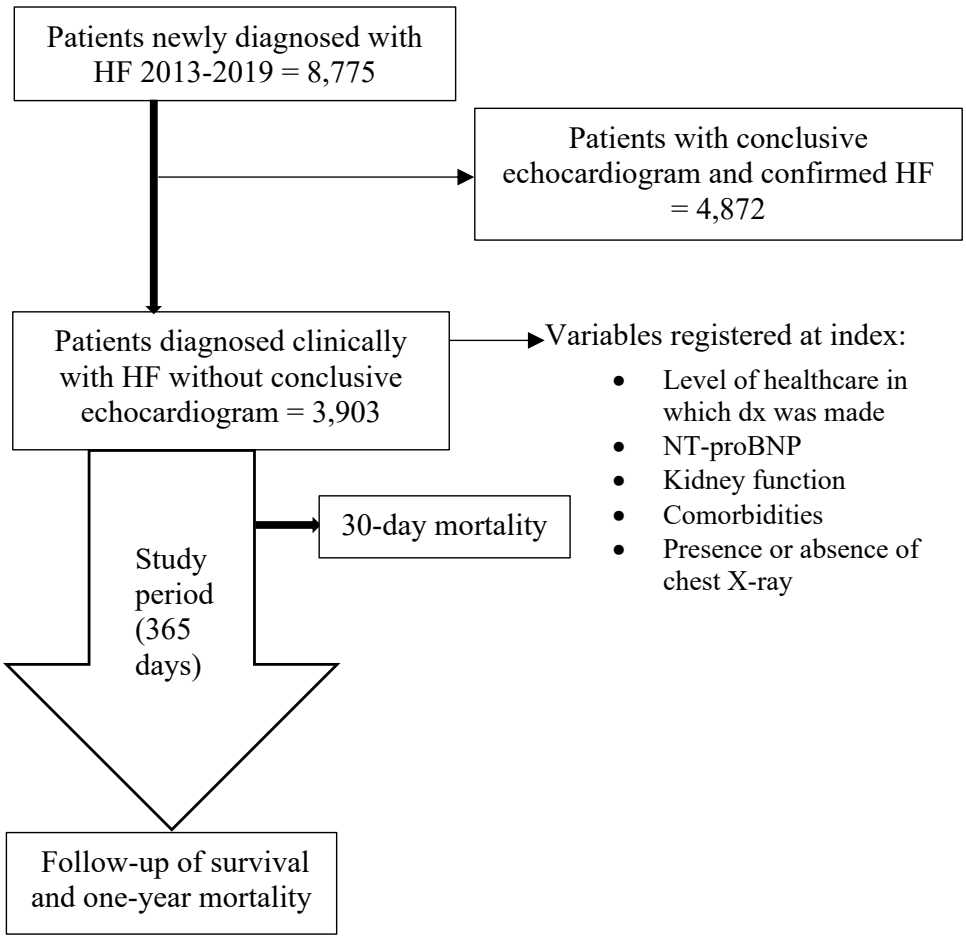
Patients must have received their care in RH. There were 115 patients that met the primary inclusion criterion but had no contact with regional healthcare during the study period. These patients considered to either have received their care outside of RH or were incorrectly diagnosed and were subsequently excluded from the study. A total of 8775 patients were newly diagnosed with HF during the study period, of which 3903 (44%) were diagnosed without the use of echocardiography.

Study procedure

Data regarding age, sex, and comorbidities were recorded at index. according to ICD-10 (Table II). The date of the first HF diagnosis was recorded, as was the level of healthcare in which the diagnosis was made: primary care (PC) or hospital care (HC). HC was presented both as a single entity and further divided into emergency department, hospital inpatient care and hospital outpatient care.

The NT-proBNP levels recorded were those closest to index but not older than three months. They were subsequently divided into three groups to determine the likeliness that they were associated with HF, as outlined in Figure 1 [59, 104]. Patients with values <300 pg/mL are unlikely to have HF, regardless of age, and were defined as 'normal'. An elevated NT-proBNP between 300-450 pg/mL for patients aged <50 years, 300-900 pg/mL for patients aged 50-75 years and 300-1800 for patients >75 years, may be associated with HF and was defined as 'grey-zone'. An NT-proBNP >450 pg/mL for patients <50 years, >900 pg/mL in patients aged 50-75 years and >1800 pg/mL in patients aged >75 years, was considered likely to be associated with heart failure, and defined therefore as 'HF likely'. Available eGFR (ml/min/1.73 m^2) and p-creatinine values were used to assess kidney function [105]. An eGFR $\geq$60 ml/min was considered as normal kidney function, between 30-59 ml/min was considered as lowered, while an eGFR <30 ml/min was defined as impaired. The values recorded were those closest to index.

Figure 5: Flow chart illustrating the study design.



Statistical analysis

The population was analysed using descriptive statistics. Continuous data were compared using Student t-tests, while Chi-2 tests were used for categorical data. When comparing mean values between groups, Kruskal-Wallis tests were applied.

NT-proBNP and kidney function were categorized as stated in the study procedure. NT-pro-BNP values were grouped as either normal or elevated, and kidney function was grouped as either normal, lowered or impaired. As

impaired kidney function can itself result in an elevated NT-proBNP value, a correlation analysis between the two was performed.

The level of healthcare that made the initial HF diagnosis, either PHC or HC, was used to categorize the patients. Those receiving their diagnosis in hospital were further grouped as either ED, hospital inpatient care or hospital outpatient care.

A logistic regression model was applied to determine the prevalence of patients diagnosed in hospital- and primary care. Additional analyses were performed to describe the clinical characteristics of the two groups, PHC versus HC, and were adjusted for age, kidney function, NT-proBNP and presence of certain comorbidities such as IHD, CVD, diabetes and COPD. Adjusted and unadjusted Cox regression models were used to examine survival at 30-, 100-, and 365-days after index. The models were adjusted for age, being diagnosed in PC, eGFR, NT-proBNP, IHD, cerebrovascular stroke, atrial fibrillation, diabetes, and COPD. A Kaplan-Meier curve was used to present one-year all-cause mortality for both PHC and HC. A p-value <0.05 is considered significant. Data was processed using IBM SPSS Statistics 27, Armonk, New York, USA.

Paper IV

Study population

This is a retrospective, population-based study of patients in RH diagnosed with HF and the subsequent primary- and secondary health care costs associated with their care during the two years following diagnosis. All patients residing in RH aged $\geq$18 years, where a HF diagnosis according to ICD-10 (Table I) was documented in the electronic medical record for the first time during the period 2015-2017 were included. Eligibility for the study required patients to have two HF diagnoses, with the second, confirmatory diagnosis occurring no less than 30 days following the initial diagnosis. Only care given within RH was registered. In total, 1769 patients fulfilled the inclusion criteria and were further subdivided based on ejection fraction values as determined by echocardiography (Figure 6).

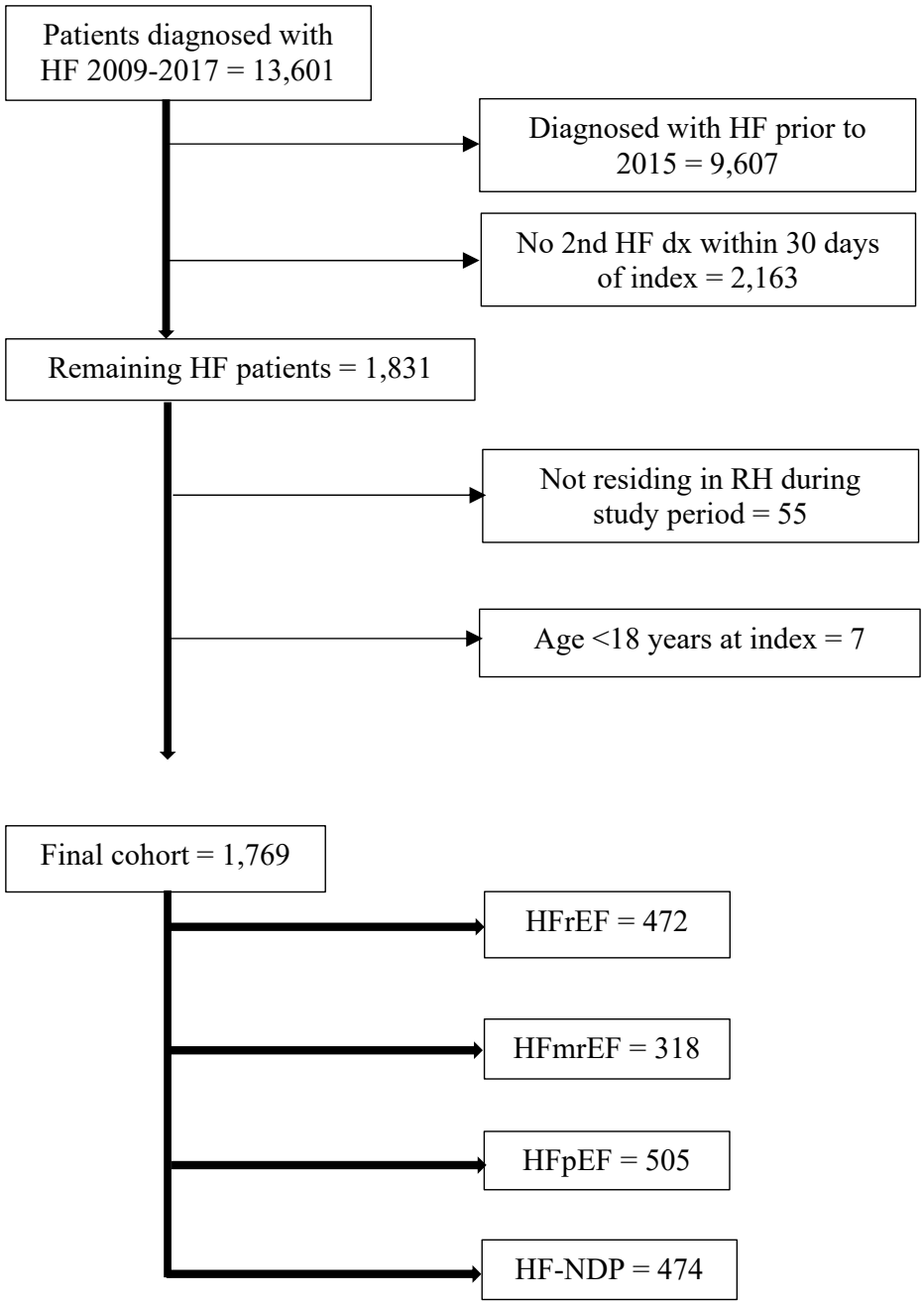
Study procedure

The patients were categorized based on the EF value measured closest to the initial diagnosis, hereafter known as index. Values exceeding one year before or after index were considered to be clinically irrelevant in determining a HF phenotype. As such, these patients were categorized together with those in which no echocardiogram was performed in the HF with no defined phenotype (HF-NDP) subgroup. The remaining three subgroups consisted of the more common HF phenotypes of HFrEF, HFmrEF, and HFpEF. Data regarding age, sex, blood pressure, heart rate, and comorbidities, as classified by ICD-10 (Table II), were collected at index. All healthcare visits in the first and second years after index were recorded. Healthcare visits were categorized as PHC and HC, which encompassed visits to the emergency department, inpatient and outpatient hospital care.

Data were collected regarding kidney function, as determined by the estimated glomerular filtration rate (eGFR), as well as for the cardiac biomarker N-terminal-pro hormone brain natriuretic peptide (NT-proBNP) [59, 104, 105]. The values registered were those closest to but not exceeding three months of index.

Data regarding healthcare costs were retrieved from the RHIP as determined by the patient encounter costing (PEC) model [106, 107]. Using PEC, costs were calculated based on unit costs for resources and quantities used, as well as separately billable procedures and attributable costs, including medications, radiological exams, and laboratory tests. This method has been employed in previous studies to account for costs related to HF and CKD [33, 77]. Costs for services that were not internally priced, such as inpatient ward utilization and physician services, were calculated based on total expenditures for that resource (e.g., an inpatient ward, outpatient clinic, ED or PC facility) divided by the actual production of that ward or clinic. For inpatient care, the unit of analysis was hospital bed days. For outpatient and PC, it was clinic visits. The cost of a particular encounter was calculated as the amount of resource used (e.g., bed days in hospital) multiplied by the unit cost for that resource, plus all separately priced procedures or other attributable costs. The cost of all encounters was added together to obtain the total cost accrued for each patient during the study year.

Figure 6: Flow chart describing the exclusion criteria and distribution of the study cohort.



Statistical analysis

Descriptive statistics were performed to describe the study cohort. Categorical data were analyzed using Chi-2 test, and Student t-tests (Mann–Whitney U-test) were used when comparing continuous data. Kruskal-Wallis tests were applied for comparison of more than two groups.

