How to create and analyze a Heart Failure Registry with emphasis on Anemia and Quality of Life.

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“Kites rise highest against the wind, not with it.”

Winston Churchill

Till Annika och pappa

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ABSTRACT

Background and aims

Heart failure (HF) is a major cause of serious morbidity and death in the population and one of the leading medical causes of hospitalization among people older than 60 years. The aim of this thesis was to describe how to create and how to analyze a Heart Failure Registry with emphasis on Anemia and Quality of Life.

(Paper I) We described the creation of the Swedish Heart Failure Registry (SwedeHF) as an instrument, which may help to optimize the handling of HF patients and show how the registry can be used to improve the management of patients with HF. (Paper II) In order to show how to analyze a HF registry we investigated the prevalence of anemia, its predictors, and its association with mortality and morbidity in a large cohort of unselected patients with HFrEF included in the SwedeHF, and to explore if there are subgroups of HF patients identifying high-risk patients in need of treatment. (Paper III) In order to show another way of analyzing a HF registry we assessed the prevalence of, associations with, and prognostic impact of anemia in patients with HFmrEF and HFpEF. (Paper IV) Finally we examined the usefulness of EQ-5D as a measure of patient-reported outcomes among HF patients using different analytical models and data from the SwedeHF, and comparing results about HRQoL for patients with HFpEF and HFrEF.

Methods

An observational study based on the SwedeHF database, consisting of about 70 variables, was undertaken to describe how a registry is created and can be used (Paper I). One comorbidity (anemia) was applied to different types of HF patients, HFrEF (EF <40%) (II) and HFmrEF (EF 40-49%) or HFpEF ($\geq 50\%$) (III) analyzing the data with different statistical methods. The usefulness of EQ-5D as measure of patient-reported outcomes was studied and the results about HRQoL were compared for patients with HFpEF and HFrEF (IV).

Results

In the first paper (Paper I) we showed how to create a HF registry and presented some characteristics of the patients included, however not adjusted since this was not the purpose of the study.

In the second paper (Paper II) we studied anemia in patients with HFrEF and found that the prevalence of anemia in HFrEF were 34 % and the most important independent predictors were higher age, male gender and renal dysfunction. One-year survival was 75 % with anemia vs. 81 % without ($p < 0.001$). In the matched cohort after propensity score the hazard ratio associated with anemia was for all-cause death 1.34. Anemia was associated with greater risk with lower age, male gender, ejection fraction (EF) 30-39%, and NYHA-class I-II.

In the third paper (Paper III) we studied anemia in other types of HF patients and found that the prevalence in the overall cohort in patients with EF $\geq 40\%$ was 42 %, in HFmrEF 38 % and in HFpEF (45%). Independent associations with anemia were HFpEF, male sex, higher age, worse New York Heart Association class and renal function, systolic blood pressure < 100 mmHg, heart rate ≥ 70 bpm, diabetes, and absence of atrial fibrillation. One-year survival with vs. without anemia was 74% vs. 89% in HFmrEF and 71% vs. 84% in HFpEF ($p < 0.001$ for all). Thus very similar results in paper II and III but in different types of HF patients.

In the fourth paper (Paper IV) we studied the usefulness of EQ-5D in two groups of patients with HF (HFpEF and HFrEF) and found that the mean EQ-5D index showed small reductions in both groups at follow-up. The patients in the HFpEF group reported worsening in all five dimensions, while those in the HFrEF group reported worsening in only three. The Paretian classification showed that 24% of the patients in the HFpEF group and 34% of those in the HFrEF group reported overall improvement while 43% and 39% reported overall worsening. Multiple logistic regressions showed that treatment in a cardiology clinic affected outcome in the HFrEF group but not in the HFpEF group (Paper IV).

Conclusions

The SwedeHF is a valuable tool for improving the management of patients with HF, since it enables participating centers to focus on their own potential for improving diagnoses and medical treatment, through the online reports (Paper I). Anemia is associated with higher age, male gender and renal dysfunction and increased risk of mortality and morbidity (II, III). The influence of anemia on mortality was significantly greater in younger patients in men and in those with more stable HF (Paper II, III). The usefulness of EQ-5D is dependent on the analytical method used. While the index showed minor differences between groups, analyses of specific dimensions showed different patterns of change in the two groups of patients (HFpEF and HFrEF). The Paretian classification identified subgroups that improved or worsened, and can therefore help to identify needs for improvement in health services (Paper IV).

Keywords

Heart failure, reduced ejection fraction, mid-range ejection fraction, preserved ejection fraction, anemia, health-related quality of life, observational study, outcomes.

LIST OF PAPERS/PUBLICATIONS

This thesis is based on the following papers, which will be referred to by their roman numbers.

- I Jonsson A, Edner M, Alehagen U, Dahlstrom U. Heart failure registry: a valuable tool for improving the management of patients with heart failure. *Eur J Heart Fail.* 2010;12(1):25-31.
- II Jonsson A, Hallberg AC, Edner M, Lund LH, Dahlstrom U. A comprehensive assessment of the association between anemia, clinical covariates and outcomes in a population-wide heart failure registry. *Int J Cardiol.* 2016 May 15; 211:124-131.
- III Jonsson A, Hallberg AC, Dahlstrom U, Edner M, Lund LH. Prevalence of, associations with and prognostic role of anemia in heart failure with mid-range and preserved ejection fraction. Submitted to *European Journal of Heart Failure*.
- IV Jonsson, A, Orwelius, L, Dahlstrom U, Kristenson M. Evaluation of the usefulness of EQ-5D as a patient-reported outcome measure for patients with chronic heart failure using different analytical models. Submitted to *Quality of Life Research*.

POPULÄRVETENSKAPLIG SAMMANFATTNING

I Sverige har nationella kvalitetsregister funnits sedan mitten av 1970-talet då de första startade inom ortopedin. De nationella kvalitetsregistren används för att följa upp och utveckla vårdens kvalitet. I registren finns strukturerad information om varje patient, till exempel med en viss sjukdom – om bakgrundsfaktorer, insatta åtgärder och resultat av vården, vilket ger oss möjlighet att studera effekter av och risker med en behandling, jämföra vårdens kvalitet mellan olika enheter och studera bakgrundsfaktorerens betydelse för sjukdomar.

RiksSvikt startade 2003 och fokuserar på patienter med hjärtsvikt. Hjärtsvikt drabbar varje år cirka 30 000 personer och omkring 200 000 personer har diagnosen hjärtsvikt i Sverige. Hjärtsvikt betraktas som ett kliniskt syndrom och är inte en primär sjukdom utan ett tillstånd sekundärt till andra sjukdomar som ger upphov till rubbad hjärtfunktion. Vanliga symtom vid hjärtsvikt är trötthet och andfåddhet såväl vid ansträngning som i vila beroende på hjärtsviktens svårighetsgrad. Hjärtsvikt är ett allvarligt tillstånd med dålig prognos, förknippat med sämre livskvalitet och drabbar oftast äldre individer. De vanligaste orsakerna till hjärtsvikt är tidigare hjärtinfarkt och högt blodtryck men alla hjärtsjukdomar kan ge upphov till hjärtsvikt. En vanlig förekommande samsjuklighet med hjärtsvikt är t.ex. anemi.

Syftet med avhandlingen är att beskriva hur man skapar och analyserar ett hjärtsviktregister med betoning på anemi och livskvalitet.

Avhandlingen omfattar fyra delarbeten och det inledande arbetet hade som syfte att beskriva hur ett nationellt kvalitetsregister för patienter med hjärtsvikt skapas och hur dess information kan användas i forskning och klinisk praxis. RiksSvikt (SwedeHF) är ett sådant vars syfte är att förbättra handläggningen av patienter med hjärtsvikt. Registret är internet baserat och deltagande enheter kan registrera sina patienter med tillhörande uppgifter on-line. RiksSvikt består av cirka 70 variabler vilka beskriver demografi, samtidiga sjukdomar, diagnostik, hemodynamik, olika laboratoriedata och mediciner. Ett år efter den första registreringen görs en uppföljning där patienten får beskriva sin aktuella mediciner, funktionella kapacitet och livskvalitet. Patienterna med hjärtsvikt registreras antingen vid utskrivningen på sjukhus eller i anslutning till ett mottagningsbesök. Data processas på Uppsala Clinical Research Center (UCR). Databasen har även koppling till befolkningsregistret och samkörning kan göras med Socialstyrelsens olika hälsodata register.

Deltagande enheter har möjlighet att on-line erhålla information angående användandet av diagnostiska instrument, såsom ekokardiografi och rekommenderad behandling såsom ACE-hämmare/ARB och BB hos de registrerade patienterna. Genom att jämföra sina egna data med ett nationellt genomsnitt kan en enhet uppskatta hur väl deras egna kliniska verksamhet följer nationella riktlinjer och göra förändringar där detta är nödvändigt. Genom insamlandet av data rörande död, sjuklighet, funktionsklass, livskvalitet och aktuell mediciner efter ett år kan resultat i olika subgrupper studeras och riskgrupper identifieras hos vilka behandling borde startats tidigt. Utöver detta kan vi utvärdera om livskvalitet eller funktionsklass är förbättrad efter behandlingen.

Vid 2007 års utgång fanns 16 117 patienter registrerade i RiksSvikt. De flesta patienterna var registrerade på sjukhus. Medelåldern för patienterna var 75 år och deras 1-års mortalitet var 21 %. Hjärtfunktionen var utvärderad med ekokardiografi hos 83 % av patienterna och 77 % av patienterna hade behandling med ACE-hämmare eller ARB, 80 % hade behandling med BB och 34 % var behandlade med MRA.

I register studier kombineras ofta data från olika datakällor. Förutom data från kvalitetsregister används ofta data från de nationella hälsodataregistren (patientregistret, läkemedelsregistret, dödsorsaksregistret, mm). I registerdata finns felkällor såsom att data kan saknas, vara fel registrerat mm. Det är också viktigt att justera för registrerade förväxlingsfaktorer (confounders) med olika statistiska metoder.

Syftet med det andra delarbetet var att undersöka förekomst av anemi, vilka patienter som löper ökad risk att ha anemi (prediktorer), anemins association med dödlighet och sjuklighet i en grupp av patienter med nedsatt hjärtfunktion (HFrEF) samt att identifiera om det finns undergrupper som har högre risk för död eller sjuklighet om de har anemi. En mer avancerad statistisk analys var gjord i detta arbete.

I detta delarbete fann vi att förekomsten av anemi var 34 %. Hög ålder, manligt kön och nedsatt njurfunktion var de tre viktigaste oberoende prediktorerna för anemi. Vi fann även att anemi var starkt associerat med ökad dödlighet och sjuklighet. De patienter med anemi som hade en högre risk för död eller sjuklighet var yngre, gifta/sammanboende män med lättare symtom och med en måttligt nedsatt hjärtfunktion.

I tredje arbetet fortsatte vi undersökning av anemins inverkan på hjärtsvikt men fokuserade i denna studie på patienterna med hjärtsvikt med en lätt nedsatt eller bevarad hjärtfunktion ($EF \geq 40\%$). Även här undersökte vi förekomsten av anemi, associationen med anemi och anemins inverkan på prognos och använde oss av andra statistiska analyser. I gruppen med bevarad hjärtfunktion hade 42 % av patienterna anemi. Anemi var oberoende associerad med bland annat hög ålder, manligt kön, nedsatt njurfunktion och svårighetsgrad av hjärtsvikt. Anemi hade även i denna typ av hjärtsvikt en ökad risk för död och för död eller inläggning på sjukhus och liksom i arbete två hade patienter med anemi en högre risk för dödlighet och sjuklighet om de var yngre och hade lättare symtom.

I fjärde delarbetet var syftet att undersöka användbarheten av EQ-5D som ett mått på patientrapporterade utfall hos patienter med hjärtsvikt genom att använda olika modeller för analys på två olika typer av hjärtsvikt. Huvudfynden var att vid användande av EQ-5D index sågs inga förändringar (HFpEF) eller små förändringar över ett år (HFrEF). När vi sedan undersökte de olika dimensionerna fann vi försämring i alla dimensioner hos patienter med HFpEF men endast i tre hos de med HFrEF där man istället såg förbättring i en dimension (huvudsakliga aktiviteter) och ingen förändring i en annan (oro/nedstämdhet). Pareto analys hjälpte sedan oss att illustrera skillnaderna i båda grupperna. Hos patienter med HFpEF och HFrEF noterades förbättring (24 respektive 34 %) och försämring (43 respektive 39 %). Vi kunde också identifiera en prediktor hos enbart de med HFrEF som inverkade på ett förbättrat resultat nämligen de patienter som vårdats på en kardiolog klinik.

Sammanfattningsvis är RiksSvikt ett värdefullt register för att förbättra handläggningen av patienter med hjärtsvikt. Genom att jämföra sina egna data med ett nationellt genomsnitt kan en enhet uppskatta hur väl deras egna kliniska verksamhet följer nationella riktlinjer och göra förändringar där detta är nödvändigt. Eftersom data rörande dödlighet, sjuklighet, funktionell kapacitet, livskvalitet och aktuell medicinering registreras möjliggör detta studier av olika subgrupper och identifiering av riskgrupper för tidig behandling. Genom att analysera en vanlig samsjuklighet vid hjärtsvikt som anemi hos olika typer av patienter med hjärtsvikt med olika statistiska metoder fann vi dels olika prediktorer för anemi men även riskgrupper där förekomsten av anemi var förknippad med högre dödlighet och sjuklighet. Slutligen studerade vi också användbarheten av ett patientrapporterat mått på livskvalitet, EQ-5D som används i RiksSvikt och fann där mycket små skillnader mellan olika typer av patienter med hjärtsvikt.

Sammantaget visar detta avhandlingsarbete hur ett hjärtsviktregister kan skapas och användas och vilka olika statistiska metoder som kan användas för att analysera registerdata.

ABBREVIATIONS

ACEI	Angiotensin Converting Enzyme Inhibitor
ARB	Angiotensin II receptor blocker
BB	Beta receptor blocker
ESC	European Society of Cardiology
EQ-5D	EuroQol 5-dimensions
HF	Heart failure
HFmrEF	Heart Failure with mid-range ejection fraction
HFpEF	Heart Failure with preserved ejection fraction
HFrfEF	Heart Failure with reduced ejection fraction
HRQoL	Health-Related Quality of Life
ICD-10	International Classification of Diseases and Related Health Problems 10 th version
LVEF	Left ventricular ejection fraction
MRA	Mineralocorticoid receptor antagonist
NP	Natriuretic Peptide
NYHA	New York Heart Association Classification

INTRODUCTION

The aim of research is to generate new knowledge or increase general knowledge with universal applicability. In evidence-based medicine, great emphasis is placed on randomized clinical trials since these reduce the risk of systematic errors when comparing different patient groups. With quality registries, large groups of patients can instead be compared in clinical day-to-day encounters. The two different ways of performing research have both its strengths and weaknesses.

