



UMEÅ UNIVERSITY

Bridging the gap between clinical trials and clinical practice

Sacubitril-valsartan in
heart failure as a model

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To my family

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Original papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals as assigned below.

- I. Norberg H, Bergdahl E, Lindmark K. Eligibility of sacubitril-valsartan in a real-world heart failure population: a community-based single-centre study. *ESC heart failure*. 2018; 5:337-43.
- II. Norberg H, Pranic V, Bergdahl E, Lindmark K. Differences in medical treatment and clinical characteristics between men and women with heart failure - a single-centre multivariable analysis. *European journal of clinical pharmacology*. 2020; 76:539-46.
- III. Norberg H, Bergdahl E, Lindmark K. Safety and Tolerability of Initiating Maximum-Dose Sacubitril-Valsartan in Patients on Target Dose Renin-Angiotensin System Inhibitors. *Cardiovascular therapeutics*. 2019:6745074.
- IV. Norberg H, Bergdahl E, Ängerud KH, Lindmark K. A systematic approach for introduction of novel treatments to a chronic patient group: sacubitril-valsartan as a case study. *European journal of clinical pharmacology*. 2020.

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Abstract

When novel treatments prove more effective than standard therapies, a swift and effective implementation is needed to reach cost-effectiveness and to benefit eligible patients. Meanwhile, women and elderly are often under-represented in clinical trials, which creates a knowledge gap on how to optimize treatment in clinical practice. The arrival of the angiotensin receptor-neprilysin inhibitor sacubitril-valsartan to patients with chronic heart failure and reduced ejection fraction (HFrEF) offered an opportunity to develop and test a new systematic introduction approach, as well as to investigate eligibility and management of sacubitril-valsartan in clinical practice. The aims of this thesis were to investigate obstacles to implement sacubitril-valsartan in a real-world heart failure population, as well as to develop a systematic and effective method to implement novel treatments in patients with chronic disease.

With an observational cross-sectional study design, patients were retrospectively included if they had a heart failure diagnosis, living within the Umeå University Hospital catchment area, and had at least one visit at the Heart Centre or Department of internal medicine between January 2010 and March 2016. Eligibility to sacubitril-valsartan was based on the enrollment criteria applied in the landmark trial, PARADIGM-HF. We showed that the primary obstacle to implement sacubitril-valsartan was that only a quarter of the real-world HFrEF population was eligible. The most prominent difference was that real-world patients were significantly older compared with the PARADIGM-HF population. Disproportionally many patients, especially women, were ineligible for sacubitril-valsartan due to intolerance of renin-angiotensin system inhibitors in target doses. With multivariable linear regression analyses, we showed that the lower target doses in women were explained by biological sex differences.

Management of heart failure treatment involve many titration steps that risk stressing the resources of both healthcare and patients. We prospectively investigated a direct switch to maximum dose sacubitril-valsartan in patients who tolerated target dose renin-angiotensin system inhibitors (equivalent to enalapril 10 mg twice daily). We showed that the simplified introduction was safe and generally well tolerated during the first year.

The systematic introduction approach is a seven-step procedure:

- 1) define a few main criteria
- 2) primary scan patients with the one or two main criteria using computerized medical records/databases/clinical registries
- 3) identify patients applying the other predefined criteria
- 4) evaluate if any examinations/laboratory test updates are required

- 5) summon identified patients with an information letter
- 6) discuss treatment with the patient and prescribe if appropriate
- 7) follow-up on initiated therapy and evaluate the process.

We evaluated the approach with a mixed method, including both a case study of the sacubitril-valsartan implementation and an interview study with qualitative content analysis. The new systematic introduction approach effectively implemented sacubitril-valsartan in clinical practice, by identifying eligible patients with limited resources and time. The patients were overall satisfied with the new approach and their confidence in healthcare was maintained.

In conclusion, we found that the strict inclusion criteria in the PARADIGM-HF trial would exclude a majority of patients with heart failure if they are implemented and that these criteria have an inherent bias versus the old and the frail, which in turn disproportionately affects women. We further found that patients who are on maximum recommended dose of renin-angiotensin system inhibitors can be safely switched to maximum dose sacubitril-valsartan and that our method of systematic introduction was effective in implementing sacubitril-valsartan to a heart failure population.

The approach is a promising example of how to reduce the gap between clinical trials and clinical practice in patients with chronic disease.