The study cohort was grouped according to sex and age. Patients were categorized based on age as >75 and ≤75 years. Age and gender were analyzed with Pearson's Chi-2 test. The NT-proBNP values were divided into three groups to determine the likeliness that they were associated with HF. Those with normal NT-proBNP levels were defined as "HF unlikely" while elevated levels were defined based on patient age as either "grey zone" or "HF likely", as illustrated in Figure 1 [59, 104]. Kidney function was considered normal with an eGFR ≥60 ml/min, reduced with eGFR 30-59 ml/min or impaired with eGFR <30 ml/min [105]. NT-proBNP and eGFR were statistically analyzed using Pearson's Chi-2 test. Kruskal-Wallis test was used to analyze the groups for age, eGFR and NT-proBNP, when comparing the HF-phenotypes.

Healthcare encounters were recorded for primary- and secondary care for each HF subgroup based on data available in the RHIP. Differences in mean healthcare utilization between the HF subgroups were analyzed using one-way ANOVA. As the data regarding healthcare costing showed a right-skewed distribution, the data were normalized using logarithmic transformation to enable parametric statistical analysis (Figures 7 and 8). Differences in mean cost values between HF subgroups were analyzed using one-way ANOVA. When the overall analysis of variance showed significance, a post hoc test with Bonferroni correction was applied to determine which of the HF subgroups differed significantly from the others for the healthcare resource in question. As the cost data were normalized using logarithmic transformation, the inverse function antilog was applied to the mean differences to determine the cost difference between HF subgroups in percent. Data concerning costing was available in Swedish kronor. To appeal to a more international readership, the costs were converted to Euros based on the conversion rate for the years in question during the study period.

As hospital admission proved to be the main cost driver in both years, a Poisson regression model was applied to examine the number of days of hospital care and the potential relationship to various factors. The analyses were adjusted for covariates including age, HF-subgroup, comorbidities, kidney function, and the NT-proBNP categorized levels. A p-value <0.05 was considered

significant. Data was analyzed using IBM SPSS Statistics 29, Armonk, New York, USA.

Figure 7: Histograms of total cost for first year after HF diagnosis, before and after logarithmic transformation.

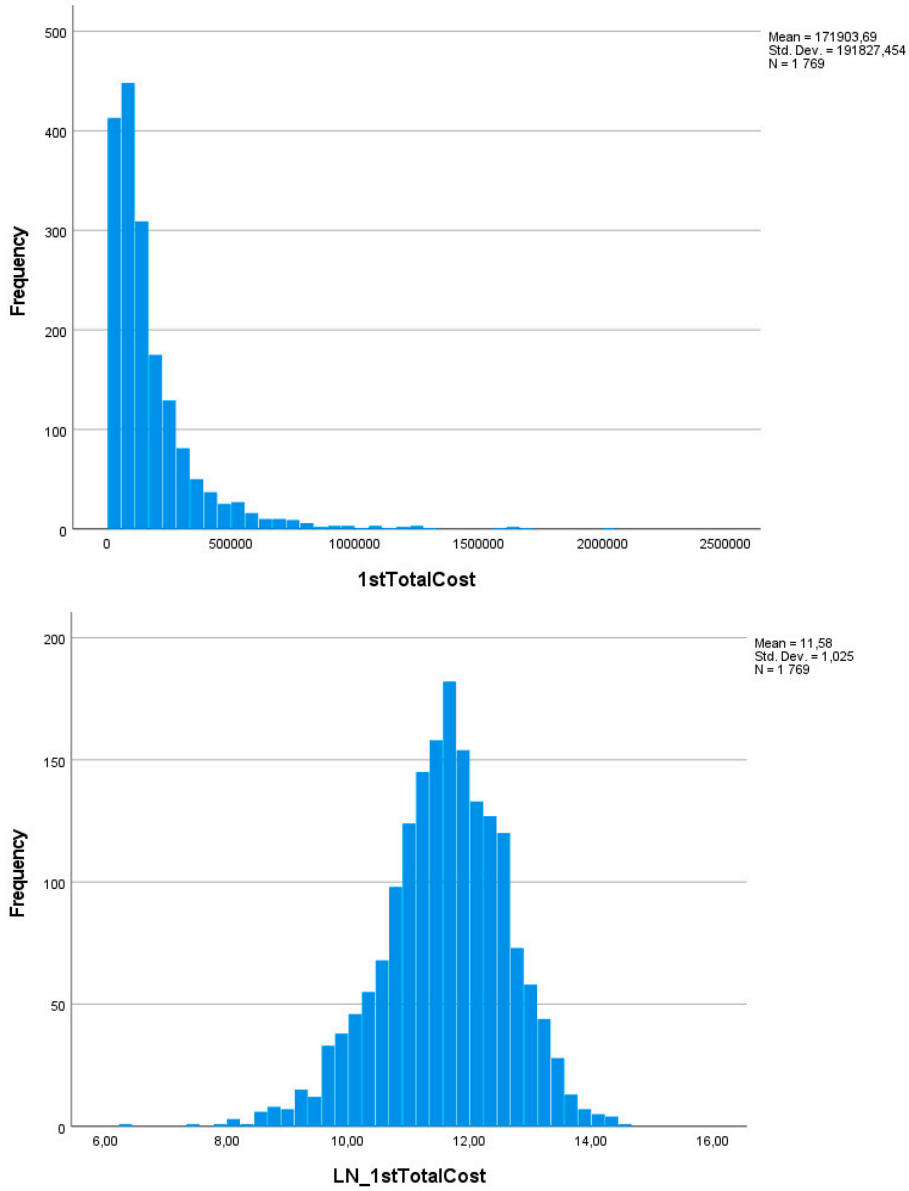
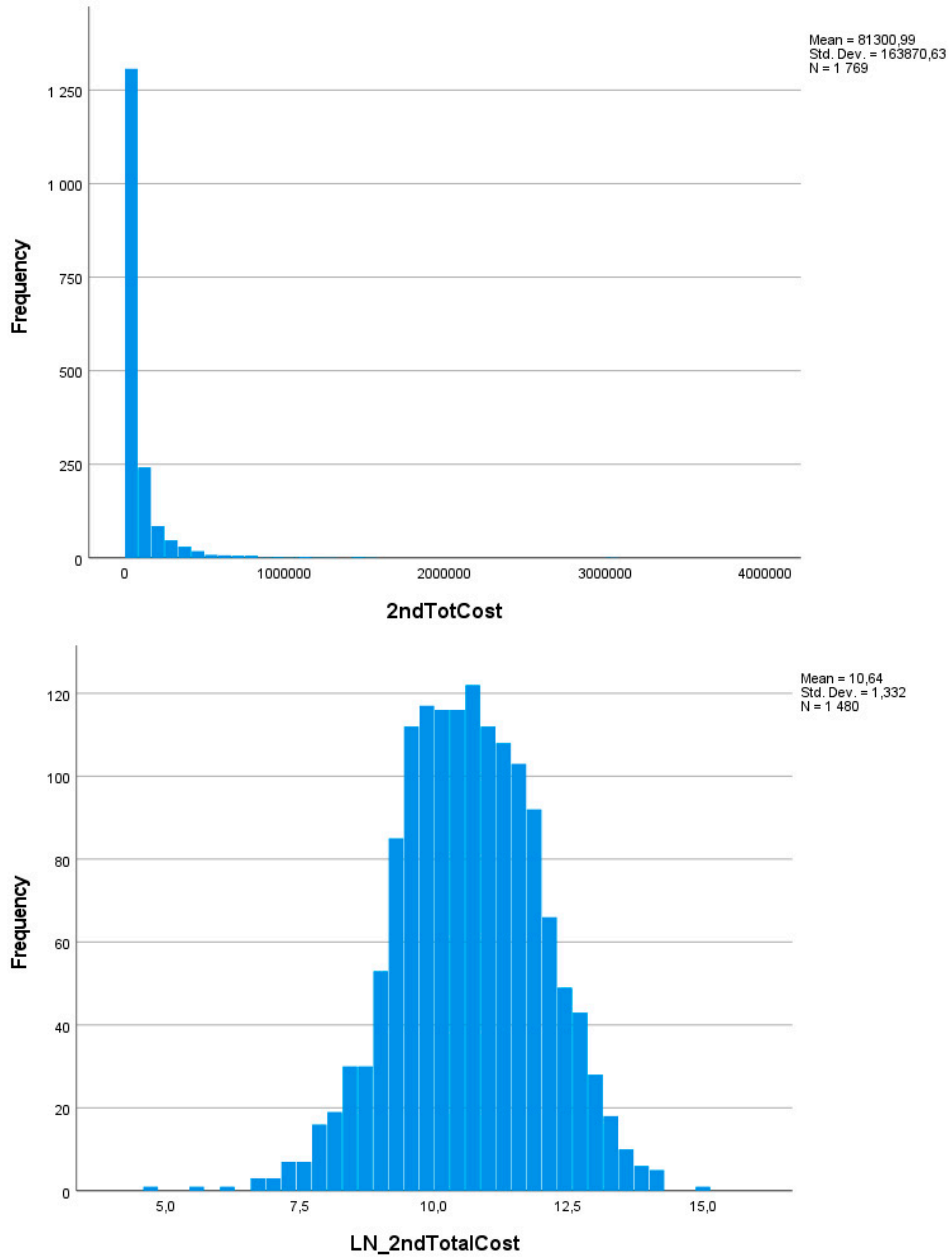


Figure 8: Histograms of total cost for second year after HF diagnosis, before and after logarithmic transformation.



Chapter 3. Results

Paper I

Extraction of EF values for phenotyping

The study revealed a total of 8775 patients with a HF diagnosis during the study period. Of these, 6665 (75%) had undergone an echocardiogram at some point. The algorithm, which was able to extract EF data from 97% of all echocardiograms performed, showed that 57% of these were performed within a year of index and were therefore considered conclusive. Those with dated echocardiograms, or in which no EF data was detected, were categorized in the HF-NDP subgroup. A total of 1695 (19%) patients had performed an echocardiogram greater than one year from index. Of these, 53 patients had an EF <50%. For the 5023 patients that had undergone a conclusive echocardiographic examination, the distribution was as follows: 35% were HFrEF, 27% were HFmrEF and 38% were HFpEF.

Patient characteristics

The distribution of the HF subgroups in relation to age, sex, comorbidities, CCI and treatment at baseline are illustrated below (Table IV).

Of the HF patients included in this study, nearly half belonged to the HF-NDP subgroup, meaning they were either diagnosed without the use of echocardiography, or the echocardiogram was too dated to be clinically significant to the diagnosis. Patients in the HF-NDP subgroup were older, with an average age of 82.8 years, and had the highest one-year all-cause mortality rate of any subgroup. The most common comorbidities were hypertension, IHD, diabetes and COPD. Patients in the HFrEF group were predominantly males of younger age with a more common occurrence of IHD. Older females were more commonly seen in the HFpEF and HF-NDP groups, where the most common comorbidity was hypertension. The CCI was significantly higher in

the HFrEF group (3,5 in average) compared to the HF-NDP-group (3,2 in average) ($p<0.001$).

Table IV: Clinical characteristics including age, sex and comorbidities at index presented both in total and between different HF subgroups. The all-echo group represents all patients that performed an echocardiography for HF diagnosis.

	Total	Performed echocardiography				HF-NDP	p-value
		All echo	HFrEF	HFmrEF	HFpEF		
Total, n (%)	8775 (100)	5023 (57)	1737 (20)	1377 (16)	1909 (22)	3752 (43)	<0.001[1]
Women, n (%)	4113 (47)	1543 (31)	567 (33)	544 40)	976 (51)	2026 (54)	<0.001[1]
Men, n (%)	4662 (53)	2936 (58)	1170 (67)	833 (60)	933 (49)	1726 (46)	<0.001[1]
Age, mean (SD)	78.8 (11.8)	75.9 (11.7)	74.3 (12.2)	75.6 (11.4)	78.4 (10.6)	82.8 (11.4)	<0.001[1]
One-year All-cause mortality	3110 (35)	1531(30)	858 (31)	417 (30)	529 (30)	1579 (42)	<0.001[1]
Concomitant diseases							
Hypertension, n (%)	6234 (71)	3475 (69)	1073 (62)	973 (71)	1429 (75)	2759 (74)	<0.001[1]
IHD, n (%)	3720 (42)	2387 (48)	952 (55)	757 (55)	678 (36)	1333 (36)	<0.001[1]
CVI, n (%)	1417 (16)	709 (14)	227 (13)	200 (14)	282 (17)	708 (18)	<0.001[1]
VHD, n (%)	1357 (15)	932 (19)	308 (18)	255 (19)	369 (19)	425 (11)	<0.001[1]
Atrial fibrillation, n (%)	4108 (47)	2351 (47)	762 (44)	675 (49)	914 (48)	1757 (47)	<0.001[1]
Diabetes mellitus, n (%)	1978 (22)	1192 (24)	445 (26)	318 (23)	429 (22)	768 (21)	0.002[1]
COPD, n (%)	1248 (14)	668 (13)	197 (11)	183 (13)	288 (15)	580 (16)	<0.001[1]
Psychiatric disorder, n (%)	1170 (13)	636 (13)	228 (13)	165(12)	243 (13)	534 (14)	0.14[1]
Dementia, n (%)	1774 (20)	951 (19)	296 (17)	243 (18)	412 (22)	823 (22)	<0.001[1]
Tumour disease, n (%)	607 (7)	313 (6)	107 (6)	66 (5)	140 (7)	294 (8)	<0.001[1]
CCI, mean (SD)	3.3 (1.7)	3.4 (1.7)	3.5 (1.6)	3.4 (1.7)	3.3 (1.8)	3.2 (1.6)	<0.001[1]
Clinical findings							
HR bpm, mean (SD)	82,7 (21.3)	83.7 (23.5)	86.9 (23.6)	81.7 (21.4)	81.6 (20.6)	81.7 (19.5)	<0.001[2]
Syst BP mm Hg, mean (SD)	140.3 (24.1)	141.2 (24.7)	137.7 (23.6)	141.8 (23.7)	143.1 (24.5)	139.0 (23.9)	<0.001[2]
Diast BP mm Hg, mean (SD)	79.9 (14.1)	81,0 (15.0)	82.3 (14.9)	81.0 (14.4)	79.8 (14.1)	78.4 (13.3)	<0.001[2]