BACKGROUND

In any research, especially those using human subjects, a confounding variable can adversely affect the relation between the independent variable and the dependent variable and skew the results wildly (Figure 1). Any experiment that relies upon selecting subjects and placing them into groups is always at risk. It is crucial that the researcher takes into account all of the potential confounding variables, which otherwise can cause severe validity issue.

Figure 1: Confounding variables impact on research.

Study designs

Randomized Controlled Trials (RCT)

The RCT is often considered the golden standard for clinical trials, if correctly designed and with adequate power, due to that it eliminates confounding factors. The RCT is a study in which people are allocated at random (by chance alone) to receive one of several clinical interventions. One of these interventions is the standard of comparison or control. The control may be a standard practice, a placebo ("sugar pill"), or no intervention at all.

The strength in a RCT is that randomization eliminates the risk of any confounders distorting the results, which gives the results a high internal validity. Its strength is at the same time its weakness. The population in a RCT is often selected due to randomization, inclusion and

exclusion criteria and the patients are frequently included at specialized study centers. Oral and written informed consents are needed from all included patients. The results are valid regarding the limited category of patients included in the study and not applicable to real world patients (less generalizability). A RCT takes long time to plan and complete, is often highly expensive and can be complicated to perform and its follow-up period is often limited.

Observational studies

In an observational study the real life situations are studied without the researcher influencing the exposure and conclusions are drawn by comparing subjects against a control group. Observational studies can be divided into descriptive research and analytical studies. The intention in descriptive studies is to learn more about the characteristics of a population at one point in time and answer the questions what, who, where and when and possibly generate a hypothesis, whereas the intention in an analytical study is to test a hypothesis about exposure-outcome relationships and to measure the association between exposure and outcome. The analytical studies answer the questions why and how. Observational studies can also study the long-term effects of certain variables, especially when it runs into decades.

Common aims in observational studies include studying, the incidence and prevalence of a disease, prognosis, risk markers and risk factors for the development of diseases or complications, treatments and interventions, and are therefore often used in epidemiological research in which the focus is to study and analyze the patterns, causes and effects of health and disease conditions in defined populations.

The main problem with observational studies is that the researcher has no control over the composition of the control group and cannot randomize the allocation of the subject. This can create bias and can also mask cause and effect relationships or alternatively suggest correlations, which are non-existing.

Quality registry related studies.

As mentioned previously, observational studies can be divided into descriptive studies and analytical studies and quality registry-related studies often have both descriptive and analytical elements.

In quality registry-related studies, data from different sources are often combined. In addition to data from quality registries, data obtained from the mandatory health data registries (the Population Registry, the Cause of Death Registry, the Patient Registry, the Drug Prescription Registry etc.) and other public registries (Statistics Sweden for socioeconomic data etc.) are frequently used.

The advantages with quality registry-related studies are that in these studies there are unselected populations (real world populations) and there are no inclusion and exclusion criteria limiting generalizability of the findings. The observational studies may include clinically important findings as “hard endpoints” (mortality and morbidity) and their association with studied variables. Important is also that most quality registry-related studies are very cheap in comparison with RCTs. Oral and written informed consent are not needed from the included patients but patients are informed about registration and are allowed to opt out. The data from a quality registry provides no final answers but can be hypothesis generating and is an important step in the scientific process.

On the downside there might be deficient data quality, missing data and confounding factors impossible to adjust for. It is not possible to compensate statistically for unmeasured or unknown confounders, but it is possible to adjust for measured confounders. However this calls for advanced statistics, which can be difficult to understand.

Registry-based Randomized Clinical trials (R-RCT)

During the last decade, an additional step has been taken in which randomization has also been carried out within the framework of a quality registry, entitled: registry-based randomized clinical trials (R-RCTs).

R-RCT is a method for carrying out large-scale randomized clinical trials in a time-efficient and cost effective manner, and is particularly suitable for larger studies with one or a few simple questions. The first truly large-scale R-RCT was entitled TASTE and compared two treatment options in patients with ST-elevation myocardial infarction – either a conventional percutaneous coronary intervention (PCI) or a thrombus aspiration followed by PCI ¹.

Many Swedish hospitals report their data to National Quality Registries, which facilitates conducting R-RCTs within the framework for registration. The computer, randomly selects who will, and who will not, receive a given treatment. This makes the studies unique because they not only recruit a large number of patients but also reflect the clinical reality and the findings can be generalized.

R-RCT is suitable for many fields within the healthcare and TASTE has been followed by several other ongoing, R-RCTs. The studies are of high quality and yet still significantly cheaper than the normal RCTs. Moreover, they permit evaluation of established treatment options that have no commercial interest for the pharmaceutical industry. In contrast to other registry based studies oral and written consent are needed from all included patients.

National quality registries in Sweden

Under Swedish law a quality registry is a structured, automated collection of information about patients established in order to develop and safeguard the quality of care, and to make comparisons at national and regional levels (The Swedish Patient Data Act 2008:355). In order to constitute a quality registry, it must bring together information about patients from *different* care providers. These national quality registries have been granted national funding and are usually referred to as national quality registries.

High quality health care involves care being knowledge-based and appropriate, safe, timely, fairly distributed, patient-centered and resource-efficient. Quality registries can be used to monitor, measure and develop these dimensions of health care to varying extent.

The national quality registries contain structured information about patients in a defined population and include specific disease diagnoses and background factors; treatment interventions received by the patient and outcome of care which give us the possibility to make comparisons at different levels to provide knowledge of the patient group and their main aim is to develop and improve patient management.

Quality registries make it possible to study the effects and risk of a certain treatment, compare the quality of care at different units and study the significance of background factors for patients with particular diseases and provide a public insight into the large and complex health care sector as a complement to information obtained in randomized clinical trials. In addition

to data from quality registries, data can be obtained from the mandatory national health data registries and other public registries such as Statistics Sweden's registries.

Since the first Swedish national quality registry, the Knee Arthroplasty Registry was started in 1975 quality registries have been developed in Sweden within many different specialist areas. These registries cover a large proportion of inpatient data, while areas such as primary care, geriatric care and psychiatric care are not yet well covered by registries.

Different types of quality registries

There are different types of quality registries in Sweden such as diagnosis registries, intervention registries (The Swedish Hip Arthroplasty Registry), patient/risk group registries (The National Pregnancy Registry) and structure/care form registries (The Swedish Intensive Care Registry). Regarding diagnosis registries there are two types of registries, chronic disease registries (The National Diabetes Registry) and episode registries (The National Stroke Registry)².

Informed consent

No explicit consent is required from a patient in order to register the patient in a Swedish national quality registry, but the individual is always entitled to say no (opt out). The individual is also entitled to have his or her details deleted from a national quality registry at any time. The health care provider who reports to a national quality registry is held accountable for the patient having been given the opportunity to obtain information about the registry and must determine the most suitable way of doing so. The health care provider has met the legal demands if the patient has been notified that registration will take place if he or she does not object to this, and where information about the registry can be found².

The patient's right to obtain information about the quality registry, registration and the opportunity to opt out is extremely important from an integrity point of view. Without this the individual has no opportunity to exercise his or her rights.

Legal responsibility of personal data

There is always a body that is legally responsible for the processing of personal data that takes place in connection with a national registry (e.g. a county or region as Region County of Östergötland). This authority must ensure that data processing meets the legislative requirements. For national quality registries, the responsibility are shared between, the reporting care provider and the authority within health care, which receives the data. Personal data in a national quality registry must have the same strong protection as data in patient records, and it is the authority responsible for the central personal data, which must ensure this.

Competence centers

The competence centers are responsible for the technical management of the national quality registries. Their role is to support quality registers in terms of start-up, development and operation of the register, help make registry data usable for different users and create synergy in cooperation between registers. In a competence center, several registries share the costs for staff and systems that a single registry could not bear.

Research using national quality registries

The use of data from national quality registries in the research field has increased the last decade and is used in a number of different ways, involving everything from generating hypothesis for new clinical trials to carrying out different observational studies and registry-based randomized studies.

To conduct research on a database from a register, it is important to have information regarding the coverage, how many centers are reporting, how big the proportion of missing data is in the registered variables. This information tells us how valid and reliable data is. When analyzing data from a diagnosis registry it is also important to know how well adjudicated the diagnosis is and if regular checking of the source data has been performed.

Coverage (completeness)

One of the most important factors is coverage. Traditionally, the term coverage in quality context in Sweden usually is used synonymous with the English term completeness. Coverage is a measure of how large a proportion of the intended target population is included in the registry. It is important that the National Quality registry has an adequate coverage since this affects how different types of results should be interpreted.

The coverage is sometimes presented in relation to individuals or hospitalizations. Sometimes the proportion of centers; number of units participating in the registry divided with all units in the country, who manage patients with the current diagnosis is calculated. Note the difference between this and completeness. A national quality registry can have 100% coverage regarding participating units but still have a low completeness, whereas a national quality registry cannot have 100 % completeness without having a 100% coverage regarding participating units. A number of different types of coverage may be needed in order to describe a registry.

In many cases, the national health data registries can be used as comparison databases in order to estimate the proportion of cases that have been registered. These registries are more extensive and widely spread, as there is legal support for registration, however even in these data is missing.

Validation

Validation is important and is primarily to determine how great a proportion of one or more variables values are correctly registered. This can be done in different ways such as with:

- Logic checks, which consists of a set of conditions, for example that the length of the input value is correct. Logic checks can also be used to verify the relationship between multiple input values.
- Source data, checking against the source data is probably the most time-consuming method of validation and it is therefore usually carried out on a selection of units and individuals. The registry data is compared with the source data at patient level.
- External registries, for most registries, there are one or more external registries that can be used for validation, including registries maintained by the National Board for Health and Welfare.
- Adjudication is a type of validation that involves evaluating the quality of a classification variable, such as a diagnosis code for a disease ².

The Swedish Heart Failure Registry (SwedeHF)

The SwedeHF registry is a national quality registry (chronic disease registry) established in 2003 with the goal of improving the management of patients with HF in all regions of Sweden. The SwedeHF is economically supported by the National board of Health and Welfare and associated to the Swedish Society of Cardiology. The inclusion criterion is clinician-judged HF. The healthcare authority, central personal data authority (CPUA) responsible for the processing of personal data at the central registry level in SwedeHF is Region Östergötland.

Since SwedeHF is a National Quality Registry, individual written informed consent is not needed to register a patient. Participating centers inform the patients that they are reporting to SwedeHF and the patient for whom data are entered in the SwedeHF has the possibility to opt out at any time. In most participating centers information regarding SwedeHF is provided on a noticeboard or in a brochure in the waiting room. Some centers have information in the appointment invitation or give oral information about where the patient can find full details about the registry.

Data collection

Patients with the diagnosis HF can be included in the SwedeHF registry at discharge from hospital or following an out-patient visit at hospital or in primary care. Annually about 7000 new patients are added to the register.

Approximately 70 mandatory variables (full protocol in Appendix A) are recorded and entered into a Web-based database. This database is built to handle sensitive information. The data exchange between users and the competence center (Uppsala Clinical Research Center (UCR)) is encoded. The registry is equipped with restricted user-dependent access to the data stored. Users can see detailed information for patients who are registered at their own unit (hospital/primary health care)

The register covers background factors such as age, sex, and previous or current diseases, diagnostic procedures, hemodynamics, laboratory data, medications, HF symptoms (shortness of breath and fatigue) and HRQoL. After one year, all patients receive a questionnaire including questions about HRQoL, functional capacity and current medications. The database is run against the National Population Registry monthly and managed by UCR.

Ethics

The Ethical review board in Linköping has approved the establishment of SwedeHF for research purpose but all new research projects based on the registry need an additional approved ethical application that conform to the declaration of Helsinki.

Coverage in SwedeHF

The National Board of Health and Welfare's registry service carried out the calculation of the coverage in SwedeHF in 2015 using a strict definition of both the numerator and the denominator.

Patients (unique individuals) registered in SwedeHF at discharge from hospital or following an out-patient visit at hospital during 2014 with information of their cardiac function assessed by echocardiography were included in the calculation. Moreover only units with more than 10 patients registered were included (both hospitalized and out-patient visits at hospitals).

In the denominator, patients (both hospitalized and out-patient visits at hospital) with the main diagnosis of HF (ICD i50) along with a registered echocardiography (activity code AF019, AF020, AF021 or AF064) within 5 years prior to the diagnosis of HF reported to the National Patient registry were included. The civic numbers in SwedeHF were matched against the civic numbers in the Patient registry. With this definition SwedeHF had a coverage of 54.3 %.

As previously mentioned data is missing even in the national health data registries, such as the visits to specialized nurses who are a central actor in the management of HF and many other chronic diseases. The lack of information regarding these visits is challenging when working with diagnosis registries since this is a considerable amount of visits not to be seen in the national health data registries as the Patient registry and therefore the estimated coverage is not completely reliable and might be underestimated.

Current European and Swedish guidelines state that the diagnosis of HF should be confirmed by objective evidence of cardiac dysfunction, preferably by echocardiography. Yet this is not always performed, which implies that all patients diagnosed with HF do not meet the recommended diagnostic criteria and question marks arise if all patients have a correct diagnosis. Other challenges are the differences in documenting the diagnosis of HF, if the disease is put as main diagnosis or second or third diagnosis due to different reasons.

Validation - Data verification in SwedeHF

To determine how great the proportion of the variables are correctly registered in SwedeHF, the registry has a number of logic checks at registration consisting of different rules to verify the relationship between multiple input values, for example that the length or format of the input value is correct; that the value of diastolic blood pressure is less than systolic blood pressure; and that the discharge date is after admission date.

Source data verification was continuously performed by comparison of the register information to the hospitals patient records. The criterion for audit was that the hospital during the year had to have more than 100 registrations. External monitor reviewed thirty randomly selected patients in 34 hospitals. Every obligatory variable has been reviewed. Discrepancies were noted when the registration was not met documentation in the medical record. The source data verification showed that the variables NYHA classification, smoking and use of alcohol had the largest number of missing data. In many cases the information is lacking in the patient record.