Abbreviations

ACEI	Angiotensin-Converting Enzyme Inhibitor
ANP	A-type (atrial) Natriuretic Peptide
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor–Neprilysin Inhibitor
ATLAS	Assessment of Treatment with Lisinopril and Survival study
BIOSTAT-CHF	BIOlogy Study to TAIlored Treatment in Chronic Heart Failure
BNP	B-type (brain) Natriuretic Peptide
CER	Comparative Effectiveness Research
CI	Confidence Interval
CIBIS-II	Cardiac Insufficiency Bisoprolol Trial II
CNP	C-type Natriuretic Peptide
COPERNICUS	Carvedilol Prospective Randomized Cumulative Survival Study
CR/XL	Controlled release/extended release
DTC	Drug and Therapeutics Committee
ECG	Electrocardiography
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EMPHASIS-HF	Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
EPHESUS	Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
ESC	European Society of Cardiology
FDA	U.S. Food and Drug Administration
HFmrEF	Heart Failure with mid-range Ejection Fraction

HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
HR	Hazard Ratio
IMPRESS	Inhibition of MetalloProtease by BMS-186716 in a Randomized Exercise and Symptoms Study
LBQ 657	sacubitrilat
LCZ 696	sacubitril-valsartan
MERIT-HF	Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure
MRA	Mineralocorticoid Receptor Antagonist
NPR	Natriuretic Peptide Receptor
NT Council	New Therapies Council
NT-proBNP	N-terminal pro-B type natriuretic peptide
NYHA	New York Heart Association
OCTAVE	Omapatrilat Cardiovascular Treatment vs. Enalapril
OVERTURE	Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events
PARADIGM-HF	Prospective Comparison of Angiotensin Receptor–Nepriylsin Inhibitor with Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure
PASS	Post-Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
RAAS	Renin-Angiotensin-Aldosterone System
RALES	Randomized Aldactone Evaluation Study
SHIFT	Systolic Heart failure treatment with the If inhibitor ivabradine Trial
SOLVD	Studies Of Left Ventricular Dysfunction
TLV	Dental and Pharmaceuticals Benefits Agency
Val-HeFT	Valsartan Heart Failure Trial

Enkel sammanfattning på svenska

När nya läkemedel och behandlingar godkänns har de studerats i kliniska studier och ofta visat bättre effekt än redan tillgängliga behandlingar. Därför är det viktigt att dessa effektivare behandlingar snabbt och effektivt börjar användas i vården. Nya behandlingar innebär dock ofta en ökad kostnad. För att använda samhällets resurser på bästa sätt gäller det att rätt patienter får tillgång till relevant behandling inom rimlig tid.

Att introducera ett nytt läkemedel i vården kallas implementering. Vanligen innebär detta att patienten måste komma till doktorn för att få en bedömning om en ny behandling kan vara lämplig. Detta kräver att den enskilde doktorn har kunskap om den nya behandlingen och dessutom är uppmärksam på om just den patient de har framför sig skulle kunna ha nytta av behandlingen. Detta är ett särskilt stort problem när den nya behandlingen är tänkt för patienter med kronisk sjukdom, som ofta behandlas inom både primär- och slutenvård, med flera olika läkare. Det tar därför ofta flera år innan nya läkemedel implementerats i denna patientgrupp.

Vidare finns det ett känt problem att kvinnor och äldre är underrepresenterade i kliniska studier. Detta skapar ett kunskapsglapp mellan de kliniska studierna och den kliniska vardagen, eftersom det inte är samma patienter som studerats som sedan ska använda behandlingen i klinisk vardag, s.k. klinisk praxis.

Med tillgång till elektroniska journaler, databaser och register borde implementering till patienter med kronisk sjukdom kunna göras på ett mer systematiskt och effektivt sätt. Godkännandet av det nya läkemedlet sacubitril-valsartan för behandling av kronisk hjärtsvikt innebar en möjlighet att studera hur implementeringen av läkemedel kan förbättras till kroniskt sjuka. Mer specifikt att testa en ny systematisk introduktionsmetod, samt att undersöka vilka patienter som skulle kunna ha nytta av läkemedlet och hur införandet bäst bör utformas i klinisk praxis.

Syftet med denna avhandling är att undersöka hinder för att implementera sacubitril-valsartan i klinisk praxis, och att utveckla en systematisk och effektiv metod för att implementera nya behandlingar hos patienter med kronisk sjukdom.

Avhandlingen baseras på journaldata från Norrlands universitetssjukhus, Umeå, Sverige. Vi studerade alla patienter med en hjärtsviktsdiagnos boende inom sjukhusets upptagningsområde och som hade minst ett vårdbesök på Hjärtcentrum eller Medicinkliniken mellan januari 2010 och mars 2016. För att

undersöka vilka patienter som skulle kunna ha nytta av sacubitril-valsartan användes studiekriterierna från den så kallade PARADIGM-HF-studien, där sacubitril-valsartan jämfördes mot standardbehandling hos patienter med hjärtsvikt. Vi visade att det främsta hindret för att implementera sacubitril-valsartan var att endast en fjärdedel av våra patienter uppfyllde alla kriterier för att bli erbjuden behandlingen. Den mest framträdande skillnaden var att Umeå-patienterna var betydligt äldre jämfört med patienterna i PARADIGM-HF-studien. Vi visade också att oproportionerligt många patienter, särskilt kvinnor, blev bortvalda eftersom de inte redan behandlades med fulldos basbehandling med läkemedel som hämmar renin-angiotensin-systemet (RAS-hämmare). Vi visade att biologiska könsskillnader, som att kvinnorna generellt sett var äldre, vägde mindre och hade sämre njurfunktion, förklarade den lägre dos hjärtsviktsmedicin som kvinnorna ofta stod på. Kvinnor har därför inte samma biologiska förutsättningar för att tolerera lika höga doser som män.