Note: n=numbers; SD=standard deviation; Echo= includes HFpEF, HFmrEF and HFpEF; HF-NDP=heart failure with no defined phenotype; IHD=ischemic heart disease; CVI=cerebrovascular insult; VHC=valvular heart disease; COPD=chronic obstructive pulmonary disease; CCI=Charlson Comorbidity Index (age-adjusted); HR=heart rate; bpm=beats per minute; Syst=systolic blood pressure; Diast BP=diastolic blood pressure;[1] Chi-2 test; [2] Kruskal-Wallis test

Kidney function, as defined by mean creatinine and eGFR levels, and NT-proBNP are presented in Table V. The mean eGFR for the total cohort was 53,8 ml/min. Of these, 904 (10%) patients had a value <30 ml/min consistent with impaired renal function. A total of 3751 (43%) had lowered kidney function, while 5024 (57%) had an eGFR $\geq$ 60 ml/min, which was considered as normal. The mean value was lowest in the HF-NDP-group (50.5 ml/min) and highest in the HFrEF-group (56.0 ml/min). Although mean values for kidney function did not differ significantly between the groups, there was a significantly higher number of patients with impaired kidney function in the HF-NDP subgroup, with 13% having an eGFR <30 ml/min. There was no significant difference in the number of patients with impaired kidney function among the three HF subgroups in which echocardiography had been performed. Decreased kidney function, defined as an eGFR <60 ml/min was seen in 59% of the HF-NDP.

NT-proBNP levels were more commonly elevated among patients with a conclusive echocardiogram. Among HFrEF and HFpEF patients, elevated values were seen in 92% and 82% of cases, respectively. In the HF-NDP subgroup, 67% of patients had an elevated NT-proBNP value. In the HFrEF subgroup, 2% of values were considered normal, while 8% of values in the HFpEF subgroup with considered normal. The number of normal values in the HF-NDP subgroup was also 8%, which also showed missing values in 25% of cases, compared to 6% and 10% for the HFrEF and HFpEF subgroups.

The distribution of HF drug treatment for each subgroup prior to and one year after diagnosis is illustrated in Table VI. Treatments recorded were those registered as picked up at the pharmacy. When all patients in the cohort were considered, 27% had been prescribed dual therapy with both BB and RAASI prior to the HF diagnosis.

Table V: Overview of kidney function and NT-proBNP values for the total cohort and by HF subgroup. The all-echo group represents all patients that performed an echocardiography for HF diagnosis.

	Total	Performed echocardiography				HF-NDP	p-value
		All echo	HFrEF	HFmrEF	HFpEF		
Total, n (%)	8775 (100)	5023 (48)	1737 (20)	1377 (16)	1909 (22)	3752 (43)	<0.001[1]
Kidney function							
Creatinine, mean (SD)	104.9 (77.7)	103.5 (79.0)	107.6 (83.4)	102.9 (83.6)	102.7 (72.4)	105.9 (75.7)	0.13[2]
eGFR, mean (SD)	53.8 (17.5)	55.5 (17.2)	56.0 (17.7)	56.1 (17.4)	53.7 (16.8)	51.7 (17.7)	<0.001[1]
eGFR ≥60	4113 (47)	2564 (51)	893 (51)	711 (52)	960 (50)	1549 (41)	<0.001[1]
eGFR 59-30	3751 (43)	2026 (40)	687 (40)	559 (41)	780 (41)	1725 (46)	
eGFR <30	904 (10)	432 (9)	157 (9)	107 (8)	168 (9)	472 (13)	
Missing GFR, n (%)	7 (0.1)	1 (0)	0	0	1 (0.1)	6 (0.2)	
Natriuretic peptide							
NT-proBNP ng/l, mean (SD)	4747 (8341)	4859 (8093)	7187 (10249)	4036 (6912)	3800 (6521)	4301 (8711)	<0.001[2]
Normal[3], n (%)	566 (6)	259 (5)	32 (2)	74(5)	153 (8)	307 (8)	<0.001[1]
Elevated[4], n (%)	6857 (78)	2897 (58)	1603 (92)	1177 (86)	1560 (82)	2517 (67)	
Missing NT-proBNP	1352 (15)	424 (8)	102 (6)	126 (9)	196 (10)	928 (25)	

Note: n=numbers; SD=standard deviation; Echo= includes HFpEF, HFmrEF and HFpEF; HF-NDP=heart failure with no defined phenotype; eGFR=estimated Glomerular filtration rate; NT-proBNP=N-terminal pro b-type natriuretic peptide; [1] Chi-2 test; [2] Kruskal-Wallis test; [3] Normal NT-proBNP= NT-proBNP ≤125 ng/l; [4] Elevated NT-proBNP is a value >125 ng/l.

Table VI: Distribution of recommended pharmacotherapy prior to and one year after HF diagnosis.

	Total	Performed echocardiography				HF-NDP	p-value
Treatment		All echo	HFrEF	HFmrEF	HFpEF		
Prior to HF diagnosis							
BB, n (%)	4016 (46)	2320 (46)	689 (40)	677 (49)	954 (50)	1696 (45)	<0.001
RAASI, n (%)	3500 (40)	2133 (42)	669 (39)	611 (44)	853 (45)	774 (31)	<0.001
MRA, n (%)	581(7)	314 (6)	102 (6)	85 (6)	127 (7)	267 (7)	<0.001
Loop-diuretics, n (%)	2678 (30)	1384 (82)	398 (23)	368 (27)	618 (32)	1294 (34)	<0.001
One year after diagnosis							
BB, n (%)	5683 (65)	3725 (74)	1399 (80)	1069 (78)	1257 (66)	1958 (52)	<0.001
RAASI, n (%)	4936 (56)	3385 (67)	1315 (76)	973 (71)	1315 (58)	1551 (41)	<0.001
MRA, n (%)	2551 (29)	1856 (37)	877 (50)	453 (33)	526 (28)	695 (18)	<0.001
Loop-diuretics, n (%)	5304 (60)	3135 (62)	1145 (66)	803 (58)	1187 (62)	2169 (58)	<0.001

Note: n=numbers; SD=standard deviation; All echo includes all HF patients with a conclusive echocardiogram including HFrEF, HFmrEF and HFpEF; HF-NDP=heart failure with no defined phenotype; BB=beta-blockers; RAASI=renin angiotensin aldosterone system inhibitor; MRA= mineralocorticoid receptor antagonists.

All analyses performed with Chi^2 test.

Baseline characteristics and associations to heart failure phenotypes

Prior to HF diagnosis, dual therapy consisting of both BB and RAASI was more commonly seen in patients in which echocardiography was part of the diagnostic workup. Combination therapy was most common among patients in the HFmrEF (32%) and HFpEF (31%) groups, while HF-NDP patients were more commonly prescribed loop-diuretics such as furosemide. Of the 4936 patients in which a RAASI had been prescribed, 45 patients were administered an ARNI. Patients in the HFrEF subgroup (70%) were more commonly prescribed either double- or triple therapy, which included the addition of an

MRA. The presence of either dual- or triple therapy was seen in 63% of HFmrEF patients, 44% of HFpEF patients and 30% in the HF-NDP subgroup.

The level of healthcare in which the first HF diagnosis was made was also recorded. Patients newly diagnosed with HF in PC were diagnosed clinically in 39% of cases, compared to 20% in which echocardiography was part of the diagnostic workup. Patients with a conclusive echocardiogram more commonly received their first HF diagnosis in HC, while 49% were diagnosed without echocardiography. As for outpatient clinics, 15% of those with a conclusive echocardiogram were newly diagnosed with HF compared to 5 % of those in the HF-NDP subgroup.

Association between conclusive echocardiography and mortality

One-year all-cause mortality was observed among HF patients with and without a conclusive echocardiogram. One-year all-cause mortality for the total patient population was 35%. All-cause mortality within two weeks of index was 7%, increasing to 15% within three months diagnosis. When comparing the two groups, mortality was highest among HF-NDP patients with 9% and 19% deceased within two weeks and three months of index, respectively. For patients in the echocardiography group, the all-cause mortality was 8% and 11% respectively at the same time intervals. Cox regression models analysed hazard ratios (HR) for all-cause mortality between the two groups. When adjusted for age, sex, kidney function, NT-proBNP, concomitant diseases and pharmacotherapeutic strategies, the HR for all-cause mortality when comparing patients with and without echocardiography was 1.26 (95% Confidence Interval [CI] 1.17-1.36) as seen in Table VII. A CCI was determined for all deceased patients. Those in the echocardiography group had a CCI of 4.0 compared to 3.4 for those in which no echocardiography was performed ($p<0.001$).

Table VII: Cox regression model of all-cause mortality comparing HF patients diagnosed with and without the use of echocardiography.

	Hazard ratio	95% CI for HR		P-value
		Lower	Upper	
Echo vs HF-NDP	1.27	1.17	1.37	<0.001
<55 years of age	-	-	-	<0.001
55-64 years of age	2.14	1.3	3.53	0.003
65-74 years of age	2.54	1.6	4.04	<0.001
75-84 years of age	3.84	2.43	6.07	<0.001
85-95 years of age	5.1	3.22	8.07	<0.001
≥95 years of age	5.85	3.6	9.5	<0.001
Man/Women	1	0.93	1.08	0.99
eGFR ≥60 ml/min	-	-	-	<0.001
eGFR 30-59 ml/min	1.02	0.94	1.12	0.64
eGFR <30 ml/min	1.3	1.16	1.46	<0.001
NT-proBNP elevated	1.71	1.4	2.09	<0.001
Hypertension	1.5	1.36	1.65	<0.001
IHD	1.87	1.7	2.06	<0.001
CVI	1.54	1.36	1.76	<0.001
VHD	1.72	1.51	1.95	<0.001
Atrial fibrillation	2.46	2.24	2.7	<0.001
Diabetes mellitus	1.66	1.48	1.86	<0.001
COPD	1.98	1.76	2.22	<0.001
No HF treatment or diuretic only	-	-	-	<0.001
BB or RAASI	0.71	0.65	0.78	<0.001
BB and RAASI	0.53	0.47	0.59	<0.001
BB, RAASI and MRA	0.58	0.51	0.66	<0.001

Note: eGFR= estimated glomerular filtration rate; NT-proBNP=N-terminal pro b-type natriuretic peptide; IHD=ischemic heart disease; CVI=cerebrovascular insult; VHD=valvular heart disease; COPD=chronic obstructive pulmonary disease; BB=Beta-blocker; RAASI=renin-angiotensin-aldosterone system inhibitor; MRA=mineralocorticoid receptor antagonist. Treatments recorded are those picked up from pharmacy within one year of index.

Association between HF phenotype and mortality

Cox regression models adjusted for age, sex, kidney function, NT-proBNP, concomitant diseases and pharmacotherapeutic strategies were applied to examine all-cause mortality amongst patients with conclusive echocardiography (Table VIII). Presence of comorbidities, older age and elevated NT-proBNP levels were associated with an increased mortality risk. The risk decreased significantly when patients were prescribed combination therapy with both BB and RAASI. There was no significant difference in the

hazard ratios for all-cause mortality when comparing phenotypes. With HFpEF patients as the reference, the HR for all-cause mortality among HFrEF patients was 0.98 (95% CI 0.86-1.12), and for HFmrEF patients it was 0.88 (95% CI 0.77-1.01).

Table VIII: Cox regression model of all-cause mortality among HF patients diagnosed with echocardiography.