Research-process using SwedeHF data

Participants in the SwedeHF with login rights have access to their own data. If the material is to be used for research with the aim to publish the results more stringent requirements are necessary. If access to the entire database is desired, a project application (including details about the project and which data they want from the registry database) must be submitted and approved by the SwedeHF Research Board. An early contact should also be made with the head of the SwedeHF Research Board to discuss whether the data in the SwedeHF can be used for the intended questions. The SwedeHF Research Board will review and approve the project application. The review involves review of ongoing projects so it does not collide with other works, clarity regarding the objectives, feasibility, etc. It is important to state that even if the project collides with ongoing projects, the SwedeHF Research Board can only inform about it, but not refuse to give access to demanded data, if all other requirements for given out data are fulfilled.

If data from other sources are planned to be used this should be mentioned in the project application.

The local project manager is responsible for writing the ethical application, preferably in communication with the head for the SwedeHF Research Board. Ethical application must be written for each project and must be approved before access to data can be given. Once a decision has been made by the SwedeHF Research Board on issuing data, and there is an approved ethical application an agreement has to be made covering issues as: costs for data extraction and guarantees that received data may not be used to answer questions other than those stated in the original application unless a new application is made and approved.

If data is to be supplemented with data obtained from other sources such as the national health data registries separate applications must be done including the approved ethical application. The issuing authority also carries out its own review. In most cases linked data from the authority will be delivered as unidentified data.

Other Heart Failure registries

In the year 2006 there was an attempt to start a European HF registry in the ESC Heart Failure Association. The registry was based on the SwedeHF registry and the Italian IN-CHF registry. Therefore necessary harmonization of included variables was performed. Today there is an ongoing European HF registry, where the numbers of sites are based on sites with different complexity and the size of the population. SwedeHF are allowed to include data from 6 hospitals (2-3 small hospitals, 1-2 regional hospitals and 1-2 university hospitals) in order to meet the required complexities of care for HF patients. The problem with the European HF registry is representativeness within the countries. The data in the European HF registry is also only allowed to be included during one week every three months. Thus, compared to the European HF registry, SwedeHF has a higher representativeness and many more patients registered. Outside Europe there are also HF registries in US and Japan but as far as we know SwedeHF is one of the largest.

Heart Failure

Definition, epidemiology, etiology and comorbidity

There are many definitions of HF but one of the latest definitions is that there is a functional or structural impairment in the heart, reducing its ability to deliver oxygenated blood corresponding to the requirements of the metabolizing tissues of the body resulting in a reduced cardiac output and/or elevated cardiac filling pressures at rest or during exercise. In combination with impaired cardiac function neuro endocrine activations occurs, including the Renin-Angiotensin system (RAS) and the sympathetic nervous system³. The hemodynamic consequences of these disturbances may explain symptoms (shortness of breath, ankle swelling and fatigue) and findings (elevated jugular venous pressure, pulmonary crackles and peripheral edema) typical for HF³. It is important to state that HF is not a disease but a clinical syndrome. It is also important to tell that a relatively large proportion of the population has an impaired cardiac function (systolic or diastolic left ventricular dysfunction) without knowing it and no symptoms characteristic of HF, a condition entitled asymptomatic left ventricular dysfunction⁴. Studies have shown that patients with an asymptomatic left ventricular systolic dysfunction have a poor prognosis in terms of mortality and morbidity⁵.

The prevalence of HF is estimated to be about 2-3 %, which means that approximately 180,000 to 270,000 individuals in Sweden suffer from it ^{4, 6, 7}. The prevalence is approximately 1 % in 40-year-old individuals, and increases to 10 % in individuals older than 75 years ^{4, 6}.

The incidence of HF has declined during the past decade ⁷, probably due to improved management, better control of risk factors and modern treatment, which in large controlled studies have been shown to improve mortality as well as morbidity and HRQoL ⁸⁻¹³.

In Sweden, HF is the most frequent discharge diagnosis within internal medicine in patients elderly than 65 years, comprising about 10 % of all patient stays ¹⁴. HF patients are often old and prone to suffer from both associated and other diseases, and non-cardiac readmissions are as common as cardiac ones ^{15, 16}. Approximately 85 % of the HF population is being treated in ambulatory care, usually by general practitioners, and 15 % of the patients are hospitalized. The total cost for HF care has been estimated to 2.5 billion SEK a substantial economic burden corresponding to about two percent of the total health care budget ¹⁷.

The most common causes of HF are ischemic heart disease and hypertension, which explain a vast majority of all cases of HF ^{6, 18-20}. Other causes are cardiomyopathies, valvular heart diseases and arrhythmias such as atrial fibrillation.

There is a considerable comorbidity among HF patients such as ischemic heart disease (59%) and hypertension (57 %), while diabetes and chronic obstructive pulmonary disease occur in approximately 25 % of patients with HF, and other frequent occurring condition such as anemia ²¹.

Anemia and Heart Failure

Anemia is a common comorbidity in HF and is associated with an increased mortality and morbidity ^{22, 23}. Anemia is defined by the WHO as hemoglobin levels below 130 g/L in men and below 120 g/L in women ^{24, 25} and is observed in 10-50 % of HF patients ^{22, 26, 27}. The prevalence of anemia increases with disease progression, although actual numbers are inconsistent due to the wide range of hemoglobin cut-off values used in different studies ²⁸.

There are many potential underlying causes of anemia in the setting of HF. The main causes of anemia in HF include nutritional deficiencies and more specific iron, folate or B12 deficiencies (e.g. malabsorption, impaired metabolism), acute blood loss (e.g. gastrointestinal bleeding, although not common), intrinsic renal disease leading to insufficient erythropoietin production or response, hem dilution from volume expansion or use of ACEI ²⁹⁻³¹. Anemia is frequently associated with chronic diseases as renal failure (in literature called the cardio-renal syndrome) and different malignant disorders as well as chronic inflammatory diseases.

Pathophysiology

HF is a progressive complex clinical syndrome that can be caused by any cardiac structural or functional disorder that impairs the ability of the ventricle to fill or eject blood.

Neurohormonal activation

The renin-angiotensin-aldosterone system (RAAS) is regulating blood pressure and the fluid balance and is always activated in patients with HF resulting in a number of effects, where the most important are the following: sodium and water retention, vasoconstriction, release of growth factors, hypertrophy of cardiac myocytes, activation of the sympathetic nervous system and development of fibrosis. These effects can be reduced by treatment with ACEIs, ARBs and MRAs (Figure 2).

Figure 2. The neurohormonal activation.

Diagnostics of Heart Failure

The diagnosis of HF is important but can be difficult in reality. In order to obtain the diagnosis of HF there are at least two criteria that have to be fulfilled. First of all, there must be symptoms that are typical of HF, which many times but not always are accompanied by typical signs. Secondly, it is necessary to verify that there is an impaired cardiac function. Even though these criteria are concrete and explicit, it can still be challenging to make the diagnosis properly (Figure 3) ³.

Figure 3. Diagnostic algorithm for diagnosis of heart failure of non-acute onset, adapted from 2016 ESC Guidelines for diagnosis and treatment of acute and chronic HF³.

Symptoms and clinical signs

The symptoms of HF can vary from patient to patient, however the most common symptoms are shortness of breath, fatigue and ankle swelling followed by typical signs as elevated jugular venous pressure, pulmonary crackles and peripheral edema³². The diagnosis of HF can be difficult since symptoms and clinical findings typical of HF are non-specific. In particular, it is difficult to interpret symptoms in elderly patients with obesity or chronic lung disease or patients in the early stages of HF³³⁻³⁵. The symptoms have usually been bothering the patient for several weeks to months and have been insidious. The patients experiencing a rapid deterioration in HF, on the other hand, usually have more obvious symptoms, which often result in an urgent visit to a hospital emergency ward.

Electrocardiography (ECG)

ECG is an important investigation in patients with HF since it can provide important information regarding damage to the myocardium, or if there is any rhythm disturbances. A normal ECG means that the probability of HF is low in patients with acute HF and in chronic HF³⁶⁻³⁸.

Laboratory blood tests

In cases when suspicion of HF arises, it is important to take blood samples. The routine blood tests recommended according to ESC guidelines are, hemoglobin, leukocytes, glucose, thyroid stimulating hormone, liver enzymes, creatinine and electrolytes. These recommended routine laboratory tests do not describe the heart function but are helpful in excluding other diseases, which might also explain the symptoms³.

Natriuretic peptides (NP)

The NP consists mainly of brain natriuretic peptide (BNP) and N-terminal pro brain natriuretic peptide (NT-proBNP) and are markers for HF with high sensitivity and specificity, which is useful when HF is suspected.

The secretion of NP is increased when the cardiomyocytes are exposed to tension. NP is secreted mainly from the ventricles of the heart; NP increases natriuresis, diuresis and peripheral vasodilation and inhibits the renin angiotensin system^{39, 40}.

An elevated level of NP implies that HF is likely, especially in an untreated patient. However, there are factors other than HF causing elevated levels of NP⁴¹⁻⁴³. When the cardiomyocytes are exposed to increased filling volumes, stiffness, ischemia, arrhythmias and when there is decreased elimination, the levels of NP will increase. Factors, which can elevate NP, are atrial fibrillation, pulmonary embolism, renal dysfunction, increasing age, unstable angina pectoris, acute myocardial infarction and valvular heart diseases. Studies have shown that women have slightly higher values of NP than men⁴⁴.

Factors which involve lower NP levels are obesity and, more commonly, pharmaceutical treatment used in the treatment of HF^{35, 45, 46}. Consequently, normal levels of BNP (<35

pg/ml) and NT-proBNP (<125 pg/ml) exclude HF in an untreated patient but elevated levels need to be investigated further with echocardiography^{3, 47}.

NP is a strong prognostic predictor. Studies have shown that patients with higher levels of NP have a worse prognosis compared to patients with lower levels of NP⁴⁸⁻⁵².

Chest X-ray

When diagnosing HF, a chest X-ray is frequently conducted even though it provides little information about the cardiac function^{53, 54}. A chest x-ray can be normal even if the patient has impaired cardiac function. The investigation is still useful but mainly to rule out other explanations, particularly diseases of the respiratory system⁵⁵.

Cardiac function

When diagnosing systolic HF, it is crucial to evaluate the cardiac function and confirm that there is an impaired cardiac function. The clinical criteria (symptoms, clinical signs) and investigations as ECG and chest X-ray are not sufficient in order to diagnose that a patient is having a HF^{3, 56, 57}.

There are several methods to determine the cardiac function but the investigation that is most used and accessible is echocardiography⁵⁸⁻⁶⁰. The echocardiography provides information about cardiac anatomy, cardiac function, and valvular function and estimates the ejection fraction (EF). EF is an objective measurement that has been used to assist health care providers in the treatment of HF; as it is an indicator of how well the heart is able to receive and then pump the blood throughout the body. The EF also gives us important prognostic information of the patient⁶¹.

The main terminology used to describe HF is historical and is based on measurement of LVEF. HF comprises a wide range of patients; from those with normal LVEF (EF≥50%) entitled HF with preserved EF (HFpEF) to those with reduced LVEF (EF<40%) entitled HF with reduced EF (HFrEF). In the latest ESC Heart Failure Guidelines a new group of HF patients has been introduced namely patients with a mid-range LVEF (EF 40-49 %) entitled HFmrEF. This group has been introduced to cover the grey area between patients with HFrEF and HFpEF and to stimulate research into underlying characteristics, pathophysiology and treatment of these patients³.

Differentiation of patients with HF based on LVEF is important due to different underlying etiologies, demographics, comorbidities and response to therapies.

HF with reduced EF (HFrEF)

Patients with HFrEF has previously been called patients with systolic HF and is defined as patients with an EF <40% and symptoms typical for HF, many times followed by typical signs of HF³.

HF with preserved EF (HFpEF)

It is well recognized that many patients presenting with HF have a normal LVEF. Left ventricular diastolic dysfunction has been a term used to describe to what capacity the heart is able to “relax” in order to receive blood. Individuals with left ventricular diastolic dysfunction may have an EF that is within normal limits or preserved. The newer term for left ventricular diastolic dysfunction that has recently been identified is HFpEF meaning HF with preserved EF. These patients will generally present with classic signs and symptoms of HF in the

presence of what is considered a normal LVEF. Many of these patients are elderly, females, have long-standing hypertension, and may have other comorbidities. Despite the substantial risks of morbidity and mortality, effective treatment options are largely empiric, given the lack of evidence to date. In the ESC guidelines HFpEF is defined as patients with typical symptoms of HF many times followed by typical signs of HF and an EF $\geq 50\%$ and on top of that elevated levels of NP. Moreover it must also be evidence of a relevant structural heart disease (left ventricular hypertrophy or left atrial enlargement) or signs indicating a diastolic dysfunction³.

HF with a mid-range EF (HFmrEF)

The 2016 ESC Heart Failure Guidelines elevated the EF 40–49% category from a “grey area” to a distinct category, “HFmrEF”. Patients with HFmrEF is defined as patients with typical symptoms of HF many times followed by typical signs of HF and an EF 40-49% and on top of that elevated levels of NP. Moreover it must also be evidence of a relevant structural heart disease (left ventricular hypertrophy or left atrial enlargement) or signs indicating a diastolic dysfunction, a definition very similar to patients with HFpEF but with another EF interval³.

New York Heart Association (NYHA) functional classification

NYHA Functional Classification (Table I) provides a simple way of classifying the extent of HF and is used to describe the severity of symptoms and exercise intolerance. It places patients in one of four categories based on how much they are limited during physical activity; the limitations/symptoms are in regard to normal breathing and carrying degrees in shortness of breath and/or fatigue. The classification is the basis for treatment and also has a prognostic significance in which those in the highest NYHA classes have the worst prognosis^{3, 62}.

Table I The New York Heart Association (NYHA) functional classification³

NYHA Class	Patients symptoms
Class I (Mild)	No limitations of physical activity. Ordinary physical activity does not cause undue breathlessness (shortness of breath), fatigue or palpitations.
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness (shortness of breath), fatigue or palpitation.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in undue breathlessness (shortness of breath), fatigue or palpitation.
Class IV (Severe)	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

Treatment of Heart Failure

When treating HF, there are different approaches. These include non-pharmacologic treatment, medications, and device treatment. The main purposes of the treatment are to reduce signs and symptoms, improve HRQoL, prevent hospitalization and improve survival and most of all try to prevent development of HF by treating patients with asymptomatic LV dysfunction.

Non-pharmacological treatment

Non-pharmacological treatment includes education of the HF patient regarding symptoms and information of appropriate diets, sodium and fluid intake and the importance of physical activity in order to improve patient’s skill and self-care behaviors ^{3, 63}.