	Hazard ratio	95% CI for HR		p-value
		Lower	Upper	
HFpEF				0.16
HFmrEF	0.88	0.77	1.01	0.07
HFrEF	0.98	0.86	1.12	0.76
<55 years of age	-	-	-	<0.001
55-64 years of age	1.83	1.02	3.28	0.04
65-74 years of age	2.19	1.27	3.76	0.005
75-84 years of age	3.3	1.93	5.65	<0.001
85-95 years of age	4.08	2.37	7.03	<0.001
≥95 years of age	4.72	2.49	8.93	<0.001
Men/Women	1.01	0.9	1.12	0.93
eGFR ≥60 ml/min	-	-	-	0.008
eGFR 30-59 ml/min	1.06	0.94	1.2	0.33
eGFR <30 ml/min	1.31	1.1	1.56	0.002
NT-proBNP elevated	1.66	1.18	2.32	0.003
Hypertension	1.61	1.41	1.85	<0.001
IHD	2.09	1.82	2.39	<0.001
CVI	1.69	1.4	2.03	<0.001
VHD	1.85	1.59	2.16	<0.001
Atrial fibrillation	2.87	2.52	3.28	<0.001
Diabetes mellitus	1.61	1.38	1.87	<0.001
COPD	1.77	1.5	2.08	<0.001
No HF treatment or diuretic only	-	-	-	<0.001
Beta-blocker or RAASi	0.71	0.62	0.82	<0.001

Note: eGFR=estimated glomerular filtration rate, NT-proBNP= N-terminal pro b-type natriuretic peptide, IHD=ischemic heart disease; CVI=cerebrovascular insult; VHC=valvular heart disease; COPD=chronic obstructive pulmonary disease. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; RAASi=renin angiotensin aldosterone system inhibitor; MRA = mineralocorticoid receptor antagonist; Beta-blockers, RAASi and MRA inhibitor treatment within one year after first diagnosed with HF.

Paper II

Patient characteristics

From 2017-2019, a total of 5029 patients, 2293 (46%) women and 2736 (54%) men, were discharged from hospital in RH with a HF diagnosis based on ICD-10 coding. Of these, 1966 (39%) were newly diagnosed with HF. The average age of the cohort was 80.0 years with 3541 (70%) patients older than 75. Patients in the HF-NDP subgroup were slightly older with a mean age of 83.3 years. Data regarding echocardiography was available in 3034 cases corresponding to 60% of all admitted HF patients. A total of 1644 (33%) had echocardiography performed for the first time during admission. Based on EF values extracted from the echocardiograms, the distribution of HF phenotypes in the cohort was 33% HFrEF, 29% HFmrEF and 38% HFpEF. The clinical characteristics of the HF patient cohort are presented in Table IX.

Kidney function and NT-proBNP values were recorded at the time of discharge (Table IX). NT-proBNP was highest in the HFrEF group with a median value of 3804 ng/l ($p < 0.001$), while the median value of for the entire cohort was 2704 ng/l. Kidney function, measured as mean eGFR (ml/min), was significantly different among the subgroups ($p < 0.001$). The mean value for the entire cohort was 51.4 ml/min. A Spearman rank correlation, applied to compare NT-proBNP and kidney function, revealed a correlation of 37%. Addition comparisons were made based on categories of eGFR values which showed correlations of 18% for those with normal kidney function, 15% for those with lowered-, and 30% for those with impaired kidney function. The presence of concomitant disease prior to hospital admission was evaluated both for the entire cohort, as well as for the various HF subgroups and is summarized in Table IX.

Table IX: Clinical characteristics of the total heart failure cohort and by subgroup. Presence of concomitant disease was recorded upon admission, while NT-proBNP and eGFR values were those registered at discharge from hospital.

Variable	Total	HFrEF	HFmrEF	HFpEF	p- value[a]	HF-NDP	p- value[b]
Total cohort	5029 (100)	1010(20)	898 (18)	1147 (23)		1974 (39)	
Women	2279 (45)	298 (30)	334 (37)	594 (52)	<0.001[1]	1053 (53)	<0.001[1]
Age, mean (SD)	79.6 (11.5)	79.1 (10.3)	77.0 (11.3)	76.0 (12.7)	<0.001[3]	82.9 (10.7)	<0.001[3]
Age ≥ 75 years	3653 (73)	609 (60)	575 (64)	840 (73)	<0.001[1]	1629 (82)	<0.001[1]
NT-proBNP, median (IQR)							
NT-proBNP, median (IQR)	2704 (1148-5946)	3804 (1443-9635)	2640 (1113-5543)	2391 (1100-4739)	<0.001[2]	2550 (1051-5407)	<0.001[2]
HF not likely, n (%)	273 (6)	30 (3)	59 (6)	82 (8)	<0.001[1]	102 (7)	<0.001[1]
Grey zone, n (%)	1055 (25)	174 (19)	173 (23)	283 (27)		429 (22)	
HF likely, n (%)	2899 (69)	714 (78)	514 (69)	690 (65)		981 (65)	
Missing, n (%)	805 (16)	92 (9)	152 (15)	91 (8)		466 (23)	
Kidney function							
eGFR, mean (SD)	51.4 (19.7)	52.4 (20.1)	53.3 (19.98)	52.4 (20.0)	0.322	50.4 (19.4)	<0.001[3]
≥60, n (%)	1826 (36)	372 (36)	371 (37)	435 (41)	<0.001[1]	648 (32)	<0.001[1]
30-59, n (%)	2437 (49)	490 (49)	408 (46)	533 (46)		1006 (51)	
<30, n (%)	753 (15)	148 (15)	115 (13)	176 (15)		314 (16)	
Missing, n (%)	11 (0)	0 (0)	4 (0)	2 (0)		5 (0)	
Concomitant diseases							
Hypertension	3760 (75)	662 (66)	637 (71)	928 (81)	<0.001[1]	1553 (78)	<0.001[1]
IHD	2306 (46)	581 (58)	528 (59)	475 (41)	<0.001[1]	722 (37)	<0.001[1]
Previous AMI	963 (19)	273 (27)	289 (33)	200 (17)	<0.001[1]	201 (10)	<0.001[1]
PAD	248 (5)	58 (6)	45 (5)	56 (5)	0.641	89 (4)	0.461
CVI	800 (16)	132 (13)	140 (16)	165 (14)	<0.001[1]	363 (18)	0.0011
VHD	1045 (21)	217 (22)	193 (22)	369 (32)	<0.001[1]	266 (14)	<0.001[1]
CKD	1166 (23)	239 (24)	205 (23)	290 (26)	0.411	432 (22)	<0.001[1]
Atrial fibrillation	2899 (58)	542 (54)	487 (54)	705 (62)	<0.001[1]	1165 (59)	<0.001[1]
Diabetes mellitus	1330 (26)	292 (29)	243 (27)	304 (26)	0.441	491 (25)	0.121
COPD	908 (18)	133 (13)	142 (16)	238 (21)	<0.001[1]	395 (20)	<0.001[1]

Note: HF=Heart failure, HFrEF=heart failure with reduced ejection fraction, HFmrEF= heart failure with mildly reduced ejection fraction, HFpEF= heart failure with preserved ejection fraction, HF-NDP= heart failure with no defined phenotype, NT-proBNP=natriuretic terminal pro brain natriuretic peptide, eGFR=estimated glomerular filtration rate (ml/min), IHD= Ischemic heart disease, AMI=acute myocardial infarction, PAD= Peripheral artery disease, CVI=cerebrovascular insult, VHD=valvular heart disease, CKD=chronic renal disease, COPD= chronic obstructive pulmonary disease.

[1] Chi-2 test; [2] Kruskal-Wallis test; [3] One-way ANOVA; [a] p-value for HF patients with conclusive echocardiogram; [b] p-value for all HF patients including the HF-NDP subgroup

Recommended HF treatment and healthcare utilization

The HF medications registered were those recommended by the 2016 ESC guidelines that had been prescribed up to and including the date of discharge from hospital (Table X). Dual therapy was most commonly seen in the HFrEF subgroup with 78% of patients having both a BB and RAASI ($p < 0.001$). Triple therapy, which included the addition of an MRA, was also highest in the HFrEF subgroup. The percentage of patients with dual- and triple therapy at the time of discharge did not differ significantly among the subgroups.

Table XI shows healthcare utilization, measured as length of stay (LoS) upon first admission, for HF patients with a conclusive echocardiogram as well as for the entire cohort. The median value was highest in the HFrEF group at 6 days (IQR 3-10). Patients <75 years of age spent more time in hospital with an average LoS of 7.9 (SD 8.9) days compared to older patients who were admitted an average of 7.0 (SD 7.1) days ($p<0.001$). LoS was further divided into groups of >6 and $\leq$ 6 days, but there was no significant difference between age the groups ($p=0.21$).

As shown in Table XI, a total of 1638 (33%) patients were readmitted at some point during the 100 days after discharge from the initial hospital admission. Cardiovascular related readmissions were seen in 1267 (35%) patients aged $\geq$ 75 years compared to 371 (27%) for those < 75 years of age. During the follow-up period, 614 (12%) patients died, and these deaths were considered as all-cause mortality. A total of 614 (12%) patients died in the 100 days after discharge, interpreted as all-cause mortality. The mortality rate higher among older patients at 545 (15%) compared to 58 (4%) for those <75 years of age. All-cause mortality was highest in the HF-NDP subgroup at 16% compared to 8% in the HFmrEF subgroup and 10% in both the HFrEF and HFpEF subgroups ($p<0.001$).

Table X: Distribution of recommended HF medications at discharge

	Total	HFrEF	HFmrEF	HFpEF	P-value	HF-NDP	P-value
Total cohort	5029 (100)	1010 (20)	898 (18)	1147 (23)		1974 (39)	
Medication							
BB, n (%)	4037 (80)	915 (91)	767 (85)	902 (79)	<0.001	1453 (74)	<0.001[1]
RAASI, n (%)	3539 (70)	869 (86)	698 (78)	774 (68)	<0.001	1198 (39)	<0.001[1]
ACEI, n (%)	2269 (45)	581 (58)	460 (51)	471 (41)	<0.001	757 (38)	<0.001[1]
ARB, n (%)	1395 (28)	304 (30)	274 (30)	344 (30)	<0.001	473 (24)	<0.001[1]
ARNI, n (%)	183 (4)	129 (13)	20 (2)	4 (0)	0.97	30 (2)	<0.001[1]
MRA, n (%)	2349 (47)	681 (67)	409 (46)	567 (49)	<0.001	692 (35)	<0.001[1]
SGLT-2-antagonist, n (%)	109 (2)	26 (3)	23 (3)	27 (2)	0.93	33 (2)	<0.001[1]
Diuretics, n (%)	3965 (79)	835 (83)	615 (68)	919 (80)	<0.001	1596 (81)	<0.001[1]
BB and RAASI, n (%)	3028 (60)	802 (79)	627 (70)	640 (56)	<0.001	58959 (49)	<0.001[1]
BB-RAASI-MRA, n (%)	1558 (31)	575 (57)	298 (33)	314 (27)	<0.001	371 (19)	<0.001[1]

Note: HF=Heart failure, HFrEF=heart failure with reduced ejection fraction, HFmrEF= heart failure with mildly reduced ejection fraction, HFpEF= heart failure with preserved ejection fraction, HF-NDP= heart failure with no defined phenotype, BB=Beta-blocker, RAASI=renin-angiotensin-aldosterone system inhibitor, ACEI=angiotensin-converting enzyme inhibitor, ARB=angiotensin II receptor blocker, ARNI=angiotensin receptor neprilysin inhibitor, MRA=mineralocorticoid receptor, SGLT-2 antagonist= sodium-glucose cotransporter-2 inhibitor, n=number; [1] Chi-2 test; [a] p-value for HF patients with conclusive echocardiogram; [b] p-value for all HF patients including the HF-NDP subgroup

Table XI: Healthcare utilization measured as length of stay in days from first admission

	Total	HFrEF	HFmrEF	HFpEF	P-value[a]	HF-NDP	P-value[b]
Total cohort	5029 (100)	1010 (20)	898 (18)	1147 (23)		1974 (39)	
LoS at index, median (IQR)	5 (3-9)	6 (3-10)	5 (3-9)	5 (3-9)	0.005[2]	5 (2-8)	<0.001[2]
LoS >6 days, n (%)	1950 (39)	454 (45)	322(36)	488 (42)	<0.001[1]	686 (35)	<0.001[1]
Readmission, n (%)	1638 (33)	349 (35)	255 (28)	411 (36)	<0.001[1]	623 (32)	<0.001[1]
Deceased, n (%)	603 (12)	101 (10)	71 (8)	116 (10)	0.18[1]	315 (16)	<0.001[1]

Note: HF=Heart failure; HFrEF=heart failure with reduced ejection fraction; HFmrEF= heart failure with mildly reduced ejection fraction; HFpEF= heart failure with preserved ejection fraction; HF-NDP= heart failure with no defined phenotype; LoS=length of stay in bed days; n=number; IQR=interquartile range; [1] Chi-2 test; [2] Kruskal-Wallis test; [a] p-value for HF patients with conclusive echocardiogram; [b] p-value for all HF patients including the HF-NDP subgroup.

A Cox regression model adjusted for HF subgroups, age, sex, LoS, concomitant diseases, clinical findings, kidney function, NT-proBNP and

recommended HF treatment was applied to determine the risk of readmission after hospital discharge. The model and results are presented in Table XII.

Table XII: Cox regression model to assess risk factors associated with readmission within 100 days of discharge

	HR	95.0% CI for HR		p-value
		Lower	Upper	
HF subgroup				
HFpEF				0.06
HFmrEF	0.86	0.72	1.03	
HFrEF	0.99	0.84	1.16	
HF-NDP	0.82	0.7	0.97	
Clinical characteristics				
Age	1.01	1.01	1.02	<0.001
Women	0.86	0.76	0.97	0.03
Hospital LoS	1.01	1.01	1.02	<0.001
Echo at admission	0.9	0.78	1.03	0.13
Concomitant diseases				
Diabetes	1.1	0.97	1.25	0.14
COPD	1.17	1.01	1.34	0.03
Clinical findings				
Pulse >70 bpm	1.17	1.02	1.33	0.02
Systolic BP	0.997	0.997	0.999	0.03
Kidney function				
Normal				0.005
Lowered	1.12	0.97	1.29	
Impaired	1.35	1.13	1.62	
NT-proBNP levels				
HF unlikely (18)				<0.001
HF Grey zone	1.29	0.94	1.77	
HF Likely	1.69	1.25	2.28	
HF treatment				
BB and RAASI	0.92	0.82	1.04	0.19

Note: HR=Hazard ratio, CI=confidence interval, HF=heart failure, HFrEF=heart failure with reduced ejection fraction, HFmrEF= heart failure with mildly reduced ejection fraction, HFpEF= heart failure with preserved ejection fraction, HF-NDP= heart failure with no defined phenotype, LoS=length of stay in bed days, COPD= chronic obstructive pulmonary disease, BP=blood pressure, Normal=eGFR=estimated glomerular filtration rate (ml/min) <60, lowered=eGFR 30-59, Impaired=eGFR <30, NT-proBNP (ng/L) levels for acute or new-onset HF based on age: (< 50 years) <300 = HF unlikely, > 450 = HF likely, 300-450 = grey-zone; (50-75 years) >900 = HF likely, 300-900 = grey-zone; (>75 years) >1800 = HF likely, 300-1800 =grey-zone, BB=beta-blockers, RAASI= renin-angiotensin-aldosterone-system inhibition (includes ACEI, ARNI and ARB).

Paper III

Patient characteristics

During the study period, 3903 patients were diagnosed with HF without a conclusive echocardiography. Of these, 1631 (42%) patients were diagnosed in PC, while 2272 (58%) received their HF diagnosis in HC. Hospital diagnoses were most common during inpatient care (82%), with the others being diagnosed in the emergency department (10%) and in hospital outpatient care (8%). A total of 373 patients had previously undergone echocardiography greater than one year from the date of diagnosis and of these 202 (54%) were diagnosed in PC compared to 171 (46%) in HC. The clinical characteristics of the patient cohort are summarized in Table XIII.

The cohort consisted of 1800 (46%) men and 2103 (54%) women with an average age of 84.2 years. The mean eGFR for the total cohort was 51.6 ml/min while the mean NT-proBNP was 4269 ng/L. A Spearman correlation analysis comparing the two laboratory parameters showed a correlation of 36% ($p<0.001$).

Clinical characteristics were further analysed by means of a logistic regression model, with those diagnosed in PC as the reference. The model revealed that patients who were diagnosed with HF without a conclusive echocardiography in PC were often older, had less commonly occurring kidney dysfunction, lower NT-proBNP levels, and fewer comorbidities compared to those diagnosed in hospital.

Mortality

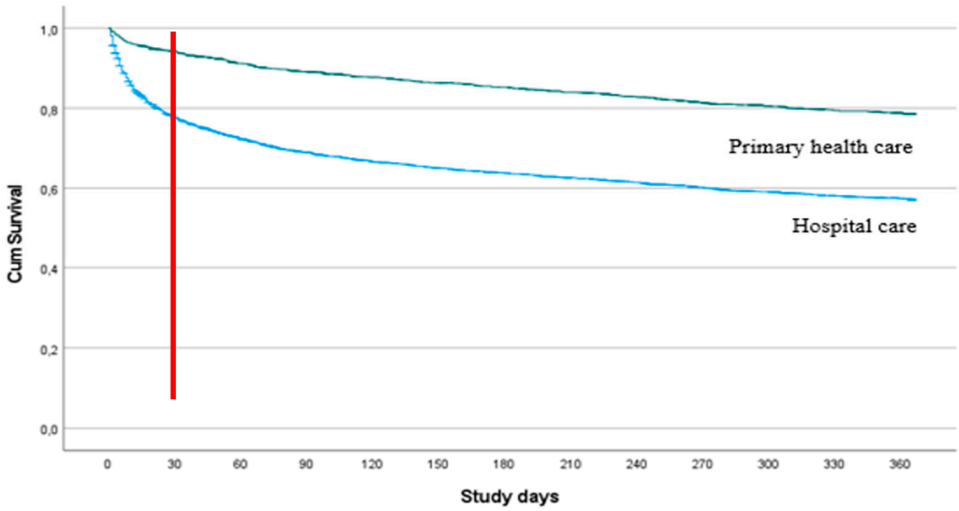
All-cause mortality was assessed at intervals of 30 days and one year after diagnosis. Of the 598 (15%) patients that died within 30 days of diagnosis, 534 (22%) patients had been diagnosed in HC compared to 112 (6%) patients diagnosed in PC ($p<0.001$). All-cause mortality one year after diagnosis was seen in 1273 (33%) patients, 42% of whom had been diagnosed in HC compared to 20% in PC. Mortality from index to one-year post-index is represented as a Kaplan-Meier curve (Figure 9).

Table XIII: Clinical characteristics of HF patients diagnosed without conclusive echocardiography both in primary and secondary care.

	Total cohort	Primary care	Secondary care	p-value
Total	3903 (100)	1631 (42)	2272 (58)	
Women, n (%)[1]	2103 (54)	864 (53)	1239 (54)	0.34[1]
Age, mean (SD)[2]	82,4 (10,9)	82,5 (10,2)	82,3 (11,3)	0.51[2]
Age groups				
< 75 years, n (%)	727 (19)	285 (18)	442 (20)	<0.001[1]
≥75 years, n (%)	3176 (81)	1346 (82)	1830 (80)	
Kidney function				
eGFR ml/min, mean (SD)	51,6 (17,4)	52,9 (15,3)	50,6 (18,7)	<0.001[2]
Normal, n (%)	1631 (42)	709 (44)	922 (41)	<0.001[1]
Lowered, n (%)	1782 (46)	785 (48)	997 (44)	
Impaired, n (%)	484 (12)	135 (8)	349 (15)	
Missing values	6 (0)	2 (0)	4 (0)	
NT-proBNP levels				
NT-proBNP ng/l, mean (SD)	4269 (8452)	2625 (5457)	5482 (9938)	<0.001[2]
HF unlikely, n (%)	464 (12)	269 (16)	195 (9)	<0.001[1]
Grey zone, n (%)	1034 (26)	510 (31)	524 (23)	
HF likely, n (%)	1472 (38)	482 (30)	990 (44)	
Missing, n (%)	933 (24)	370 (23)	563 (25)	
Comorbidities				
Hypertension, n (%)	2880 (74)	1187 (73)	1693 (74)	0.22[1]
IHD, n (%)	1391 (36)	551 (31)	880 (39)	<0.001[1]
CVI, n (%)	728 (19)	270 (17)	458 (20)	0.0041
Atrial fibrillation, n (%)	1830 (47)	708 (43)	1122 (49)	<0.001[1]
Diabetes, n (%)	826 (21)	289 (18)	537 (24)	<0.001[1]
COPD, n (%)	601 (15)	204 (12)	397 (18)	<0.001[1]
Treatment				
BB, n (%)	2056 (53)	881 (54)	1175 (52)	0.16[1]
RAASI, n (%)	1641 (42)	792 (49)	849 (37)	<0.001[1]
MRA, n (%)	724 (18)	268 (16)	456 (20)	0.004[1]
Loop-diuretics, n (%)	2258 (58)	990 (61)	1268 (56)	0.002[1]
Digoxin, n (%)	329 (8)	126 (8)	203 (9)	0.18[1]

Note: n=number; SD=standard deviation; eGFR=estimated glomerular filtration rate; normal=eGFR >60 ml/min; lowered=eGFR 30-60 ml/min; impaired=eGFR <30 ml/min; NT-proBNP=n-terminal pro b-type natriuretic peptide; IHD=ischemic heart disease; CVI=cerebrovascular disease; COPD=chronic obstructive pulmonary disease; BB=beta-blocker; RAASI=renin-angiotensin-aldosterone system inhibitor; MRA=mineralocorticoid receptor antagonist. [1]Chi-2 test; [2]Kruskal-Wallis test.

Figure 9: Kaplan-Meier curve showing mortality from diagnosis until one-year post-index for patients diagnosed in primary care and in hospital. The red line indicates the 30-day mark.



A logistic regression model adjusted for age, level of healthcare in which the diagnosis was made, kidney function, NT-proBNP and concomitant diseases was applied to analyse all-cause mortality at 30 days and one year after index. The results are shown in Table XIV. Age > 75 years, impaired kidney function, elevated NT-proBNP levels and certain comorbidities including CVI and COPD were associated with higher risk of mortality at both 30- and 365-day intervals.

Table XIV: Logistic regression model comparing risk factors associated with all-cause mortality at 30- and 365 days after diagnosis.

	30 days				365 days			
		95.0% CI for HR				95.0% CI for HR		
	HR	Lower	Upper	p-value	HR	Lower	Upper	p-value
≥ 75 years	1.92	1.32	2.78	0.001	2.06	1.62	2.62	<0.001
Level of care for diagnosis								
Secondary care	-	-	-		-	-	-	
Primary care	0.21	0.15	0.3	<0.001	0.43	0.36	0.51	<0.001
Kidney function (eGFR)								
Normal	-	-	-		-	-	-	
Lowered	0.93	0.71	1.22	0.59	0.99	0.84	1.18	0.95
Imparied	2.31	1.72	3.11	<0.001	1.95	1.6	2.39	<0.001
NT-proBNP levels								
HF unlikely	-	-	-		-	-	-	
Grey-zone	1.17	0.73	1.87	0.51	1.33	0.98	1.81	0.07
HF likely	1.9	1.21	2.97	<0.001	2.58	1.92	3.45	<0.001
Concomitant diseases								
IHD	0.92	0.73	1.15	0.46	0.89	0.77	1.04	0.14
CVI	1.36	1.06	1.76	0.02	1.22	1.02	1.45	0.03
AF	0.69	0.55	0.86	0.001	0.69	0.59	0.8	<0.001
Diabetes	1.22	0.95	1.56	0.12	0.99	0.84	1.18	0.94
COPD	1.49	1.15	1.94	0.003	1.3	1.09	1.55	0.004

Note: Note: HR=Hazard ratio; eGFR=estimated glomerular filtration rate; normal=eGFR >60 ml/min; lowered=eGFR 30-60 ml/min; impaired=eGFR <30 ml/min; NT-proBNP=n-terminal pro b-type natriuretic peptide; IHD=ischemic heart disease; CVI=cerebrovascular disease; AF=atrial fibrillation; COPD=chronic obstructive pulmonary disease.

Paper IV

Patient characteristics

A total of 1769 patients were included in the study, 987 (56%) men and 782 (44%) women. The distribution of subgroups was 472 (27%) HFrEF, 318 (18%) HFmrEF, 505 (28%) HFpEF, and 474 (27%) HF-NDP. Patients in the HFrEF and HFmrEF subgroups were more commonly men (67% and 63%, respectively), and had a higher prevalence of arteriosclerotic cardiovascular disease (ASCVD). Patients in the HFpEF subgroup were more commonly women with a higher occurrence of hypertension, atrial fibrillation, and COPD were. Clinical characteristics of the patient cohort are summarized in Table

XV. Mortality during the two-year follow-up period was observed among 475 (27%) patients, 282 (16%) of whom died in the first year after diagnosis.

Healthcare utilization and associated costs

Healthcare encounters per patient during the first and second year after diagnosis are summarized in Table XVI for the total cohort and for each HF-subgroup and the associated costs are illustrated in Table XVII. The main cost driver for all subgroups was hospitalization/inpatient care, accounting for 68% of the total cost of patient care in the first year alone. HFrEF patients were the costliest subgroup in the first year with a mean total cost per patient of €18682. In the second year, it was the HFpEF subgroup with a mean total cost per patient of €9289. Healthcare costs per patient were lower for all subgroups in the second year after HF diagnosis. This was most notable among HFrEF patients in which the average annual cost per patient reduced by €11599 from the first year (Figure 10).

Table XV. Distribution and clinical characteristics of the study population at diagnosis in total and by HF-subgroups.