Follow up visits at an HF nurse based out-patient clinic after hospitalization improved survival, reduced the number of events, readmissions, and days in hospital and increased self-care ¹². The non-pharmacological treatment strategies demand a multidisciplinary HF team comprising of at least a cardiologist, and a HF nurse dedicated to management of HF and if available a physiotherapist, a dietician and a primary physician ³.

Most commonly, the information to the patient and their family is provided as a patient education so the patients understand the cause of HF and why symptoms occur. The education involves observing symptoms so the patients can recognize worsening signs and symptoms of HF. The patients are advised to record their weight repeatedly and recognize weight gain. The patient receives information about self-care including knowledge of when and how to reach a health care provider and how to use flexible diuretic therapy when necessary. The non-pharmacological treatment involves understanding indications, dosing, effects and possible side effects of treatment recommendations, avoid excessive fluid consumption and to exercise regularly. It also includes the importance of smoking cessation, reducing alcohol consumption, and recommendations regarding vaccinations.

Pharmacological treatment

The pharmacological treatment of the HF patient is complex, with different combinations of pharmacological agents. There are three different agents that affect the renin angiotensin aldosterone system in the treatment of HF; ACEIs, ARBs and MRAs (Figure 4).

Diuretics to relieve signs/symptoms of congestion
Digoxin in patients with symptomatic HF and AF with rapid heart rate

Figure 4. Medical treatment for patients with chronic symptomatic HF, adapted from 2016 ESC Guidelines for diagnosis and treatment of acute and chronic HF ³.

Angiotensin-converting-enzyme inhibitor (ACEI)

Treatment with ACEIs is the first in line treatment for HF with reduced LVEF and is well documented to reduce morbidity and mortality and improve symptoms in HF ^{3, 8, 9, 13, 64}. Studies have shown that ACEI have beneficial effects when doses used in the RCT studies are used ⁶⁵. ACEI has a remarkable effect on the LV remodeling, and is recommended in the treatment of all patients with HFrEF ³.

Angiotensin receptor blocker (ARB)

The effect of ARB in HF is equivalent to ACEI. ARB is recommended when there are adverse reactions to ACEI ⁶⁶⁻⁶⁸. There are also studies that have shown that ARBs may be used in addition to ACEI in patients with HFrEF ⁶⁹. ARBs have been shown to reduce morbidity and mortality and to improve symptoms ^{3, 66, 69}.

Angiotensin receptor neprilysin inhibitor (ARNI)

The first ARNI (sacubitril/valsartan) is recommended as replacements for an ACEI to further reduce the risk of HF hospitalization and mortality in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACEI, a BB and a MRA ^{3, 70, 71}.

Beta-receptor blocker (BB)

BB is recommended in combination with ACEI or ARB in patients with HFrEF but should be given only to HF patients who are in a stable condition and should be used cautiously in unstable, decompensated HF patients ^{3, 72, 73}. BB has been shown to reduce morbidity and mortality, and improve quality of life in patients with HFrEF in addition to treatment with ACEI or ARB ^{11, 74-76}. BBs have also an effect on LV remodeling similar to ACEIs. In addition it has been shown that BBs reduce sudden cardiac death in HF ¹¹.

Mineralocorticoid receptor antagonist (MRA)

A drug that blocks aldosterone receptors is MRA, which has a well-documented effect on survival and morbidity in patients with HFrEF ⁷⁷⁻⁷⁹. MRA is recommended in the treatment of HF patients who still have symptoms despite having already been treated with ACEI or ARB and BBs ³. Although MRA has an effect in patients with HFrEF there is a risk, particularly in elderly patients, of developing impaired renal function and hyperkalemia ⁸⁰. Therefore it is recommended during treatment with MRA to carefully monitor electrolytes and kidney function ³.

Diuretics

Loop diuretics are useful in HF when there is fluid retention to relieve symptoms as shortness of breath and excess of fluid. The apparent advantage of loop diuretics is the rapid effect of increasing diuresis ⁸¹⁻⁸³. The thiazides, another type of diuretics, increase the diuresis but do not have the same rapid diuretic effect. Despite the evident effect of loop diuretics on diuresis and in reducing HF symptoms, there is no evidence if diuretics affect morbidity or mortality in RCTs ³.

Digoxin

Digoxin has beneficial effects in HF regarding, symptoms, quality of life and physical function ^{84, 85}. Digoxin increases the cardiac contractility and decreases the heart rate and studies have shown that treatment with digoxin results in a reduction in hospitalization in

patients with worsening HF. Digoxin is however mostly used when there is a need to reduce the heart rate in patients with atrial fibrillation and when BBs are not tolerated. However, digoxin can also be used to increase cardiac contractility in patients with HFrEF and sinus rhythm but other treatments are preferred.

Device therapy

Some patients who have severe HF or serious arrhythmias (irregular heartbeats) are candidates for device therapy either by cardiac resynchronization therapy (CRT) also known as biventricular pacing or automatic implantable cardioverter defibrillators (ICD). These devices are implanted surgically and help either by delivering pacing or an electric counter shock to the heart when life-threatening arrhythmias are detected. Patients with very severe HF refractory of medication and no benefits of devices mentioned above may be candidates for implantation of left ventricular assist devices or cardiac transplantation ³.

Cardiac Resynchronization Therapy (CRT)

Some patients with HF develop abnormal conduction in the electrical system of the heart affecting how efficiently the heart beats. This can be treated by implanting a CRT device, which is “resynchronizing” the heart by making the ventricles contract more like normal and in synchrony. This therapy can improve cardiac function, reduce hospitalization risk, and improve survival ³.

According to guidelines CRT is recommended for symptomatic patients with HF in sinus rhythm, NYHA class III-IV, left bundle branch block, reduced LVEF and optimal medical therapy in order to improve symptoms and reduce morbidity and mortality ³.

Implantable cardioverter defibrillators (ICD)

A high proportion of deaths among patients with HF, especially in those with milder symptoms, occur suddenly and unexpectedly. Many of these are due to electrical disturbances, which can be caused by a variety of reasons including age, myocardial damage and medications. ICDs are effective in preventing and correcting potentially lethal ventricular arrhythmias ³.

For patients with ventricular tachycardia or fibrillation (VT / VF) and cardiac arrest or fainting with or without LV dysfunction, treatment with an ICD significantly improves the prognosis compared with antiarrhythmic medication ³.

Left ventricular assist devices (LVADs)

In patients with severe HF refractory of all types of treatment a LVAD can be implanted in selected patients either as a bridge to transplantation or as a destination treatment in patients with contraindications for cardiac transplantation or in selected patients for recovery of cardiac function (e.g. certain cases of myocarditis) ³.

Heart transplantation (HTX)

In selected patients with severe HF refractory of all types of treatment a HTX can be performed. According to clinical studies long term survival after HTX is rather good with a one-year survival more than 80% and a 5-year survival about 75-80% ⁸⁶. The problem we have all over the world is lack of suitable donors so many patients candidates for HTX die before they have a chance to have a HTX.

Prognosis

HF is associated with a poor prognosis in terms of high mortality, morbidity, disability and reduced quality of life, and the one-year mortality is approximately 20-30 % while the 5-year mortality is approximately 50-65 % in population-based studies⁸⁷⁻⁹¹. HF has a higher mortality than many of the common malignancies⁹². The long-term mortality after the first hospitalization for HF has decreased in Sweden during the past two decades⁹³. These results have been most apparent in younger patients, in men and more for ischemic than for non-ischemic HF, but the mortality remains high, especially in patients in need of hospital care.

Health-related Quality of Life (HRQoL)

Measuring quality of life is challenging as it is a multidimensional evaluation comprising the areas of physical symptoms, psychological well-being, social ability and perceptions about one's own health. There is today no consensus on how to define HR-QoL⁹⁴ however, HR-QoL can be said to originate from the World Health Organization (WHO) definition of health "Health is a state of physical, social, mental well-being and not merely the absence of disease or infirmity"⁹⁵. Traditional objective biomedical markers on health do not always correlate with the patients' perception of well-being. To caregivers it is essential to evaluate quality of life, in research as well as in every day practice as a guide to modify treatment.

Health-related quality of life (HRQoL) in patients with Heart Failure

HF patients have reduced HRQoL compared to a normative population in the community as well as when compared to patients with other chronic diseases such as patients with a history of angina pectoris, previous myocardial infarction, atrial fibrillation, hypertension, history of chronic pulmonary diseases, and arthritis⁹⁶⁻⁹⁸.

Patients with HF suffer from a combination of signs and symptoms (i.e. shortness of breath, fatigue, ankle swelling and signs as elevated jugular venous pressure, pulmonary crackles and peripheral edema), which can lead to functional limitations, for example impaired exercise capacity and psychological stress such as worries or depression and decreased HRQoL⁹⁸⁻¹⁰⁰.

With worsening HF and an increase in NYHA class there is a decrease in HRQoL¹⁰¹. Studies have shown that gender has an impact on HRQoL since women with HF usually reported poorer HRQoL compared to men with HF^{102, 103}.

HRQoL is a uniquely personal perception and indicates how the individuals' feels about their ordinary life and/or health status¹⁰⁴. In medicine and clinical trials there is more interest in evaluating HRQoL aspects, which are affected by disease and treatment. However HRQoL has different meanings to different individuals and also different meanings according to the area of application, in HF this means that patients with the same severity of HF, reflected by EF and/or elevated NP can perceive and value the impact of symptoms differently and thereby also value their HRQoL differently.

Measurement and evaluation of HRQoL

HRQoL can be measured with generic instruments (EQ-5D, SF36), disease-specific instruments (Minnesota living with heart failure, Kansas City Cardiomyopathy Questionnaire) or a combination of instruments. Generic instruments are intended for general use, irrespective of the illness^{94, 105}. A generic instrument makes comparison of HRQoL between patient groups with different chronic diseases and also against a general population possible. Disease-specific instruments are constructed to measure how a disease such as HF specifically

influences HRQoL, for example how the magnitude of dyspnea impacts on the patient's physical function.

EQ-5D

EQ-5D is a generic instrument, developed and applied by an international multidisciplinary research group. The instrument is well known internationally. The EQ-5D comprises of two parts. The first involves a health state classification scheme of five items (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each having three alternatives (1= no problems, 2=moderate problems, and 3= severe problems). The second part of the EQ-5D is a visual analogue scale, ranging from 0 (worst possible health state) to 100 (best possible health state)¹⁰⁶.

AIMS OF THE THESIS

General aim

Create and show how to analyze a Heart Failure Registry with different statistical methods with emphasis on anemia and quality of life.

Specific aims

- To describe the creation of the Swedish Heart Failure Registry (SwedeHF) as an instrument which may help to optimize the handling of HF patients and show how the registry can be used to improve the management of patients with HF.
- In order to show how to analyze a HF registry the aim was to investigate the prevalence of anemia, its association with mortality and morbidity and predictors in a large cohort of unselected patients with HF_rEF included in the SwedeHF, and to explore if there are subgroups of HF patients identifying high-risk patients in need of treatment.
- In order to show another way of analyzing a HF registry the aim was to assess the prevalence of, associations with and prognostic impact of anemia in patients with HF_mrEF and HF_pEF included in the SwedeHF.
- To examine the usefulness of EQ-5D as a measure of patient-reported outcomes among HF patients using different analytical models and data from the Swedish Heart Failure Registry, and comparing results about HRQoL for patients with HF_pEF and HF_rEF.

POPULATIONS

This research is based on four different papers where the data is obtained from two specific populations

- Data from 16 117 patients treated for HF at hospitals and primary care in Sweden and entered into the SwedeHF database per 2007-12-31 (I)
- Data from 88 265 (55251 unique patients) patients with HF at hospitals and primary care in Sweden and entered into the SwedeHF database per 2013-11-23 (II, III, IV)

Population I

The study included 16 117 patients from the SwedeHF database entered by 78 different centers (45 hospitals and 33 primary care centers) up to 31 December 2007. The geographical distribution was spread equally between the southern, western and eastern parts of Sweden.

Population II

The study included 24 511 unique patients with EF < 40% from the SwedeHF database, entered up to 23 November 2013. Patients entered in primary care and patients lacking information on echocardiography or having EF $\geq$ 40% were excluded.

Population III

The study included 18 052 unique patients with EF $\geq$ 40% from the SwedeHF database, entered up to 23 November 2013. Patients entered in primary care and patients lacking information on echocardiography or having EF < 40% were excluded.

Population IV

Data from the EQ-5D questionnaire were included in the registry from 1 February 2008. Between 1 February 2008 and 11 November 2013 there were 9621 unique index recordings with baseline EQ-5D data from 65 of 75 hospitals in Sweden. The index date was defined as the date the first record was entered. Patients who were entered in primary care or had no EQ-5D at baseline or at the one-year follow up were excluded which resulted in a study population including 6768 unique patients from the SwedeHF database.

METHODS

Methods I

This was an observational study based on the SwedeHF database to describe how a registry is created and can be used. The SwedeHF (previously entitled S-HFR) consists of about 70 mandatory variables including demography, concomitant diseases, diagnostic procedures, hemodynamics, laboratory data, and medication. After one-year of follow-up, data on mortality and morbidity are collected from national health databases. Information concerning medication, quality of life, and functional capacity are collected from a questionnaire sent out to all patients after one-year of follow-up. Patients diagnosed with HF should be registered either at discharge from hospital or following an out-patient visit and it is recommended that patients are re-registered after every new hospitalization due to HF.

The database is also connected to the National Population Registry to receive regularly information about mortality and might after special application be connected to the national health data registries for the collection of data on hospitalizations and causes of death and drug prescriptions.

Methods II

In this paper, one comorbidity (anemia) was applied to a defined type of HF (HFrEF). EF is in SwedeHF categorized in four different categories; less than 30 %, 30% to 39%, 40% to 49%, and 50 % or higher. The two lowest EF categories define HFrEF, which we used for setting

our inclusion criteria. However we also performed pre-specified subgroup analyses of patients with EF less than 30 % and 30% to 39%. According to the criteria from the World Health Organization, anemia was defined as hemoglobin less than 130 g/L in men and less than 120 g/L in women. In the registry we have also divided anemia in mild anemia (110-130 g /L in women and 100-120 g/L in men) and moderate to severe anemia (< 110 g/L in women and < 100 g/L in men).

Information about mortality was obtained monthly from the National Population Registry. For cardiovascular mortality and hospitalization we included information regarding the ICD-10 diagnoses I00-I99, and for HF hospitalization the ICD 10 diagnoses I50, I42-43, I25.5, I11.0, I13.0, I13.2 from The National Patient Registry, maintained by the Swedish National Board of Health and Welfare.

Methods III

In this paper anemia was applied to a different kind of HF, EF 40-49% (HFmrEF) and $\geq 50\%$ (HFpEF). Anemia was defined according to the World Health Organization (WHO) as hemoglobin less than 120 g/L in women and less than 130 g/L in men.

Follow up was until 23 November 2013: The primary outcome was time to all-cause mortality, obtained from the Swedish Population Registry, maintained by the Tax Agency (www.skatteverket.se). The secondary outcome was time to death or first HF hospitalization, obtained from the national patient registry, maintained by the Swedish National Board of Health and Welfare (www.socialstyrelsen.se), and defined as ICD-10 diagnoses I50, I42-I43, I25.5, I11.0, I13.0, I13.2 in the first position.

Methods IV

In this study we examined the usefulness of EQ-5D as a measure of patient-reported outcomes among HF patients using different analytical models and data from SwedeHF, and comparing results about HRQoL for patients with HFpEF and HFrEF. Data from a public health survey of the county of Östergötland were used as a reference group.

STATISTICS

Statistics I

Only limited statistical analyses have been performed because the main purpose of this paper is to describe how such a registry can be created and used. The results are presented as percentage or mean and SD, or as median when values were not distributed normally. In the case of continuous variables, analysis was done using Student's unpaired t-test, whereas for discrete variables the chi-square test was used. No statistical methods were used for adjusting for potential confounders in this paper.

Statistics II

Descriptive statistics are presented as numbers (n) and percentages (%) or means with standard deviation (SD). For comparison of continuous variables, we used Student's unpaired two-tailed t-test whereas the chi-square test was used for categorical variables.

To investigate which risk factors makes patients particularly prone to anemia, multiple logistic regressions was performed where several baseline variables such as renal dysfunction were included.

Propensity scores (0-1) for occurrence of anemia was estimated for each patient by use of logistic regression, clinically relevant baseline variables as independent variables and anemia as the dependent variable. Missing data were imputed with the non-parametric Random Forest methodology using the R-package missForest, version 1.4. Using matching without replacement a cohort was constructed matching each patient without anemia to the next closest patient based on propensity score. In the final cohort there were 7465 matched pairs.

The pre-specified primary outcome was all-cause mortality. Secondary outcomes were cardiovascular mortality as well as the composite endpoint of cardiovascular mortality or heart failure hospitalization, previously defined and based on ICD codes. Survival analyses in the overall cohort were assessed with Kaplan-Meier analysis and univariable Cox regression. Adjustment for confounders using propensity scores was made by assessing outcomes in the matched cohort.

The scaled Schoenfeld residuals and dfbetas from the models were investigated to detect violations to the proportional hazards assumption and possible influential outliers, respectively. Interactions between anemia and pre-specified clinically important variables were estimated by Cox regression and displayed in a forest plot.

Statistical analyses were performed using SAS 9.3, descriptive statistics using IBM SPSS Statistics 22 and R version 3.1.1 for imputation. The level of significance was 5% and all p-values and confidence intervals were 2-sided.

Statistics III

Descriptive statistics were presented as numbers (n) and percentages (%) or means with standard deviation (SD) and compared with chi square or Student's unpaired t-tests as appropriate. For multivariable analyses, missing data were handled by multiple imputation. Nine datasets were imputed and in all nine cases multiple linear regressions was used to impute the continuous variables and logistic regression the dichotomous variables. The mean for the continuous variables and the type value (the mode) for the dichotomous variables were calculated over the nine sets.

To assess the crude and independent associations between baseline characteristics and anemia at baseline, univariable and multivariable logistic regressions was performed with 29 baseline variables (marked with * in Table 1 in paper III) as independent variables and anemia as the dependent variable.

Crude outcomes in the overall cohort and in HFmrEF and HFpEF separately were assessed with Kaplan-Meier analysis and compared with log-rank tests. The crude and independent associations between anemia and outcomes were assessed with univariable and multivariable Cox regressions, using the same 29 baseline variables as in the logistic regression above plus anemia itself as an independent variable and the primary and secondary outcomes as dependent variables. Cox regressions were performed adjusting for few select variables as well as for all 29 variables, to assess which variables, when adjusted for, most attenuated the association between anemia and the outcomes. The scaled Schoenfeld residuals and dfbetas from the models were investigated to detect violations to the proportional hazard assumption and possible influential outliers, respectively; none were detected. Interactions between anemia and EF category as well as numerous others pre-specified clinically important

variables were estimated by Cox regression and hazard ratios by EF category and other relevant sub-groups were displayed in a forest plot. In these models, only the variables displayed in the Forest plot were included. For interactions, multiple adjustments was addressed with Bonferroni adjustments. Statistical analyses were performed using SAS 9.4 and Kaplan-Meier curves were created using Minitab 17.2.1. The level of significance was 5% and all p-values and confidence intervals were 2-sided.

Statistics IV

Descriptive statistics are presented as number (n) and percent (%). For comparison of categorical variables the chi square test was used.

Prevalence of reported problems at level 1, 2, and 3 (no, moderate, or severe problems) at baseline and follow up were calculated for each subscale of EQ-5D and mean value of EQ-5D index for the patients with HFpEF and HFrEF, and reference group data using age-adjusted data (from the Swedish HF Registry).

For each subscale of EQ-5D the prevalence of reported problems at 2 or 3 (moderate, or severe problems) and EQ index at baseline and follow up were calculated for the groups with HFpEF and HFrEF as well as the changes in prevalence of reported problems at levels 2 or 3 between baseline and follow up.

Changes in overall health states for the groups with HFpEF and HFrEF were calculated using the Paretian Classification of health change. The analyses were made in three steps. In the first step, the group with no problems both at baseline and at follow up was included in the study population. In the second step, this group was defined as one group ("no problem"), and in the third step the group "no problems" was excluded from analysis. This was necessary as this group can change in only one direction - for the worse.

Univariate logistic regression analysis was used to identify the variables that significantly predicted improvement and worsening. Multiple logistic regression analyses were then used to identify which combinations of variables together predicted outcome. The group with no problems (n=1097 (16%) at baseline and follow up) was excluded from these logistic regression analyses.

Statistical analyses were made with the aid of IBM SPSS Statistics (version 22, IBM Corp, Armonk, NY, USA). All tests were two-tailed, and the level of significance was defined as a p value < 0.05.

RESULTS – REVIEW OF THE PAPERS

Results I

The first paper describes the Swedish HF registry (S-HFR) later entitled SwedeHF and exemplifies how the registry may be used to stimulate improvements in the management of patients with HF. Only limited statistical analyses have been performed because the main purpose of this paper is to describe how such a registry can be created and used.

Up to December 2007, 16 117 patients from 78 units had been included in the registry. All results presented in this paper are examples of data that can be obtained from a HF registry. The mean age of the patients included was 75 years (range 17-103). Baseline characteristics in patients who had undergone an echocardiographic examination are presented in table 2. Of these, 10229 patients had been followed for at least 1 year, and 2133 deaths were recorded (one-year mortality 21 %).

Table 2. Characteristics of the patients included in the registry as on 31st December 2007 who have undergone an echocardiographic examination.

Variable	EF ≥50% (n = 2825)	EF <50% (n = 10596)	Primary health care (n = 631)
History			
Age, years	77	73 ***	76
Male, %	47.5	69.0***	56
Female, %	52.5	31.0***	44
IHD, %	43.7	58.7***	43.3
Hypertension, %	54.2	42.6***	51.5
Atrial fibrillation, %	55.5	45.7***	43.3
Diabetes, %	25.5	26.0	26.5
VOC, %	30.2	24.9***	11.0
Pulmonary disease, %	23.4	18.2***	30.3
DCM, %	3.5	17.2***	4.0
HCM, %	3.7	2.3***	0.3
Blood pressure			
Systolic blood pressure <100 mmHg	3.7	7.4***	2.9
Systolic blood pressure 100–140 mmHg	65.8	73.1***	63.8
Systolic blood pressure >140 mmHg	30.5	19.6***	33.3
Heart rate, bpm	74	73	73
Cardiac parameters			
Revascularization, %	18.8	30.4***	18.4
Pacemaker, %	10.7	12.6**	6.2
Heart valve surgery, %	7.9	6.4**	4.4
Lab. values			
Creatinine, µmol/L	111.4	115.5**	102.3
Haemoglobin, g/L	128.7	133.6***	135.0

IHD, ischaemic heart diseases; VOC, heart valve diseases; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy.
n, number; values are expressed as mean values; **P < 0.01; ***P < 0.001.

ECG was recorded from 97 % of the patients. Sinus rhythm was found in 51 % of the patients and atrial fibrillation in 38 %. Cardiac function was evaluated by Doppler echocardiography in 78 % of the women compared with 87 % of the men (total mean 83%). This diagnostic procedure was used less often in older patients.

Overall, 44 % of the patients had a new onset HF (< 6 months duration) and were in NYHA functional classes II-IV. Furthermore 77 % of the patients were treated with ACEI or ARB, 80 % were on BB, 34 % on MRA and 83% on diuretics. More than 3600 patients (23%) were

not, however, receiving treatment with ACEIs or ARBs. Similarly 3026 (19%) were not on BB treatment. The percentage of patients in different age groups treated with conventional HF drugs is shown in figure 5.

Figure 5. The percentage of patients in different age groups treated with conventional heart failure drugs.

Results II

In this prospective propensity-score matched registry analysis 24 511 patients with LVEF < 40% were included. We applied one comorbidity (anemia) to a group of patients with reduced HF (HFrEF) with the aim to investigate the prevalence of, predictors of and association with mortality and morbidity. The prevalence of anemia defined according to the WHO criteria was 34 %.

In the overall HFrEF cohort differences could be seen in many variables indicating that the two cohorts could not directly be compared and therefore the distributions of the propensity scores were different. However after matching, the baseline differences were considerably smaller or eliminated and the propensity score distributions were well matched and all had standardized differences below 10 %.

In the overall study cohort, patients having anemia were older, more often male, had a longer duration of their HF and had more severe HF according to NYHA classification. They were also having a higher frequency of comorbidities.

Several independent predictors for anemia were found where the most important were higher age ≥ 76 years, male gender and renal dysfunction (e-GFR <60)

The pre-specified primary outcome was all-cause mortality. Secondary outcomes were cardiovascular mortality as well as the composite endpoint of cardiovascular mortality or heart failure hospitalization.

In Cox regressions, the hazard ratios (HRs) 95% Confidence Interval (CI) for patients with anemia and all-cause mortality were in crude analysis in the overall cohort 2.19 (95 % CI, 2.11-2.28; $p < 0,001$) in the same cohort after adjusting for propensity core 1.37 (95 % CI, 1.32-1.43; $p < 0,001$) and finally in the propensity core matched cohort 1.34 (95 % CI, 1.28-1.40; $p < 0,001$).

The occurrence of anemia was strongly associated with increased adverse outcomes as mortality and morbidity after propensity scored adjustment and matching in all subgroups analyzed. In the overall cohort, crude one-year survival was 73% in patients with anemia vs. 88% in those without anemia and 3- and 5-year survival was 50 % vs. 74 % and 35% vs. 61 % respectively. After dividing anemia into two subgroups, one with patients with mild anemia and one with patients with more severe anemia, it was found that in patients with more severe anemia one-year survival was only 62% and the corresponding 3- and 5-year survival was 40% and 27% (Figure 6a and 6b).

Figure 6a Kaplan–Meier plot illustrating all-cause mortality on those with anemia versus no anemia in the unmatched and matched study population.

Figure 6b Kaplan-Meier plot illustrating all-cause mortality on those with no anemia or those with anemia divided into two subgroups (mild anemia and moderate to severe anemia).

All-cause mortality associated with anemia for clinically relevant subgroups in the matched cohort were presented in a forest plot (Figure 7). There were some significant interactions and after using necessary correction/ad modum Bonferroni still a few remained (gender, age, NYHA class, EF and civil status). The influence of anemia on these outcomes was significantly greater in males vs. females, $p<0,001$, younger patients < 76 years vs. older patients, $p< 0,001$, in patients in NYHA classes I and II vs. NYHA classes III and IV, $p<0,001$, in patients with LVEF 30-39%, vs. LVEF $< 30\%$, $p=0.002$ and in married or cohabitating patients, $p< 0,001$.

Figure 7 Forest plot depicting independent hazard ratios for all-cause mortality of those with anemia versus those without anemia in the matched population. The p-value is for the interaction between anemia and the variable on the y-axis. Squares represent the hazard ratio and lines represent the 95% confidence interval. Continuous variables were dichotomized at clinically relevant cut-offs.

Results III

Patients

Between 11 May 2000 and 23 November 2013 there were 88,265 registrations from approximately 65 of approximately 75 hospitals in Sweden. After exclusions, there were 18,052 individual patients with EF $\geq$ 40%. Of these, 42% had anemia, 49% had HFmrEF (38% anemia) and 51% had HFpEF (45% anemia; $p<0.001$ vs. HFmrEF).

Baseline characteristics

In the overall cohort, patients with anemia had a greater preponderance of HFpEF vs. HFmrEF and were older, mean $\pm$ SD age 78 $\pm$ 10 vs. 74 $\pm$ 12, $p<0.001$, and more commonly male, 57% vs. 51%, $p<0.001$ (although the hemoglobin was 132 $\pm$ 18 in men vs. 125 $\pm$ 16 in women, $p<0.001$; thus the higher prevalence of anemia in men partly reflecting different WHO cut-offs in men and women). Patients with anemia also had generally characteristics reflecting more severe HF and/or comorbidity and frailty: longer duration of HF, worse NYHA class and renal function (eGFR), lower systolic blood pressure and higher heart rate, more commonly diabetes and ischemic heart disease, and less use of ACE-inhibitors / ARBs and BBs and more requirement for diuretics.

Independent associations with anemia

In univariable analysis, nearly all baseline variables had a positive or negative association with anemia. In multivariable analysis, most associations remained significant but were less strong. After adjusting for covariates that may be associated with anemia, HFpEF vs. HFmrEF remained strongly independently associated with anemia (odds ratio [95% CI] HFmrEF vs. HFpEF, univariable 0.75 [0.71-0.80] and multivariable 0.83 [0.78-0.89]). Many additional characteristics were associated with anemia, including higher age, worse NYHA class, lower systolic blood pressure and higher heart rate, ischemic heart disease, non-use of ACEI/ARB and BBs and use of diuretics. Male sex was associated with anemia as defined by the WHO. As expected, lower eGFR (an estimation measure of renal function) was strongly associated with anemia, but notably, diabetes was also associated with anemia, independently of eGFR and other covariates. Atrial fibrillation and pulmonary disease were associated with lower risk of anemia.