	Total	HF confirmed by echocardiography			No echo	
		HFrEF	HFmrEF	HFpEF	HF-NDP	p-value
Total, n (%)	1769 (100)	472 (27)	318 (18)	505 (28)	474 (27)	<0.001[1]
Women, n (%)	782 (44)	158 (33)	118 (37)	245 (49)	261 (55)	<0.001[1]
Men, n (%)	987 (56)	314 (67)	200 (63)	260 (51)	213 (45)	
Age, mean (SD)	78.4(11.5)	73.4(11.8)	75.6 (10.6)	79.4 (10.1)	84.1 (10.2)	<0.001[1]
Age ≥ 75 years (%)	1204 (68)	239 (51)	180 (57)	373 (74)	412 (87)	<0.001[1]
Comorbidities						
Hypertension, n (%)	1214 (69)	258 (55)	210 (66)	400 (79)	346 (73)	<0.001[1]
ASCVD, n (%)	858 (49)	252 (53)	177 (56)	224 (44)	205 (43)	<0.001[1]
Atrial fibrillation, n (%)	889 (50)	184 (39)	157 (49)	303 (60)	245 (52)	<0.001[1]
Diabetes mellitus, n (%)	396 (22)	108 (23)	72 (23)	123 (24)	93 (20)	0.35[1]
COPD, n (%)	261 (15)	54 (11)	42 (13)	88 (17)	77 (16)	0.03[1]
Kidney function						
eGFR, mean (SD)	55.5 (18.2)	59.2 (19.2)	56.8 (18.8)	54.4 (17.3)	52.1 (17.1)	<0.001[2]
eGFR ≥60 ml/min, n (%)	778 (44)	250 (53)	158 (50)	205 (41)	165 (35)	<0.001[1]
eGFR 59-30 ml/min, n (%)	829 (47)	182 (39)	126 (40)	257 (51)	264 (56)	
eGFR <30 ml/min, n (%)	151 (9)	38 (8)	30 (10)	43 (9)	40 (9)	
Natriuretic peptide						
NT-proBNP ng/l, mean (SD)	7426 (11283)	10669 (14563)	6974 (1097)	5719 (7512)	5877 (9974)	<0.001[2]
HF Unlikely[3], n (%)	9 (0.01)	0 (0)	1 (0)	0 (0)	8 (0.02)	<0.001[1]
"Grey Zone"[4], n (%)	833 (47)	236 (50)	163 (51)	211 (42)	223 (47)	
HF Likely[5], n (%)	927 (52)	236 (50)	154 (48)	294 (58)	243 (51)	

Note: Note: n=numbers; SD=standard deviation; HFrEF=Heart failure (HF) with reduced ejection fraction (EF); HFmrEF=HF with mildly reduced EF; HFpEF=HF with preserved EF; HF-NDP=heart failure with no defined phenotype; ASCVD=atherosclerotic cardiovascular diseases including ischemic heart disease, peripheral artery disease, myocardial infarction and stroke; COPD=chronic obstructive pulmonary disease; eGFR=estimated Glomerular filtration rate; NT-proBNP=N-terminal pro b-type natriuretic peptide. [1] Chi-[2] test; [2] Kruskal-Wallis test; [3] HF Unlikely = NT-proBNP <300 pg/mL for all ages; [4] "Grey Zone" = NT-proBNP 300-450 pg/mL age <50; 300-900 pg/mL age 50-75; 300-1800 pg/mL age >75; [5] HF Likely= >450 pg/mL age<50; >900pg/mL age 50-75; >1800 pg/mL age >75

Table XVI: Distribution of per patient healthcare utilization within the first two years after HF diagnosis based on subgroup.

	All Patients	**HFrEF**	**HFmrEF**	**HFpEF**	**HF-NDP**	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	**p-value**
Healthcare utilization						
1st year (n=1769)						
Inpatient care						
LoS	14.5 (7.3)	16.7 (8.0)	15.1 (7.2)	15.7 (7.1)	10.7 (6.3)	<0.001
Admissions	2.0 (1.8)	2.1 (1.6)	2.1 (2.0)	2.2 (2.0)	1.7 (1.6)	<0.001
Hospital OPC						
ED visits	2.2 (2.3)	2.2 (2.1)	2.3 (2.9)	2.4 (2.4)	1.9 (1.9)	0.002
OPC visits	9.3 (14.8)	13.8 (14.3)	11.2 (16.6)	9.0 (13.1)	4.0 (13.9)	<0.001
Primary health care						
PC visits	20.2 (14.8)	19.1 (17.6)	20.1 (16.2)	23.4 (17.5)	18.0 (17.6)	<0.001
2nd year (n=1487)						
Inpatient care						
LoS	5.0 (6.3)	3.8 (5.4)	5.0 (7.1)	6.5 (6.5)	4.2 (6.0)	0.001
Admissions	0.8 (1.4)	0.7 (1.3)	0.7 (1.4)	1.0 (1.6)	0.7 (1.3)	<0.001
Hospital OPC						
ED visits	0.9 (1.7)	0.8 (1.7)	0.9 (1.6)	1.2 (1.9)	0.9 (1.5)	0.003
OPC visits	5.4 (13.9)	7.2 (15.5)	5.1 (11.5)	6.0 (14.9)	3.3 (12.4)	<0.001
Primary care						
PC visits	14.0 (16.8)	13.7 (16.6)	13.0 (14.5)	16.7 (18.3)	12.3 (16.4)	<0.001

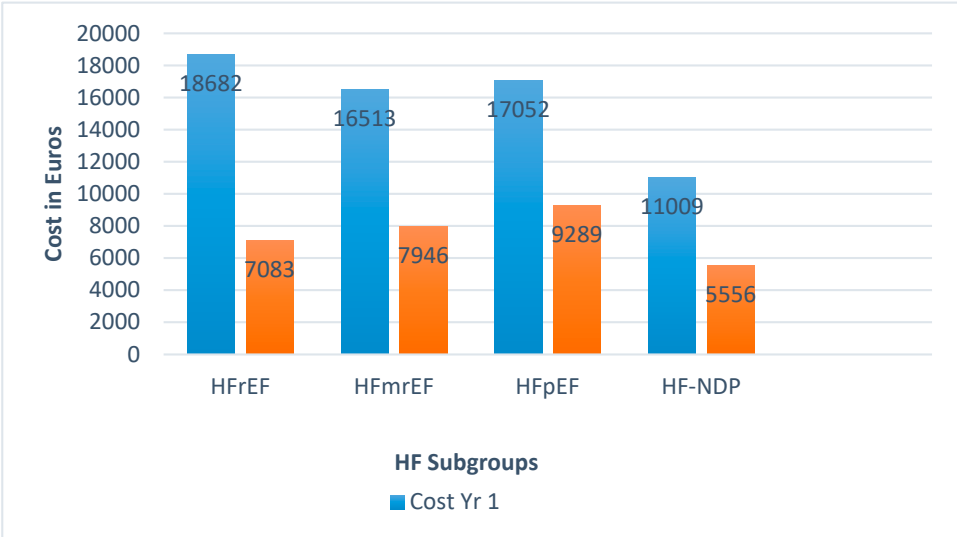
Note: n=number; HF=Heart failure; HFrEF=HF with reduced ejection fraction (EF); HFmrEF=HF with mildly reduced EF; HFpEF=HE with preserved EF; HF-NDP=HF with no defined phenotype; LoS=Length of stay; OPC=Outpatient care; ED=Emergency department; PC=Primary care facilities.

Table XVII: Distribution of per patient healthcare costs within the first two years after HF diagnosis based on subgroup.

	All Patients Mean (SD)	**HFrEF** Mean (SD)	**HFmrEF** Mean (SD)	**HFpEF** Mean (SD)	**HF-NDP** Mean (SD)	**p-value**
Healthcare costs						
1st year (n=1769)						
Inpatient care						
LoS	11465	14102	11231	12523	7868	<0.001
Hospital OPC						
ED visits	823	807	888	943	669	0.04
OPC visits	1984	2545	2517	1941	1112	<0.001
Primary care						
PC visits	1035	1054	1002	1105	965	0.01
Medications	1382	1262	1837	1533	1037	<0.001
Costs for first year	**15771**	**18682**	**16513**	**17052**	**11009**	<0.001
2nd year (n=1487)						
Inpatient care						
LoS	4216	3610	4569	5397	3322	0.15
Hospital OPC						
ED visits	374	307	404	478	312	0.29
OPC visits	1569	1835	1367	2069	907	0
Primary care						
PC visits	529	576	493	554	480	0.63
Medications	1183	1149	1552	1304	1354	<0.001
Costs for second year	**7459**	**7083**	**7946**	**9289**	**5556**	<0.001

Note: n=number; HF=Heart failure; HFrEF=HF with reduced ejection fraction (EF); HFmrEF=HF with mildly reduced EF; HFpEF=HE with preserved EF; HF-NDP=HF with no defined phenotype; LoS=Length of stay; OPC=Outpatient care; ED=Emergency department; PC=Primary care facilities.

Figure 10: Displays the costs for each HF-subgroup representing the first and second year after a heart failure diagnosis.



Note: HF= Heart failure; HFrEF=HF with reduced ejection fraction (EF); HFmrEF=HF with mildly reduced EF; HFpEF=HF with preserved EF; HF-NDP=heart failure with no defined phenotype; Cost Yr 1=costs for the first year; Cost Yr 2=costs for the second year.

A Poisson distribution was applied to identify factors increasing the probability of longer hospital stays (Table XVIII). In the first year, longer hospital stays were associated with ASCVD, COPD, diabetes, higher NT-proBNP levels, and impaired kidney function with an eGFR <30 ml/min, among patients in the HFrEF subgroup. In the second year, patients in the HFpEF subgroup had the highest incidence rate ratio of 1.81 (CI: 1.70-1.94). The presence of ASCVD, COPD, and higher NT-proBNP levels were also associated to extended hospital stays in the second year.

Table XIII: Poisson regression analysis showing factors associated with longer hospital stays in the first and second year after HF diagnosis.

	First year				Second year			
	IRR	**95% Wald CI**		**p-value**	**IRR**	**95% Wald CI**		**p-value**
		Lower	**Upper**			**Lower**	**Upper**	
Age	1.00	1.00	1.00	0.57	1.00	1.00	1.00	0.00
Sex								
Female	1				1			
Male	0.86	0.84	0.89	<0.001	1.03	0.98	1.09	0.20
HF Subgroup				<0.001				<0.001
HFrEF	1.00				1.00			
HFmrEF	0.89	0.88	0.93		1.16	1.01	1.26	<0.001
HFpEF	0.98	0.94	1.01	0.20	1.81	1.70	1.94	0.00
HF-NDP	0.75	0.72	0.79	<0.001	1.13	1.04	1.22	0.00
Comorbidities								
ASCVD	1.34	1.30	1.38	0.001	1.22	1.16	1.28	<0.001
COPD	1.34	1.30	1.39	0.001	1.31	1.23	1.39	0.00
DM	1.14	1.10	1.12	<0.001	1.35	1.28	1.43	0.00
AF	0.98	0.95	1.01	0.10	1.01	0.96	1.06	0.71
eGFR								
≥60 ml/min	1				1			
30-59 ml/min	0.91	0.88	0.94	<0.001	0.91	0.86	0.96	<0.001
<30 ml/min	1.33	1.27	1.39	0.00	0.92	0.85	0.99	0.23
NT-proBNP								
HF Unlikely[1]	1				1			
Grey Zone[2]	1.43	1.29	1.58	<0.001	1.62	1.38	1.90	<0.001
HF Likely[3]	2.28	2.07	2.51	0.00	1.90	1.63	2.22	<0.001

Chapter 4. Discussion

Chapter 4.1 Summary of main findings

Paper I

This study benefits from the application of a novel algorithm to extract EF values for all HF patients in RH, Sweden, during the study period. The algorithm was able to extract EF data from 97% of echocardiograms performed with an accuracy of 99% upon validation. It was determined that 57% of patients had undergone a conclusive echocardiogram, defined as an echocardiographic examination performed less than one year from the date of HF diagnosis. This relatively large, unselected patient cohort provides new insights pertaining to the clinical characteristics of HF patients in the community. Furthermore, the population-based approach offers a distribution of HF phenotypes that varies from those seen in registry-based studies, with HFrEF patients and more HFpEF patients. It was determined that the remaining 43% of patients, in which echocardiography was not performed or data related to a conclusive echocardiogram was not available, were diagnosed clinically. This patient group was deemed to be clinically relevant to the study and a fourth subgroup was created to represent those HF patients with no defined phenotype, HF-NDP. This subgroup had a significantly higher one-year all-cause mortality compared to patients with a conclusive echocardiogram, which underlines the importance of echocardiography as part of the diagnostic workup for HF.

Echocardiography is a fundamental tool for diagnosing HF by retrieving EF values which determine HF phenotypes and therapeutic strategies. As EF is a dynamic measurement, changing over time in response to treatment and remodeling of the heart musculature, it is clinically optimal to perform echocardiography in conjunction with a diagnosis of HF. EF values from echocardiograms performed more than a year from the date of diagnosis are considered clinically irrelevant for the determination of HF phenotypes. A total of 57% of patients in the present study had a conclusive echocardiogram.

Previous studies in Sweden showed that 30% and 36.6% of HF patients underwent echocardiography as part of the diagnostic workup allowing for the determination of HF phenotypes [108, 109]. Although wait times and availability of echocardiography vary regionally, which may in part explain the variation in percentages, it remains clear that a large proportion of the HF patient community is diagnosed clinically, carrying with it the risk of incorrect diagnosis and inappropriate pharmacotherapy.