Outcomes

Over a median (IQR) follow-up of 811 (320-1575) days, there were 7991 deaths and 2596 first HF hospitalizations. Kaplan-Meier curves with numbers for percent survival and percent survival free from HF hospitalization for anemia yes vs. no are shown for HFmrEF and HFpEF separately in figure 8 A-D. One-year survival with vs. without anemia was 73 vs. 87% overall, 74% vs. 89% in HFmrEF (Figure 8A) and 71% vs. 84% in HFpEF (Figure 8B) ($p<0.001$ for all). Anemia conferred distinctly worse outcomes over the short, intermediate and long term, with continued divergence of survival curves and event-free survival curves up to 8 years of follow-up. For both outcomes the difference was greater in HFmrEF (Figures 8A and 8C) than in HFpEF (Figures 8B and 8D).

Figure 8C

Figure 8D

Figure 8 A-D. Kaplan-Meier survival (A-B) and survival free from HF hospitalization (C-D) in HFmrEF (A and C) and HFpEF (B and D) according to presence vs. absence of anemia.

Independent association between anemia and outcomes

The large differences in crude Kaplan-Meier outcomes may be confounded by e.g. comorbidities, severity of disease and medication use. Therefore we conducted univariable and multivariable Cox regressions with single covariates to assess how each variable may change the risk associated with anemia, and with all baseline covariates to assess the independent prognostic role of anemia. For mortality the hazard ratio (HR)(95% CI) went gradually from 1.97 (1.88-2.05) to 1.40 (1.34-1.46) after adjusting for age, sex, eGFR and finally all baseline covariates. Much of the reduction in HR was accounted for by age and eGFR. For the composite outcome, the HR went from 1.93 (1.85-2.01) to 1.39 (1.33-1.46), again with most reduction in the multivariable HR accounted for by age and eGFR.

Interactions with EF and other covariates

A majority of the baseline covariates had significant interactions with anemia in determining outcomes. Anemia was overall associated with greater risk of both all-cause death and the composite of all-cause death and HF hospitalization in patients with younger age, milder HF and less comorbidity. The $p_{interaction}$ between anemia and EF category for mortality was 0.008 and for the composite 0.007. The adjusted HRs were considerably greater in HFmrEF, 1.47 (1.37-1.58) and 1.46 (1.37-1.56), respectively, than in HFpEF, 1.34 (1.26-1.42) and 1.34 (1.26-1.42), respectively.

Results IV

The aim of this study was to examine the usefulness of EQ-5D as a measure of patient-related outcomes measures for patients with HF using different analytical models. At baseline, patients with HFpEF were, compared to patients with HFrEF more often females, more than 75 years old, had a longer duration of their HF and more often a history of hypertension, atrial fibrillation/flutter, diabetes pulmonary disease, anemia, multiple comorbidity and low e-GFR. Patients with HFrEF were more often in NYHA class III/IV and had a history of ischemic heart disease (IHD) and previous myocardial infarction and were more frequently on ACEI or ARB, BB and MRAs. A higher proportion of the HFrEF patients were followed up at hospital or/and had visits to a HF nurse.

When comparing changes in EQ-5D index over one year there were no changes in HFpEF patients and only small changes among HFrEF patients (Figure 9A).

Figure 9a. EQ-5D dimensions in overall cohort reporting levels 2 or 3 at baseline and follow-up in patients with HFpEF (EF ≥ 50 %) and HFrEF (EF < 40 %).

When specific dimensions were examined, we found worsening (higher proportions reporting level 2 or 3) in all five dimensions in HFpEF patients (Figure 9B). This was found in only three dimensions for HFrEF patients, who instead showed improvement in one dimension (usual activities) and no change in one dimension (anxiety/depression) (Figure 9C).

Figure 9b EQ-5D dimensions in patients with HFpEF (EF $\geq$ 50 %) patients reporting levels 2 or 3 at baseline and follow-up

Figure 9c EQ-5D dimensions in patients with HFrEF (EF < 40 %) patients reporting levels 2 or 3 at baseline and follow-up

The Paretian classification judging overall improvements in EQ-5D profiles illustrated the heterogeneous response in both groups. “Improvement” (in at least one dimension), was seen in 24 % of the HFpEF patients and in 34% of the HFrEF patients, and “worsening” (in any other dimension) was seen in 43 % of the HFpEF and 39% of the HFrEF patients (Figure 10).

Figure 10 – Proportions of patients in the two groups HFpEF (EF > 50%) and HFrEF (EF < 40%) in different groups of Paretian Classification of health change as measured by the EQ-5D.

Finally, in multiple logistic regression analysis of factors affecting outcome in patients within the HFpEF group, atrial fibrillation, use of diuretics, low e-GFR, change in fatigue, and shortness of breath, which were significantly related to worsening in change of health as measured by the EQ-5D. The only factor affecting improved outcomes in the HFpEF group was change in fatigue. Factors affecting outcome in HFrEF patients were treatment at cardiology clinic, change in fatigue, and change in shortness of breath, which were significantly related to worsening in change of health as measured by the EQ-5D. Factors affecting improved outcome in the HFrEF patients were treatment at cardiology clinic, NYHA classification, change in fatigue, change in shortness of breath, and e-GFR < 60.

GENERAL DISCUSSION

Study designs

The RCT is often considered the golden standard for clinical trials. The strength in a RCT is that randomization eliminates the risk of any confounder distorting the results, which gives the results a high internal validity. The weakness is that the population in a RCT is often selected due to randomization, inclusion- and exclusion criteria. Oral and written informed consents are needed from all included patients. The results are valid regarding the limited category of patients included in the study and not applicable to real world patients (less generalizability) and with limited follow-up. The results, however, are despite this frequently used even in patients not included in the RCT and during long time not evaluated in the RCT.

In an observational study as quality registry-related studies are as in this thesis, there are unselected populations (real world populations) and no inclusion- and exclusion criteria limiting generalizability of the findings. The main problem with these studies is that the researcher has no control over the control group and cannot randomize the allocation of the subject. This can create bias and can also mask cause and effect relationships or alternatively suggest correlations, which are non-existing. Drawbacks are also that there might be deficient data quality, missing data and confounding factors impossible to adjust for. Only measured confounders can be adjusted for not unmeasured or unknown. This calls for advanced statistics as we have used in paper II and III.

Important to point out is also that data from a quality register provides no final answers but only associations with studied variables even if hard endpoints as mortality and morbidity are evaluated. The results however might be hypothesis generating.

National quality registers – SwedeHF

The national accredited quality registers in Sweden are unique since we know that they fulfil a number of conditions and they are granted to obtain national funding in order to run and develop the register but no financial support to perform research. During the period 2012-2016 there was a special financial effort from the government given to the quality registers and during that period we have seen that many registers have been improved in many aspects as for example coverage but also the research based on the data in the registers. The number of publications has been heavily increased and many have been published in scientific journals of high standard. During 2017 a national working group has been set up in order to decide the future organization of the quality registers so just now we do not know anything about the future for the quality registers.

Informed consent

Another unique feature of the quality registers in Sweden is that no explicit consent is required from a patient in order to register the patient in a quality register. The patient must however always has an opportunity to obtain information about the registry (in SwedeHF frequently provided in a brochure in the waiting room, on the notice board or in the appointment invitation) and is always entitled to opt out. The individual is also entitled to have his or her details deleted from a national quality registry at any time. The patient's right to obtain information about the quality registry, registration and the opportunity to opt out is extremely important from an integrity point of view. Without this the individual has no opportunity to exercise his or her rights. In the European Union there has lately been a lot of discussion if it is correct to register a patient without a formal approved consent. So far no decisions have been taken.

Coverage

To conduct research on a database from a register as SwedeHF, it is important to have information regarding the coverage, how many centers are reporting, how big the proportion of missing data is in the registered variables. This information tells us how valid and reliable data is. In SwedeHF we have a high number of hospitals reporting to the register (65/75 about 86%) but far less in the primary health care (114/1100 about 10 %). However the most important measure is the coverage or completeness of the register, telling us how large a proportion of the intended target population is included in the registry. Our coverage in SwedeHF was roughly 54% 2014 when we used a strict definition of both the numerator and the denominator set up by the National Board of Health and Welfare comparing our registered

patients with those included in the National Patient Registry. The problem with this calculation is that the visits to specialized nurses, who are central actors in the management of HF, is missing in the National Patient Registry and this is a considerable amount of visits and therefore the estimated coverage is not completely reliable and might be underestimated.

Validation - Data verification in SwedeHF

As previously mentioned SwedeHF has a number of logic checks to ascertain correctly registered data. Moreover source data verification is continuously performed in randomly selected hospitals by external monitors. The results found were that the variables NYHA classification, smoking and use of alcohol had the largest number of missing data, indicating certain efforts to be instituted.

Heart Failure

The prevalence of HF is estimated to be about 2-3 %, which means that approximately 180,000 to 270,000 individuals in Sweden suffer from it ^{6, 7}. Since the mean age of patients with HF is increasing in the community the prevalence over time probably is going to increase despite the beneficial results in many well controlled studies ⁸⁻¹². Interesting is that the incidence of HF has declined during the past decade ⁷ probably due to improved management, better control of risk factors and modern treatment.

In Sweden, HF is the most frequent discharge diagnosis within internal medicine in patients elderly than 65 years, comprising about 10 % of all patient stays ¹⁴. HF patients are often old and prone to suffer from both associated and other diseases, and non-cardiac readmissions are as common as cardiac ones ^{15, 16}.

There is a considerable comorbidity among HF patients such as ischemic heart disease (59%) and hypertension (57 %), while diabetes and chronic obstructive pulmonary disease occur in approximately 25 % of patients with HF, and other frequent occurring conditions such as anemia ²¹.

SwedeHF

SwedeHF is one of the largest HF registries in the world and at the end of 2016; there were 130 281 registrations in 75 933 unique patients reported. During the years minor modifications of included variables have been made and also 2006 an international harmonization.

When analyzing data from a diagnosis registry as SwedeHF it is important to know how well adjudicated the diagnosis is. Patients with a clinician-judged HF are included in SwedeHF.

Current European and Swedish guidelines state that the diagnosis should be confirmed by objective evidence of cardiac dysfunction, preferably by echocardiography ³. Yet this is not always performed, which implies that all patients diagnosed with a clinician-judged HF do not meet the recommended diagnostic criteria and question marks arise if all patients do really have a HF. Other challenges are the differences in documenting the diagnosis of HF, since HF is not a disease but a clinical syndrome. Dependent of that and other reasons HF is not always put as the main diagnosis.

Cardiac function

As pointed out above it is crucial to evaluate cardiac function when diagnosing HF. HF comprises many different types of patients from those with a normal EF to those with a severely reduced EF. Previously we have divided HF into two major types, namely HFrEF and HFpEF but in the latest ESC Heart Failure Guidelines a new group of HF patients has been introduced namely patients with a mid-range LVEF (EF 40-49 %) entitled HFmrEF. This group has been introduced to cover the grey area between patients with HFrEF and HFpEF and to stimulate research into underlying characteristics, pathophysiology and treatment of these patients. The latest ESC HF guidelines, for the first time, provide us also with strict definitions regarding these three types of HF patients³. In Paper III we have especially evaluated this group of patients in patients with and without anemia.

Prognosis

It is well known that HF is associated with a poor prognosis in terms of high mortality, morbidity, disability and reduced quality of life. Interesting is that the long-term mortality after the first hospitalization for HF has decreased in Sweden during the past two decades⁹³. These results have been most apparent in younger patients, in men and more for ischemic than for non-ischemic HF, but the mortality remains high, especially in patients in need of hospital care.

Characteristics of patients in SwedeHF (paper I)

In paper I we have tried to show the characteristics of our patients in SwedeHF, who were registered up to the end of 2007. Most of our findings in this study are in line with results from previous studies, there are, however some interesting differences compared with other HF studies. In SwedeHF, the mean age of patients was 75 years, which corresponds to the age of HF patients in the community. However in the majority of HF studies, the mean age of included patients is considerably younger, ranging from 57 to 71 years^{16, 107-109}. All-cause mortality at 1 year in the SwedeHF was 21%, which is within the range reported in other studies^{89, 91, 110}. In SwedeHF 78% of women and 87% of men had undergone evaluation by Doppler echocardiography, which is within the range of, reported usage of echocardiography in the literature^{111, 112}. Of these patients, less than 20% had a normal systolic function (HFpEF). The number of patients with HFpEF increases with age and this is in line with previous publications showing that patients with HFpEF are elderly and more frequently women but have mortality rates similar to those among patients with reduced systolic function (HFrEF), as was also shown in this study^{113, 114}.

An advantage of a HF registry is the creation of a database that includes information about a number of important parameters from a large number of patients with a clinical diagnosis of HF, making it possible to initiate new research projects and may also help generate new hypotheses and correlations that can be used for research purposes.

Anemia and SwedeHF

There is a considerable comorbidity among HF patients and one such is anemia, which we have evaluated in paper II and III. Anemia is associated with an increased mortality and morbidity in HF and there are a number of underlying causes of anemia as previously mentioned.

Anemia and HFrEF (paper II)

The prevalence of anemia was in our study 34%, which was similar to what has been found in a previous large meta-analysis (37%)²³ and differs to what was found in clinical trials (lower 10-25%)^{22, 27, 115} and in patients with acute heart failure (higher 58%)¹¹⁶. Well known is also that patients with anemia are older, most often men, having a more severe disease, reduced renal function, more comorbidities which was also found in our study verifying that these findings are reliable and generalizable.

The most important independent predictors for anemia were not surprisingly higher age (>76 years), male gender and renal dysfunction (e-GFR < 60). However we also found that patients with severe HFrEF in NYHA class III-IV and those with concomitant diseases were independent risk markers for anemia.

The occurrence of anemia was indeed strongly associated with increased adverse outcomes as mortality and morbidity after adjustment and matching in all subgroups analyzed.

Short one-year survival was 75% and the long-term 5-year survival was only 38%. Looking at survival in those with more severe anemia only 27% of the patients remained after 5 years. These findings are supported by other studies looking at short-term as well as long-term mortality in patients with anemia^{117, 118}. Anemia was highly significantly associated with a higher risk of death and hospitalization, which is also supported by previous studies^{22, 117, 118}, these findings, however, are in contrast to those reported by Mentz et al.¹¹⁹. Different study populations may explain these differences.