Previous registry-based studies have shown a distribution of HF phenotypes ranging from 48-53% HFrEF, 17-21% HFmrEF, and 18-26% HFpEF [110, 111]. Patients in heart failure registries are often enrolled while admitted to hospital, increasing the chances that echocardiography be part of the diagnostic workup [110]. HFrEF patients, often younger men, are represented in higher numbers than HFpEF patients, which are more commonly women [19, 112-114]. Compared to studies based of HF registries, the phenotypes in the present study were more evenly distributed as HFrEF 35%, HFmrEF 27% and HFpEF 38%. This is likely due to the fact the patient cohort was fully unselected.

In the present study, the most commonly occurring comorbidities observed prior to a diagnosis of HF were hypertension and IHD, followed by diabetes and atrial fibrillation. These findings are consistent with results published in previous studies [108-112].

In the HFrEF subgroup, treatment with BB and RAASI was seen in 27% of patients, and 44% had triple therapy with the addition of MRA, for a total of 71% of patients treated with the combination of BB and RAASI. By comparison, 30% of the HFpEF subgroup were prescribed BB and RAASI in combination and 14% had triple therapy with the addition of MRA. This discrepancy may in part be explained by the fact that MRA were not recommended for the HFpEF subgroup according the 2016 ESC therapy guidelines [1]. A Cox regression analysis of all-cause mortality showed that patients with dual therapy consisting of both BB and RAASI had a HR of 0.53 (95% CI 0.47-0.59), implying a significantly lower risk compared to monotherapy, independent of HF phenotype. Triple therapy, with the addition of MRA, did not significantly impact the risk for all-cause mortality compared to treatment with BB and RAASI alone (HR, 0.55 [95% CI 0.47-0.65]). This is likely the result of treatment guidelines current during the study period, which only recommended MRA in cases of more advanced HF [1].

HF is a life-threatening syndrome with poor prognosis. Previous studies estimate the 30-day survival rate to be 92%, while the 5-year survival rate is only 50% [17, 94, 110]. In the present study, one-year all-cause mortality was 35 %

for the total cohort, which is consistent with findings from a previous Swedish HF registry study [115]. One-year all-cause mortality in the present study was highest among patients in the HF-NDP subgroup at 42%. One possible explanation is that these patients were diagnosed in a late phase of life. Patients in the present study that had a conclusive echocardiography, however, showed one-year mortality rates consistent with previous findings: 31% for HFrEF, 30% for HFmrEF, and 30% for HFpEF [73, 109, 115]. A review of the ESC long-term registry showed one-year mortality rates of 8.8% for HFrEF, 7.6% for HFmrEF and 6.3% for HFpEF, notably lower compared to results from the present study [16]. This discrepancy is likely explained by the patient data involved with the present study being based on an unselected population compared to a relatively selected cohort from the HF registry.

Paper II

In the present study, patients admitted to hospital for HF and subsequently discharged were followed for 100 days to determine potential risk factors associated with readmission due to a cardiovascular event. Of the 5029 patients involved in the study, 1586 (33%) were readmitted with a CVD diagnosis within 100 days of discharge. The variables determined to be associated with an increased risk of readmission were older age, elevated NT-proBNP levels, lowered- or impaired kidney function, elevated and longer stays in hospital during the initial admission. Patients who had undergone echocardiography during the initial hospital admission and those with combination therapy with both BB and RAASI were associated with a lower risk of readmission. Echocardiographic data from the period of hospital admission was available in 3034 cases corresponding to 60% of the study population. In 1644 (33%) cases, no previous echocardiography had been performed. All-cause mortality in the 100-day follow-up period was 12%.

One-third of the patients in the current study were readmitted to hospital with a cardiovascular diagnosis within 100 days of discharge. A previous study in Sweden showed similar results with 36.6% of HF patients readmitted during a three-month period post-discharge [116], while a further study, following patients for a year after discharge, showed a readmission rate of 46% [117]. Of the 603 patients that died during the follow-up period, 315 were part of the HF-NDP subgroup in which no echocardiography was performed. The mortality rate was highest in this subgroup at 16%, followed by HFpEF and HFrEF at 10%, and lowest among HFmrEF patients at 8%.

A 2019 study determined that nearly 80% of newly diagnosed HF patients received their diagnosis while in hospital and that echocardiography was associated with a decreased risk of cardiovascular readmission [14]. The same study revealed, however, that only 36% of the patient population had undergone echocardiography during hospital admission. In the present study, which only considered patients who had received a HF diagnosis at discharge, 60% underwent echocardiography while admitted to hospital. This discrepancy is to be expected considering the nature of the study populations. The present study showed that 39% of patients were newly diagnosed with HF during admission, yet first-time echocardiographic data were only available in 33% of the cases. Patients admitted to hospital for HF present either as new onset or due to a worsening of symptoms from a pre-existing condition. In either case, an updated echocardiogram should be performed to determine the current EF and course of pharmacotherapeutic action. While serial echocardiography does not appear to offer additional information to the clinician, a new echocardiographic examination should be considered upon deterioration of the patient's clinical status [19].

An appropriate treatment plan at discharge is paramount to reducing the risk of CV readmission for HF patients. In the present study, patients with a high burden of comorbidity were already associated with an increased risk of readmission even prior to discharge. The same was true for those admitted to hospital longer than 6 days. Additional factors associated with an increased risk of readmission were elevated NT-proBNP levels and kidney dysfunction. Consistent with findings from similar studies, data regarding NT-proBNP levels during admission were available in 84% of cases [109, 117]. As this is a relatively uncomplicated laboratory test with important ramifications in terms of HF patient risk stratification, one should expect data to be available for an even larger percentage of the patient population. In the total cohort, 58 % of patients had elevated NT-proBNP levels considered likely to be associated with HF [100]. When considering only patients in the HFrEF subgroup, that number increased to 71%. There is a physiological connection between NT-proBNP and kidney function, namely that the biomarker is excreted by the kidneys through glomerular filtration [118]. As the eGFR decreases, as seen in lowered- and impaired kidney function, NT-proBNP cannot be properly excreted, which may result in higher levels in the blood. As such, a Spearman rank correlation analysis was applied to compare the two parameters. It revealed a correlation of 35%, becoming more robust as kidney function declined. As a result, the association between elevated NT-proBNP levels and readmission was strongest among patients with normal kidney function.

As the field of medicine continues to evolve, so too do the treatment guidelines and recommendations of various diseases and illnesses. Regarding HF, recommended pharmacotherapy for patients with reduced- and mildly reduced EF consisted of BB, RAASI, MRA, ARNI and SGLT-2 inhibitors according to guidelines current at the time of publication [19]. However, guidelines current during the study period were those from the 2016 edition which did not list SGLT-2 inhibitors as recommended pharmacotherapy, and it is therefore understood that patients in the cohort in which SGLT-2 inhibitors had been prescribed received them most likely as treatment for diabetes rather than HF [1]. These guidelines recommend the use of both BB and RAASI for all HF patients with reduced EF. In the present study, 80% of patients were prescribed a BB and 70% were prescribed a RAASI at the time of discharge. Although one could expect the entirety of these subgroups to have been prescribed these recommended treatments, the findings are in accordance with another Swedish study from 2021 that showed treatment with BB and RAASI to be 88% and 76%, respectively [116]. Combination therapy with both BB and RAASI was observed in 60% of cases at discharge, 78 % in the HFrEF subgroup, and was associated with a decreased risk cardiovascular readmission. Triple therapy, which included the addition of a MRA, was seen in 1558 cases corresponding to 31% of the total cohort and was again most common among HFrEF patients. A previous study concluded that 30% of the HF cohort had been prescribed a MRA at discharge but did not present the data in terms of combination therapy [116]. When considering the hemodynamic properties of the heart, one would expect patients with reduced ejection fraction to receive the greatest benefit from this treatment, however other HF patients may also benefit even if the effects are not fully known.

Paper III

This retrospective, observational study examined patients in RH diagnosed with heart failure without the use of echocardiography. Over half of the 3903 patients included in the study were diagnosed at the secondary care level (58%) with the bulk of these receiving their diagnoses as inpatients. The remaining 1631 (42%) patients were diagnosed at the PC level. One-year all-cause mortality was highest amongst those diagnosed in hospital (42%) compared to 20% for those diagnosed in PC. Patients diagnosed at the secondary care level had a significantly higher 30-day mortality rate of 22%, however mortality rates in both groups stabilized after the first month post-index. A logistic

regression analysis showed that patients receiving their diagnosis at the primary care level were more often older (≥ 75 years) while those diagnosed in hospital more commonly had elevated NT-proBNP levels and a heavier burden of comorbidity including the prevalence of ischemic- and cardiovascular diseases, diabetes and chronic obstructive pulmonary disease.

A previous HF study in Sweden showed the rates of patients diagnosed without echocardiography to be between 26-30 % [109]. The 43% of patients diagnosed without echocardiography in the current study may reflect the comprehensiveness of the patient population. The same Swedish study, based on the Swedish Heart Failure Registry, showed that patients who received their HF diagnosis at the primary care level were older, had a decreased prevalence of concomitant diseases and were more often treated according to therapeutic guidelines relative to those diagnosed in HC. An additional registry-based study from 2010 showed similar results in terms of age and comorbidities apart from hypertension, which was more common amongst HF patients diagnosed in PC [82]. Findings in the present study were in accordance with these previous studies, with a lower prevalence IHD, cardiovascular disease, diabetes and COPD compared to patients diagnosed in hospital.

There was a notable difference in 30-day all-cause mortality amongst patients diagnosed at the secondary- (22%) and primary care levels (6%). Lower all-cause mortality was also observed in previous studies among patients diagnosed in PC relative to those diagnosed in hospital [78, 82]. A plausible explanation for this phenomenon is the heavier burden of comorbidity observed among patients diagnosed in hospital, suggesting an increased severity of illness. Although patient frailty was not explored in the present study, one could postulate that patients in a fragile state with more advanced HF need not be ladened with additional examinations such as echocardiography, which may influence the clinician's decision to abstain. The present study went on to show, however, that mortality rates began to stabilize and were effectively the same in both study groups beyond the 30-day mark, making it harder to explain why echocardiography would not be included in the diagnostic work-up. Particularly, since all patients with a life-expectancy beyond a month stand to benefit from appropriate pharmacotherapy and the correct treatment strategy is based on HF phenotype as determined by echocardiography.

In a previous, registry-based study in Sweden, patients that were diagnosed at the primary care level were shown to have a higher prevalence of concomitant diseases relative to those diagnosed in hospital [7]. However, in the present study, patients diagnosed in PC had relatively fewer comorbidities. An

important distinction is that the registry-based study focused on HFpEF patients while this study included HF patients who were diagnosed clinically in which the phenotype is unknown, which ultimately would provide more variation in the patient cohort.

As access to echocardiography is greater at the secondary care level relative to PC, one may suspect that more patients be diagnosed clinically at the primary care level. However, the majority of patients diagnosed without echocardiography in the present study received their HF diagnosis in hospital. In addition, patients who have been diagnosed clinically with HF at the secondary care level and subsequently referred to a primary care physician, have often been prescribed one or more medications which may alter the original EF value, thus limiting the relevancy of echocardiography once the patient status has stabilized.

Paper IV

This retrospective, observational study examined healthcare utilization and associated costs in the first two years following a HF diagnosis. Costs for all HF subgroups were highest in the first year and decreased by varying degrees in the second year. This was particularly evident for patients in the HFrEF subgroup which had the highest total cost in the first year and the greatest decrease in cost by the second year. The result was expected since HFrEF patients also had the longest length of stay (LoS), measured as days in hospital, in the first year (16.7) and the shortest by the second year (3.8), with hospitalization being the main cost driver for all subgroups in both years. The costliest subgroup in the second year was HFpEF, which, consequently, also had the longest LoS of any subgroup in year two. Factors associated with increased number of hospital days included elevated NT-proBNP, impaired kidney function and comorbidities such as ASCVD, COPD and diabetes mellitus.

During the first year following HF diagnosis, healthcare consumption was substantial, particularly in terms of inpatient hospital care. The average LoS per patient for the total cohort was 14.5 days, decreasing to 5.0 days by the second year. The initial demand for hospital care is obvious in the near-term following a HF diagnosis, and previous studies have also illustrated an increased risk of readmission following discharge from HF-related hospitalizations [112, 119, 120]. Previous studies involving robust HF patient cohorts

showed an average of 6.6 hospital days per patient per year [77, 90, 112]. In terms of outpatient care, patients with HF made an average of 20.2 visits to PC in the first year, which decreased to 14.0 visits in the second year. During the first year, patients with HFrEF predominantly visited outpatient clinics at the hospital, while patients with HFpEF more commonly visited primary care clinics.

The total cost of HF patient care amounted to €15771 per patient in the first year after diagnosis, decreasing significantly to €7459 in the second year. Inpatient care emerged as the main cost driver, which was also noted in similar studies [77, 90, 93, 98, 112, 93, 121]. One study reported annual costs per patient as €9790, notably lower than the average yearly healthcare costs found in this study [77]. A study in Sweden highlighted particularly high healthcare utilization and costs associated with HF, especially in the initial year post-diagnosis [93]. These costs were predominantly driven by frequent hospitalizations, with total secondary care expenses reaching €12890 per patient in the first year. As costs in the present study were based on both secondary- and primary care utilization, it is not surprising that the total cost be higher.