Surprisingly we found that the influence of anemia on mortality was significantly greater in men, younger than 76 years, in patients in NYHA class I and II, in patients with EF 30-39% and in married or cohabitating patients. In a previous study in patients hospitalized due to acute decompensated HF syndrome it was found that in patients younger than 75 years with anemia had a greater influence on mortality than in elderly patients¹¹⁶. In our cohort we have a median age of 76 years and we also find that anemia was associated with more harm in younger compared to older patients. Kerzner et al. found that there was no correlation between the hemoglobin value and mortality for patients 75 years or older supporting our finding that anemia in elderly patients is not as important predictor for mortality and comorbidity as in younger patients¹²⁰. The reason behind this we only can speculate about. We know that elderly patients have a more stiff heart due to structural changes and this might play a role regarding among other things for the ability for the heart to undergo remodeling, which has been proposed to be one of the mechanisms involved in worse outcomes in patients with HF and anemia^{22, 23}.

The influence of anemia was much greater in men than women, supported by the findings by Teng et al.¹¹⁸ but in contrast to the findings by Waldum et al.¹¹⁷. A reasonable explanation to the gender difference has been proposed pointing out the difference in oxygen affinity of hemoglobin¹²¹.

Patients in the lower NYHA class I and II had a greater influence of anemia on mortality than those in NYHA class III and IV. This finding is similar to what has been found in another observational study pointing out that anemia is not an independent predictor of all-cause mortality in patients with severe HF¹¹⁷. Our finding that HFrEF patients with anemia and a moderate reduction of EF (30-39%) are also exposed to a higher risk of mortality is in line with these findings. The most possible explanation behind this is that patients with more advanced HF to a higher extent die from this or other diseases and not from the concomitant

anemia. Thus, even though anemia was and is generally less common in HF patients with lesser degrees of impairment, once anemia was present, it actually conferred a higher independent risk in those patients measured by both EF and NYHA class.

Finally we also found that patients living together with somebody have a higher risk to die if they have anemia. We know from many studies that patients with severe chronic diseases living alone are exposed to a higher risk of death than married or cohabitating patients¹²². This finding is probably due to that single living HFrEF patients die in a higher extension of their HF and other diseases than from their anemia, where married patients have a greater risk from comorbidities such as anemia.

Anemia and HFmrEF and HFpEF (paper III)

In this study evaluating patients with HFmrEF and HFpEF we found that (1) anemia was common in both but more common in HFpEF (38% and 45%); (2) independently associated with age, male sex, worse renal function, severity of HF and numerous other factors; and (3) over long-term follow-up, independently associated with considerably increased risk of death and the composite of death and HF hospitalization, but more so in HFmrEF (47% and 46% increased risk, respectively) than in HFpEF (34% increased risk for both outcomes). Very similar results as in paper II.

The prevalence of anemia has been studied extensively in chronic and acute HF with wide prevalence ranges in studies from 10% to 68% in HF overall, 21-68% in HFpEF^{113, 123, 124} and 10-50% in HFrEF^{113, 124, 125} with the higher prevalence in cohorts, especially in the acute setting, and lower prevalence in trial databases¹²⁶⁻¹²⁸ as found in paper II. The prevalence overall in our study of 42% is in the higher range, consistent with the non-selective and generalizable nature of our registry. It was however much higher than in another observational study, where it was only 14% in HFrEF, 20% in HFmrEF and 22% in HFpEF¹²⁹. It is increasingly apparent that anemia is more common with higher EF, with 34% in HFrEF in SwedeHF¹³⁰ and here 38% in the novel HFmrEF category, which has previously not been studied, and 45% in HFpEF. This can likely be explained by higher age and more comorbidity with higher EF but even after extensive covariate adjustment, anemia remained strongly associated with higher EF. This raises the possibility that it is not only a marker of the age, renal insufficiency and comorbidity related phenotype, but also may contribute to symptoms and potentially drive physical inactivity; deconditioning and progressively worsening exercise tolerance.

In previous reports, patients with anemia tend to be older and with worse renal function and more comorbidities, but as previously shown for other comorbidities and biomarkers¹³¹, the extent to which these are independent predictors of anemia is less well studied¹³². This association of age with anemia was only modestly attenuated by multivariable adjustment; suggesting the ageing itself or ageing-related covariates not adjusted for here, such as cognitive decline¹³³ may contribute. Notably, diabetes was associated with a 52% increased risk of anemia, independent of renal function and all other covariates which highlights the potential interplay between anemia, chronic kidney disease (CKD), and diabetes in patients with HFpEF and HFmrEF. Furthermore, as expected, CKD was associated with considerably increased risk of anemia, which was minimally attenuated on adjustment. These data suggest that multiple comorbidities independently are associated with and may drive anemia and contribute to one another, and are consistent with the hypothesis of a constellation of comorbidities driving HFpEF¹³⁴⁻¹³⁶.

In previous studies, anemia has been independently associated with worse outcomes regardless of EF, although the HFmrEF has been poorly represented^{128, 137-139}. Many potential mechanisms have been put forth, but the risk marker vs. risk factor roles are difficult to distinguish^{30, 138, 140-143}. Here, the risk associated with anemia was independent of most potential confounders, including CKD, which is both closely linked to anemia and poor outcomes¹⁴⁴. In previous studies, the risk for mortality or composite outcomes have been elevated by 20% to over 50% but covariate adjustment has been variable^{23, 138, 145}. Unlike in previous smaller studies, the risk associated with anemia in our study was clearly greater in HFmrEF than HFpEF. This may be relevant for our understanding of the risk for, progression and outcomes in HF. While comorbidities including anemia may be contributors to the HFpEF syndrome, they are also age related comorbidities and potentially less relevant bystanders in determining outcomes in HFpEF. In contrast, in HFmrEF (and HFrEF), anemia may more commonly be a consequence of HF, and the cardiorenal syndrome, particularly with progressive and more severe HF, and thus being more directly related to outcomes in HFmrEF and HFpEF. Moreover anemia was associated with considerably greater risk for both outcome not only in HFmrEF compared to HFpEF, but also in younger patients, milder NYHA class, better renal function, and absent diabetes. This suggests that anemia may be more harmful when other factors such as comorbidity and severity of HF are less important. Almost similar findings were found in paper II evaluating anemia in patients with HFrEF.

Health-related Quality of Life (HRQoL) – SwedeHF

HF patients have reduced HRQoL compared to a normative population in the community as well as when compared to patients with other chronic diseases⁹⁶⁻⁹⁸. Studies have shown that gender has an impact on HRQoL since women with HF usually reported poorer HRQoL compared to men with HF^{102, 103}. In SwedeHF HRQoL is measured by a generic instrument, EQ-5D, making it possible to compare the HF patients HRQoL with HRQoL among patients with other chronic diseases and also against a general population

EQ-5D – SwedeHF

The aim of this study was to examine the usefulness of EQ-5D as a measure of patient reported outcome for patients with HF using different analytical models. The main findings comparing changes in EQ-5D over one year in two groups with different types of HF (HFpEF and HFrEF) were firstly when using the EQ5D index that no changes were found in HFpEF patients, and only small changes over one year among HFrEF patients.

Secondly, when we examined the specific dimensions, we found worsening in all dimensions in HFpEF patients, but only in three dimensions for HFrEF patients, who instead showed improvement in one dimension and no change in one dimension.

Thirdly, the Paretian classification judging overall improvements in EQ-5D profiles helped to illustrate the heterogeneous response in both groups. “Improvement”, was seen in 24 % of the HFpEF and in 34% of the HFrEF patients, and “worsening” in 43 % of the HFpEF and 39% of the HFrEF patients. Finally, we were able to identify predictors of outcome, where treatment at cardiology clinic affected improved outcome in the HFrEF but not in the HFpEF patients.

Our findings are in accordance with the clinical characteristics of these two groups of patients and confirm findings from previous studies. Patients with HFpEF were older, predominantly women, and had more coexisting conditions, whereas HFrEF patients were more often younger men with a history of ischemic heart disease and previous myocardial infarction¹¹³.

^{146, 147}. They had also had HF for a shorter time, and were more likely to be assessed as NYHA class III-IV than HFpEF patients, who were more often NYHA class I-II and had had HF for longer. In contrast to the clinical NYHA classification, more patients in the HFpEF group assessed their symptoms of fatigue and shortness of breath as severe limitations than those in the HFrEF group. This confirms the results of Ekman et al., who pointed out that patients' self-assessed symptoms and their NYHA classification did not necessarily agree ^{148, 149}.

This divergence between the results of medical examinations and those of patients' self-assessed symptoms, adds weight to the argument in favor of the assessment of patient-reported outcomes ¹⁵⁰. At the time of discharge, patients with HFrEF were more likely to be prescribed RAS antagonists, BBs, and MRAs, but less likely to be given diuretics, than those with HFpEF, probably because the guidelines for the latter patients were less specific than those for patients with HFrEF ³. Compared with a normal population, both groups showed large differences in the EQ5 index and for all dimensions except for pain and discomfort. This also confirms earlier studies, the results of which have shown that patients with HF have reduced HRQoL compared with a normal population as well as with patients with other chronic diseases ⁹⁶⁻⁹⁸.

While the EQ-5D index showed small differences, we identified larger variations over time by using data for each dimension. These also showed differences between the two groups, where the HFpEF patients showed worsening on all dimensions, and the HFrEF patients showed worsening in only three dimensions and improvement in one. Notably, using the Paretian classification, we could identify those who had an overall improved HRQoL within each group, and those who had an overall worsening. Within both groups large percentages showed improvements in all dimensions. More patients in the HFpEF group showed worsening in all dimensions, and more patients in the HFrEF group showed improvements in all.

The findings are, again, in accordance with what we expected, as the patients in the HFpEF group are mainly elderly women who are treated according to less specific guidelines, and are often followed up in primary care, while patients in the HFrEF group are younger men who are followed up in hospital and treated according to established guidelines ¹⁴⁷.

In a logistic regression analysis the main difference between factors that indicate a worsened or an improved outcome was being treated at a cardiology clinic, and this was significant only for patients with HFrEF ^{12, 151}. The factors are supported by clinical experience and other studies

Studies have shown how to treat HFrEF patients but failed to show how to treat HFpEF patients and therefore we need evidence-based studies even for these patients. This is important, as previous studies have shown that the prognosis is similar in the two groups of patients with poor survival and high rates of hospitalization ¹¹³, and this has now been corroborated by our findings of differences in HRQoL.

METHODOLOGICAL CONSIDERATIONS (paper I-IV)

In quality registry-related studies, data from different sources are often combined. In addition to data from the quality registry, data might be obtained from the mandatory health data registries as the Patient Registry, which we did in paper II, and III. In these papers information about mortality, was obtained from the National Population Registry and for cardiovascular mortality and hospitalization we received information from the Patient Registry.

As pointed out the main problem with results from observational studies are confounding factors, which can violate the results and therefore must be compensated for as far as possible.

In paper I we have only performed limited statistical analyses and no adjustments, because the purpose of the paper is not to prove the importance of the results, but instead to describe how a registry can be created and used.

In this study (paper II) we have used a propensity score matching analysis. As previously mentioned propensity score is the propensity from 0 to 1 to have a particular characteristic (anemia) given a set of known variables and is used to adjust for confounding and other types of differences in observational studies. The score is calculated by using logistic regression methods. In this paper we also used matching in order to balance the two groups those with anemia and those without anemia. By using matching without replacement a cohort was constructed matching each patient without anemia to the next closest patient based on propensity score. Propensity score matching analysis is mostly used in an observational study when the aim is to estimate a treatment effect but can also be used as in our study when evaluating the effect of a comorbidity as anemia or other type of intervention. Our study is illustrating one way to analyze registry data and in paper III we have used another way.

In this study (paper III) we have used univariable and multivariable logistic regression analysis to assess crude and independent associations between baseline characteristics and anemia. This type of analysis is mostly used in observational studies to adjust for potential confounding or other differences when the aim is not to estimate a treatment effect, when it is more accurate to use a propensity score matching analysis. The reason of using different analyzing models in paper II and III was to give examples how to analyze data from a register.

In paper IV we have evaluated the usefulness of EQ-5D and our results also suggest that the method used is important, as we found only small differences over time and between groups in the EQ-5D index so this measure does not give enough information about patients with HF. This is not merely a matter of sensitivity, but more a matter of the danger of using an index for composite measures and in complex groups. Small differences in the index are paralleled by notable differences between changes in specific dimensions. The results also illustrate the important feature of the Paretian classification, in giving an instrument to help identify differences within groups of patients. The Paretian classification has been used to explain differences before and after surgery with great success¹⁵².

Limitations

In all observational studies there are a number of limitations to consider when evaluating the results. Our studies (paper II and III) were extensively adjusted with different statistical methods, but still subject to unmeasured confounding. Our registry contains extensive baseline variables and with access to nationwide health and statistical registries. We cannot rule out inaccuracies in the registry data or residual unmeasured confounding. Some variables had missing data. This was handled by multiple imputations, which eliminates bias due to data not missing at random and increases external validity, but may compromise internal validity. Although our registry is nationwide it does not have complete coverage, and patients enrolled may be different than those not enrolled¹⁵³. Moreover the hemoglobin level was obtained as a single measure at hospital discharge/clinical visit, therefore, we cannot clarify and quantify the changes in hemoglobin to verify how many patients were affected with transitory anemia or hem dilution and we do not know the true etiology of anemia since the pathogenesis is still unclear even if a number of underlying causes contributing to anemia have been suggested.

In paper IV we have evaluated a different population of patients defined as those who had responded to EQ-5D at baseline, and of these patients 2853 (30%) were excluded because they had had no EQ-5D at follow up. However, this was mainly drop out for clinics and not for individual patients. One explanation was that it is not part of the clinical routine to assess HRQoL in patients with HF. However, the characteristics of the patients in our study were representative of HF patients in general according to a number of studies. As in other observational studies we cannot rule out inaccuracies in recorded data or unmeasured confounding variables.

CLINICAL IMPLICATIONS (paper I-IV)

Clinical implications (paper I)

In paper I it is described how a HF registry is created. A HF registry makes it possible to increase our knowledge of the management of HF patients and retrieve information about the extent to which clinicians follow recommended guidelines. By collecting follow-up data on mortality, morbidity, ongoing medication, functional capacity and estimates of quality of life, we can study outcome data in different subgroups of patients with HF and identify specific risk groups in whom appropriate treatment should be started early, as suggested in paper II and III. We can also evaluate whether quality of life or functional capacity is improved as a result of the treatment.

A HF register also enables comparisons of potential differences in clinical routines between hospitals and primary health care centers. Use of registry information may result in better management of HF patients with improved quality of life, reduced need for hospital care and reduced health costs. This should benefit patients, health care professionals, and society alike. Recently we have published a paper based on the SwedeHF database showing the difference between patients enrolled in SwedeHF and those not enrolled in terms of improved survival. The results are probably explained by demographic differences and better utilization of guidelines recommended cardiovascular and HF-medication¹⁵³.

Clinical implications (paper II and III)

So far all treatment studies trying to correct anemia or iron deficiency have failed in terms of beneficial effects regarding mortality and morbidity. This large observational study (Paper II) has demonstrated that the influence of anemia on mortality is greater in younger patients, in males with a more stable and moderate HFrEF (NYHA classes I and II and EF 30-39%). These findings are telling us that anemia is not only a prognostic marker but might also be a target for treatment in selected subgroups of HFrEF. We could suggest that the target for treatment of anemia should be the identified subgroups above, where we believe the greatest benefit of correction therapy might be obtained. The clinical implications in paper III evaluating anemia in patients with HFmrEF and HFpEF show results very similar to those mentioned in paper II evaluating patients with HFrEF. In both studies it has clearly been shown that the influence of anemia is greater in younger patients, in males with a milder NYHA class and better renal function. Again telling us that anemia is not only a prognostic marker but might also be a target for treatment in certain subgroups.

Clinical implications (paper IV)

First we can discuss if EQ-5D is the best patient reported outcome measure to use in patients with HF or if it is better to use more disease-specific instruments as Minnesota living with HF or Kansas City Cardiomyopathy Questionnaire. The drawbacks of using the Minnesota questionnaire are that it has been argued if it discriminates in patients with mild HF.

Another important finding is that self-assessed symptoms by the patients and their NYHA class did not agree. It has also been discussed if there should be specific questionnaires for males and females. Our study also highlights the Paretian classification as one tool to help to identify differences within groups of patients, but more studies are needed.

Another question, without any consensus today, when it is best to assess quality on life in patients with HF.

As you can see there are a lot of remaining questions to answer before we know how to best assess quality of life in HF patients.

ETHICAL CONSIDERATIONS

The establishment of the registry and registration and analysis of data for the different studies were approved by the Ethical review board and conform to the declaration of Helsinki. Individual patient consent was not required, but the patients were informed of entry into national registry and allowed to opt out as previously mentioned.

CONCLUSIONS

General conclusion

The SwedeHF is a valuable tool for improving the management of patients with HF, by using the online reports provided. By analyzing a common comorbidity in HF, anemia in patients with HFrEF, we found that anemia was prevalent with a high risk of adverse outcomes. Important predictors for anemia were higher age, male gender and renal dysfunction. The influence of anemia was associated with greater risk in younger patients, men and with

moderate HFrEF. Anemia was less prevalent in patients with HFmrEF compared to HFpEF but when present associated with greater risk of death and hospitalization. Evaluating the usefulness of EQ-5D, used in SwedeHF to assess quality of life, it was found that it was dependent on the method used. The four included papers show how a registry can be created and which different statistical analyses that can be used to analyze data from such a registry.

CONCLUSIONS I

- A HF registry makes it possible to increase our knowledge of the management of HF patients and retrieve information about the extent to which clinicians follow recommended guidelines.
- A HF register also enables comparisons of potential differences in clinical routines between hospitals and primary health care centers.
- In SwedeHF, the mean age of patients was 75 years, which corresponds to the age of HF patients in the community.
- All-cause mortality at 1 year in the SwedeHF was 21%.
- In SwedeHF 78% of women and 87% of men had undergone evaluation by echocardiography.

CONCLUSIONS II

- The prevalence of anemia in patients with HFrEF was 34%.
- The occurrence of anemia was strongly associated with increased mortality. Short one-year survival was 75% and the long-term 5-year survival was only 38%.
- Important independent predictors for anemia were higher age (>76 years), male gender and renal dysfunction (e-GFR < 60), but also severe HFrEF in NYHA class III-IV.
- In subgroups of anemia, as younger patients (<76 years), men and moderate HFrEF (NYHA classes I and II and EF 30-39%) the influence of anemia on mortality was significantly greater.

CONCLUSIONS III

- Anemia was present in nearly half of the patients with EF $\geq$ 40% and portended 40% increased risk of death.
- In HFmrEF vs. HFpEF, anemia was less common, but when present associated with greater risk of death and HF hospitalization.

CONCLUSIONS IV

- The results showed that the usefulness of EQ-5D is dependent on the method used.
- The EQ-5D index showed minor differences over time and between the two patient groups (HFrEF and HFpEF), while analyses of specific dimensions showed different patterns of change between the two groups.
- The Paretian classification additionally identified subgroups characterized by overall improvement or worsening.

FUTURE RESEARCH

The amount of data being collected in our quality registries and stored is vast and expanding rapidly. Our quality registries may generate new knowledge since they offers the potential to create an observational evidence base for clinical questions that would otherwise not be possible to evaluate due to high costs and issues of generalizability. The latter issue limits the application of conclusions derived from randomized trials performed on a narrow spectrum of patients who exhibit very different characteristics.

Due to the amount of data and complexity of handling these datasets, statistical expertise is of great importance to enable organizations to convert this vast resource into information and knowledge that helps them achieve their objectives.

A new and important concept for clinical research is R-RCT. The R-RCTs combine the benefits with RCTs and observational studies. Important to say is that R-RCTs are a complement to RCTs and do not replace RCTs. The R-RCTs calls for a simple hypothesis, one question and one answer and that the treatment options are available.

Regarding quality of life in the context of HF there are a number of remaining questions to answer. What is the best patient reported measure to use, generic or more disease-specific instruments. Should there be special instruments for men and women and when is the best time to assess quality of life in patients with HF after a hospitalization or worsening episode.

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APPENDIX A

Date of Admission/date of visit: _____ Date of discharge: _____

DEMOGRAPHY and LIFESTYLE AT ADMISSION (BOLD *= obligatory)

Caregiver *		1=Institutional Care, 2=Non Institutional Care, 3=Heart Failure Clinic
Clinic *		1= Dept of Internal medicine, 2= Dept of Cardiology, 3= Dept of Geriatrics
Reason for hospitalization/visit*		1=Worsening Heart Failure, 2=De novo Heart Failure, 3=Routine visit, 4=Other
Previous Chronic Heart Failure hospitalization *		0=No, 1=Yes<30 days, 2>= 30 days, 9=Unknown
Duration of Heart Failure *		1=< 6 months, 2>= 6 months
Tobacco – Smoking habits *		0=Never been smoking, 1=Quit smoking more than 6 months ago, 2=Quit smoking less than 6 months ago, 3=Smoking but not on a daily basis, 4=Smoking daily 9=Unknown
Tobacco – snuff habits *		0=Never, 1=Quit snuff more than 6 months ago, 2=Quit snuff less than 6 months ago, 3=Yes but not daily., 4=Yes daily, 9=Unknown
Alcohol * How many standard drinks do You drink a usual week?		0= < 1 standard drink per week or not at all, 1= 1-4 standard drinks per week, 2= 5-9 standard drinks per week, 3= 10-14 standard drinks per week, 4= 15 or more standard drinks per week, 9= Unknown
Alcohol* How often do You as a woman drink 4 standard drinks and You as a man 5 standard drinks or more at one time?		0= Never, 1= Less than once a month, 2= Every month, 3= Every week 4= Every day or almost every day, 9= Unknown

PRIMARY AETIOLOGY (BOLD *= obligatory)

Primary aetiology *		1=Hypertension, 2=Ischemic heart disease, 3=Dilated cardiomyopathy, 4=Known alcoholic cardiomyopathy 5=Heart valve disease, 6=Other, 9=Unknown
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PREVIOUS OR CURRENT DISEASES (BOLD *= obligatory)

Previous MI *		0=No, 1=Yes, 9=Unknown
Hypertension *		0=No, 1=Yes, 9=Unknown
Atrial fibrillation/flutter *		0=No, 1=Yes, 9=Unknown
Diabetes *		0=No, 1=Type 1, 2=Type 2 diet, 3=Type 2 insulin, 4=Type 2 oral anti diabetics drugs, 5=3+4, 9=Unknown
COPD *		0=No, 1=Yes, 9=Unknown
Heart Valve disease *		0=No, 1=Yes, 9=Unknown
Dilated cardiomyopathy *		0=No, 1=Yes, 9=Unknown
Other serious illness that causes deviations from treatment guidelines *		0=No, 1= Cancer, 2=Dementia 3=Other, 9=Unknown

PERFORMED PROCEDURES EVER (BOLD *= obligatory)

Revascularization *		0=No, 1=CABG, 2=PCI, 3=CABG+PCI, 9=Unknown
Heart Valve Surgery*		0=No, 1=Aortic, 2=Mitral, 3=Aortic+Mitral, 4= Other, 9=Unknown

DIAGNOSTICS AT DISCHARGE OR AFTER VISIT (BOLD *= obligatory)

ECG rhythm *		1=Sinus rhythm 2=Atrial fibrillation/flutter 3=Pacemaker rhythm 4=Other rhythm 9=Unknown	BNP *		
Left Bundle Branch Block (LBBB) *		0=No, 1=Yes, 9=Unknown	NT-proBNP *		
QRS-width *		ms	LVEF % *		1=Normal global LV-function (LVEF> 50 %), 2=Mild reduction LV-function (LVEF 40-49%), 3=Moderate reduction LV-function (LVEF 30-39 %), 4=Severe reduction LV-function (LVEF<30%), 9=Unknown
Heart Rate*		bpm	LVEF method *		1=ECHO 2=MR 3=Scintigraphy 9=Unknown

OTHER INVESTIGATIONS PERFORMED AT DISCHARGE OR AFTER VISIT (NON OBLIGATORY)

Chest X-ray for diagnosis		0=No, 1=Normal, 2=Pulmonary congestion, 3=Cardiomegaly, 4=2+3, 9=Unknown
Exercise ECG for diagnosis		0=No, 1=Exercise ECG, 2=6 min walk test, 3= Peak VO ₂ (ml/kg/min), 9=Unknown
Spirometry for diagnosis		0=No, 1=Yes, 9=Unknown

BIOMETRICS AND PHYSICAL SIGNS AT DISCHARGE OR AFTER VISIT (BOLD *= obligatory)					
B-HB *		g/L	BP diastolic *		mmHg
S-Creatinine *		µmol/L	Height*		cm
S-Potassium*		mmol/L	Weight *		kg
S-Sodium		mmol/L	e-GFR		Calculated automatically at registration on-line at specified creatinine, age, gender
BP systolic *		mmHg	NYHA classification *		1=NYHA I, 2=NYHA II, 3=NYHA III, 4=NYHA IV, 9=Unknown

PATIENT SELF RATED SYMPTOMS AT DISCHARGE OR AFTER VISIT (NON OBLIGATORY)					
Fatigue		1=No fatigue or limitation at ordinary physical activity. 2=Fatigue and slight limitation during ordinary activity. 3=Marked limitation in activity due to fatigue, even during less-than-ordinary activity (e.g. walking short distances >20-100 m) comfortable only at rest. 4=Severe limitations due to fatigue. Experiences fatigue even while at rest, mostly bed bound.	Usual activities		1= I have no problems when performing my usual activities 2= I have some problems when performing my usual activities 3= I am unable to perform my usual activities
Shortness of breath		1= No shortness of breath or limitation at ordinary physical activity 2= Shortness of breath and slight limitation during ordinary activity 3= Marked limitation in activity due to shortness of breath, even during less-than-ordinary activity (e.g. walking short distances, >20-100m) comfortable only at rest 4=Severe limitations due to shortness of breath. Experiences shortness of breath even while at rest, mostly bed bound.	Pain/discomfort		1= I have no pain or discomfort 2= I have moderate pain or discomfort 3= I have extreme pain or discomfort
Mobility		1= I have no problem in walking around 2= I have some problems in walking around 3= I am confined to bed.	Anxiety/depression		1= I am not anxious or depressed, 2= I am moderately anxious or depressed, 3= I am extremely anxious or depressed
Self Care		1= I have no problems with self care 2= I have some problems washing or dressing myself 3= I am unable to wash or dress myself	Quality of Life		0-100

TREATMENT AT DISCHARGE OR AT DATE OF VISIT (BOLD *= obligatory)					
ACE-Inhibitor *		0=No, 1=Yes, 9=Unknown	Pharmacological name of the ACE-inhibitor		
If target dose is not reached state reason		1=Side effects, 2=Active choice, 3=Planned, 9=Unknown	Substance: *	Dose: *	mg/24hrs
A2-blocker/ARB *		0=No, 1=Yes, 9=Unknown	Pharmacological name of the ARB		
If target dose is not reached state reason		1=Side effects, 2=Active choice, 3=Planned, 9=Unknown	Substance: *	Dose: *	mg/24hrs
If the patient is not treated with RAS – state reason *		1=Side effects, 2=Contraindication, 3= Active choice, 9=Unknown			
Betablocker *		0=No, 1=Yes, 9=Unknown	Pharmacological name of the Betablocker		
If target dose is not reached state reason		1=Side effects, 2=Active choice, 3=Planned, 9=Unknown	Substance: *	Dose: *	mg/24hrs
If the patient is not treated with a Beta receptor blocker – state reason *		1=Side effects, 2=Contraindication, 3= Active choice, 9=Unknown			
Mineralocorticoid Receptor Antagonists (MRA) *		0=No, 1=Yes, 9=Unknown	If MRA state * Dose: _____mg/24hrs if Loopdiuretics state * Dose: _____mg/24hrs or Dose: _____mg occasionally		
Mineralocorticoid Receptor Antagonists (MRA) Type *		0=Spironolactone 1=Eplerenone			
Diuretics *		0=No 1=Loop diuretics 2=Thiazides 3=1+2 9=Unknown			
Digitalis *		0=No, 1=Yes, 9=Unknown			
Statins *		0=No, 1=Yes, 9=Unknown			
i.v. inotropic support type*		0=Nej, 1=Dobutamine, 2=Levosimendan, 3=Milrinone, 4=Other, 9=Unknown			
Long acting nitrates *		0=No, 1=Yes, 9=Unknown			
Anticoagulants *		0=No, 1=Yes, 9=Unknown			
ASA or antiplatelet *		0=No, 1=Yes, 9=Unknown			
Number of non CV drugs		n			
Device therapy *		0=No, 1=Pacemaker, 2=CRT , 3=CRT-D, 4= ICD, 9=Unknown			
Participating/participated in organized physical training		0=No, 1=Yes, 2=Previous participation, 9=Unknown			
Deceased during hospitalization*		0=No, 1=Yes			
PLANNED FOLLOW-UP (BOLD *= obligatory)					
Follow up – level of care *		1=Hospital 2=Primary care, 3=Other, 9=Unknown			
Follow up – HF Clinic *		0=No, 1=Yes, 9=Unknown			

ORIGINAL PAPERS I-IV

Papers/Publications

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