Given that inpatient care is the primary cost driver and hospitalization is most critical in the first year, it's understandable that costs peak during this period, especially for patients with HFrEF. A prior study highlighted significant resource utilization among HFpEF patients, largely driven by hospitalizations [118]. Specifically, HF-related admissions accounted for 50% and cardiovascular-related admissions for 32% of total resource utilization. Moreover, findings indicated that 60% of HFpEF patients were hospitalized at least once during the follow-up period. These hospitalizations, particularly those related to heart failure, constitute a substantial amount of the overall healthcare burden for HFpEF patients in Sweden. In the present study, significant costs were also accrued by HFpEF patients throughout the study period, with HFpEF patients representing the costliest subgroup in the second year after diagnosis. Patients with HFpEF face prolonged healthcare utilization and extensive expenditures, which often involve PC to a greater extent compared to patients with HFrEF. Managing patients with HFpEF has been challenging, but in recent years, SGLT-2 inhibitors have been recommended along with treatments addressing the underlying causes, cardiovascular issues, and other health conditions to mitigate hospital admissions [50]. Implementing comprehensive management strategies in this context could potentially decrease hospital admissions, a responsibility that predominantly lies at the primary care level.

Factor associated with the highest number of hospital bed days in both years were elevated NT-proBNP levels, as well as the presence of ASCVD, COPD

and diabetes. Previous studies have reported similar associations between morbidity and these comorbidities, but the current study finds that this association persists over time [93]. These factors consistently impact the need for inpatient care over time and should be considered when assessing patients with HF. Particular attention should be paid to patients with comorbidities associated with HF, as a previous study suggests that as many as 70% of hospital readmissions are attributed to non-HF-related causes [122]. However, there is a degree of variability across HF subgroups and as such, the approach to planned follow-up should take this into consideration in an attempt to limit healthcare costs [21, 29, 121].

Chapter 4.2 Strengths and limitations

Paper I

The foremost strength of paper I is the extensiveness of the dataset. Data was collected from electronic medical records for HF patients at both the primary- and secondary care levels, offering an unselected, population-based cohort. The opt-out rate was negligible allowing for a comprehensive, real-world examination of HF patients in RH.

The first limitation that must be addressed concerns the validity of the HF diagnoses themselves. Patients included in the study must have received a heart failure diagnosis according to ICD-10 coding. At the time of publication, there had yet to be a nationwide study in Sweden regarding the validity of ICD-10 codes for HF. A regional study from Sahlgrenska University in Gothenburg did however show a high overall validity of HF diagnosis for patients admitted over a 12-year period [99]. Studies from other Scandinavian countries showed low sensitivity but high specificity positive predictive value for HF diagnoses [100, 101]. Together, this may infer a high validity in the national HF registry in Sweden as well as other regions in the country including RH.

A second limitation involves the HF-phenotypes, which are determined based on the EF values extracted by the algorithm from the medical records. Although the algorithm itself was reliable, with a precision of 99% upon validation, it is possible that the data may have been registered incorrectly, that the patient may have undergone echocardiography in a region outside of RH which would not be seen in the regional medical records, or that the patient was diagnosed using techniques other than echocardiography. Upon reflection,

the number of such potential cases was projected to be quite small and the risk that they would influence the final results was considered insignificant.

The patient cohort in the present study is considered to be comprehensive and offer a heterogenous representation of HF patients. However, the findings are based on healthcare routines and management strategies in RH which may vary slightly in other regions and generalizing them may not accurately depict the actual results on a grander scale.

Finally, residual unmeasured confounders must be considered. This is particularly pertinent in the HF-NDP subgroup which were older, had a high mortality and often lacked HF pharmacotherapy. As patients in this subgroup were diagnosed clinically, there is an inherent degree of uncertainty regarding the HF diagnosis. Although we did not encounter other studies involving HF patients diagnosed without echocardiography, numerous validation studies have proven that the diagnostic work-up of HF is often lacking or flawed and as such, we believe the results of this study to be comparable to previous research.

Paper II

A possible limitation of this project, which examined readmissions within 100 days of discharge, is that hospital admissions were only recorded once per patient during the study period. The decision to do so was based on the fact that patients admitted to hospital on multiple occasions likely had a quite severe HF with high morbidity which would invariably alter the final outcomes.

A further limitation concerns missing values, particularly those involving NT-proBNP values, in which data was not available in 16% of cases. The values registered were those from admission to hospital and NT-proBNP may not have been part of the initial battery of laboratory testing. In other cases, patients may not have been admitted through the ER at all or admitted to non-cardiac wards in which NT-proBNP may not be a routine laboratory parameter and may have been overlooked.

Paper III

This study examined differences in mortality and clinical characteristic among patients diagnosed with HF without the use of echocardiography at the primary- and secondary care levels. Patients diagnosed in PC had fewer comorbidities relative to those diagnosed in hospital. A possible limitation of the study is the frequency in which ICD diagnoses are used at the primary- and secondary care levels. In HC, a reimbursement system based on diagnoses is in place which does not exist in PC, which may affect registration of concomitant diseases. However, it is not expected that this would alter the results to any great extent, as data regarding ICD codes for concomitant diseases were recorded from a defined time period from primary- and secondary care, independently.

Data regarding the biomarker NT-proBNP showed a higher frequency among patients diagnosed in HC. Laboratory tests are analysed in hospital allowing for quick results which may influence the clinician's decision to include NT-proBNP as part of the diagnostic work-up.

It is important to note that the researchers had no way of discerning why echocardiography was not included in the diagnostic work-up of HF as numerous factors been have been involved in the decision-making process. Finally, this is a retrospective, observational study and as such, the results are purely associative and neither conclusive nor correlative.

Paper IV

As in the first paper, the foremost strength of paper IV is the extensiveness of this unselected, population-based study population and the comprehensiveness of the dataset. It is believed that this cohort shows greater variation compared to patients enrolled in a heart failure registry and allowing for a real-world examination of HF in the community. An additional strength is the exclusion of patients who did not receive a second, confirmatory HF diagnosis within a month post-index. Previous research concerning the economics of HF patient care have included all patients with at least one healthcare encounter. The aim of this study was to examine healthcare utilization and associated costs in the two years following a heart failure diagnosis. Since it is known that mortality is highest for HF patients in the period after diagnosis, a patient with severe symptoms could theoretically be diagnosed and pass away within a very

narrow. In which case they would no longer have contact with the healthcare system and would not add to the cost of HF patient care. In addition, the lack of a second, confirmatory diagnosis might suggest that the initial diagnosis was incorrect, which would negatively impact the results of a HF patient study.

Identifying costs specifically related to HF poses a challenge as HF patients often carry a considerable burden of comorbidity. The present study focused solely on direct costs, as calculating indirect costs was not feasible, even though inclusion of indirect cost would have been even more comprehensive in cost calculations concerning A further limitation is that the results are based on encounters with clinics that manage HF. As such, encounters and associated costs attributed other departments, such as psychiatry, were not considered. Finally, the results of this observational study are purely associative and definitive conclusion cannot be made.

Chapter 4.3 Significance of main findings

Heart failure is a syndrome associated with high mortality rates, high morbidity, and decreased quality of life, all of which become worse under the burden of comorbidity. Previous studies have shown the positive effect of appropriate pharmacotherapy on mortality and morbidity, particularly among patients with reduced ejection fraction. Treatment, in general, is based on HF phenotype as determined by ejection fraction values from echocardiograms. Despite the availability of guidelines regarding diagnostic procedure and treatment, studies have shown that many patients are still diagnosed clinically and lack recommended pharmacotherapy. Furthermore, the majority of studies in Sweden are based on hospital registries, which may not truly represent the entirety of the HF patient population.

Paper I applied a novel, native language algorithm to extract EF values from electronic medical records, providing an unselected, real-world HF patient population for further investigation. The results of this study showed a distribution of HF phenotypes that varied compared to those seen in registry-based studies. In addition, nearly half of the cohort was diagnosed without a conclusive echocardiogram and these patients had a significantly higher one-year all-cause mortality rate compared to those diagnosed with echocardiography. Furthermore, administration of two recommended HF medications as dual therapy was associated with a significantly lower mortality risk for the entire cohort.

In paper II, a third of the patient population admitted to hospital with a HF diagnosis were readmitted within 100 days due to cardiovascular complications. Echocardiography upon admission and dual therapy with recommended HF medications were associated with a lower risk of readmission. However, EF data from echocardiograms was only available for 60% of the entire cohort and less than two-thirds of the patients had dual therapy.

Considering the relative ease of access to echocardiography in secondary care, one could postulate that patients are more commonly diagnosed clinically in primary care. However, paper III showed that 58% of these patients were diagnosed in hospital, the majority as inpatients. The 30-day mortality rate was significantly higher among hospital-diagnosed patients but stabilized thereafter and essentially reflected the mortality rate of patients diagnosed in PC. In addition, recommended pharmacotherapy was generally lacking for the entire cohort but particularly among patients diagnosed in HC.

Paper IV showed high resource consumption and costs among all subgroups in the first year after a HF diagnosis, especially among HFrEF patients. Healthcare utilization and costs decreased in the second year to varying degrees with HFpEF patients representing the costliest subgroup.

Collectively, the results of these studies underscore the importance of correct diagnostic procedure and treatment. Echocardiography and recommended pharmacotherapy were missing to a great degree in the study population, particularly at the secondary care level, despite evidence associated with lower risks of readmission and one-year mortality. Hopefully, these results will encourage the use of echocardiography for the determination of HF-phenotypes, to improve patient management and prognosis. Healthcare plans and follow-up strategies should consider HF subgroup and comorbidities associated with increased mortality and morbidity, to improve patient outcomes and subsequently reduce healthcare related costs.

Chapter 5. Conclusions

Chapter 5.1 Conclusions of research conducted

Paper I

Using a novel algorithm to extract ejection fraction values from medical records, this observational study of an unselected HF patient cohort identified HF phenotypes and examined the distribution in a real-world population. A conclusive echocardiogram was available for 57% of patients diagnosed with HF. Of these, the algorithm was able to identify an EF in 97% of cases with 99% accuracy upon validation. The remainder of this HF patient cohort was considered to be clinically diagnosed without the use of echocardiography. One-year all-cause mortality was significantly higher among these patients, highlighting the importance of including echocardiography as part of a structured diagnostic work-up for all patients with suspected HF. In so, healthcare providers can provide appropriate therapy based on HF phenotype which will ultimately improve the prognosis of HF patients.

Paper II

After an initial admission to hospital due to HF, one third of the patients in the study cohort were readmitted due to cardiovascular complications within 100 days after. Although 39% of the admitted patients were newly diagnosed with HF, the results show that echocardiography is often lacking as part of the diagnostic work-up is. HF patients with reduced ejection fraction, elevated NT-proBNP levels and impaired kidney function were associated with the highest risk for readmission. Adequate management and follow-up strategies at discharge are imperative to limit the risk of readmission, particularly among patients already associated with a higher risk.

Paper III

This study showed that heart failure patients diagnosed without the use of echocardiography more commonly received the diagnosis in HC and had a higher one-year mortality rate compared to those diagnosed in PC. Patients diagnosed in hospital had a significantly higher mortality rate in the first 30 days after diagnosis. However, the rate stabilized beyond this point and was essentially equal to that of patients diagnosed in PC. In addition, recommended pharmacotherapy was more commonly seen among patients diagnosed in PC. The results indicated that improvement is needed both in terms of diagnostics and treatment, particularly at the secondary care level. We conclude, therefore, that patients with a life-expectancy beyond one month should undergo echocardiography as part of the diagnostic work-up of HF in order to improve patient management and prognosis.

Paper IV

Heart failure places a heavy burden on healthcare systems both in terms of resource utilization and healthcare economics. The present study observed high mean total costs for all subgroups in the first year after diagnosis, most notably among HFrEF patients. Healthcare encounters and attributed costs reduced considerably in the second year. Hospital inpatient care accounted for the highest costs for all subgroups in both years. Elevated NT-proBNP levels, impaired kidney function and comorbidities including ASCVD, diabetes and COPD were associated with longer hospital stays. Healthcare consumption was greatest among HFrEF patients in the first year, while HFpEF patients had the most healthcare encounters in the second year after diagnosis. Efforts should be made to provide personalized healthcare plans based on HF subgroup and associated comorbidities to improve patient outcomes and subsequently lower healthcare related costs.

Chapter 5.2 Considerations for future projects

The extensiveness of the cohort and the robustness of the dataset afford numerous opportunities for further studies. To date, analysis has been focused primarily of quantitative research. The results of these and other studies could

well be enhanced with qualitive research, providing a more comprehensive analysis of the heart failure patient population. This approach would explore how individual patients experience the condition, offering a more insightful perspective of heart failure.

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