Att implementera sacubitril-valsartan enligt de behandlingsrekommendationer som finns innebär flera dosjusteringar. I tillägg till dosjusteringar av övrig hjärtsviktsmedicinering riskerar det att kräva ytterligare resurser från både sjukvården och patienten själv. I vår studie valde vi därför att direkt byta över till fulldos sacubitril-valsartan hos patienter som redan stod på fulldos RAS-hämmare. Vi visade att denna förenklade introduktion var säker och överlag tolererades väl av patienterna, under de 12 månader som de följdes upp.

Den nya systematiska introduktionsmetoden består av sju steg:

- 1) bestäm några få huvudkriterier
- 2) gör en primär selektion av patienter med hjälp av elektroniska journaler
- 3) gör en noggrann selektion av patienter utifrån de resterande förbestämde kriterierna
- 4) utvärdera om nya undersökningar eller laborationsprover krävs
- 5) kalla identifierade patienter med ett informationsbrev
- 6) diskutera behandlingen med patienten och sätt in behandling till lämpliga patienter
- 7) följ upp patienterna och utvärdera processen.

Vi utvärderade hur metoden fungerar i kliniken med en fallstudie och en intervjustudie. Fallstudien visade att metoden effektivt implementerade sacubitril-valsartan genom att identifiera patienter som hade nytta av behandlingen enligt objektiva kriterier och med begränsade resurser. Intervjustudien visade att patienterna generellt sett var nöjda med metoden att bli kallad för att diskutera en ny behandling med ett informationsbrev och att de har fortsatt högt förtroende för vården.

Sammanfattningsvis, fann vi att de strikta kriterierna i PARADIGM-HF-studien sällar bort majoriteten av patienter med hjärtsvikt i klinisk vardag. Kriterierna slår särskilt hårt mot äldre och sköra patienter, vilket i sin tur påverkar andelen kvinnor oproportionerligt mycket. Vi fann också att patienter som behandlas med fulldos RAS-hämmare kan byta över till fulldos sacubitril-valsartan med bibehållen säkerhet och att vår metod för systematisk introduktion effektivt implementerade sacubitril-valsartan hos en hjärtsviktspopulation.

Vår nya systematiska metod för att implementera ny behandling är ett lovande exempel på hur det är möjligt att minska glappet mellan kliniska studier och klinisk vardag hos patienter med kronisk sjukdom.

Introduction

To bridge the gap between clinical trials and clinical practice

When novel treatments prove more effective than conventional therapies, a swift and effective implementation is needed to reach cost-effectiveness and to benefit eligible patients. The implementation process works like a bridge between clinical trials and initiation in clinical practice.

Implementation to patients with chronic disease is a challenge since they are often treated both in primary and/or secondary care settings. Previous studies have shown that the conventional approach to implement novel therapies, when waiting until the patient visits the doctor, often takes several years [1-13]. In this thesis, we investigated possibilities of using electronic medical record systems, databases and local registries in a more systematic way to introduce novel treatments.

Further, there is a general problem with under-representation of women and elderly in clinical trials [14, 15]. The under-representation creates a knowledge gap in how to optimize treatment for women and elderly. We do not know whether the studied treatments are as effective and safe in real-world patients as the study result show since the majority of included patients often are middle-aged men.

The regulatory approval of sacubitril-valsartan in patients with chronic heart failure and reduced ejection fraction (HFrEF) offered an opportunity to develop and test a new systematic introduction approach, as well as to investigate eligibility and management of sacubitril-valsartan in clinical practice. Therefore, the implementation of sacubitril-valsartan in patients with chronic HFrEF was used as a model in this thesis.

To better understand the obstacles of heart failure treatment, including sex and age-related differences in heart failure, a summary of the heart failure syndrome and the development of available heart failure medications is first presented.

Heart failure

Heart failure is a major global health problem that causes high morbidity, mortality and costs [16]. It is a leading cause of death and hospitalizations in developed countries. More than 37.7 million adults are living with heart failure worldwide and the number is increasing [17-19].

In Sweden, the prevalence of heart failure is about 2%, which corresponds to about 200,000 persons [20, 21]. The prevalence increases with time and age, with over 10% suffering from the disorder in those aged ≥ 85 years. The mortality is high with 20-30% 1-year all-cause mortality and about 50% 3-year all-cause mortality [16, 20]. Additionally, the 5-year survival rate from the first recorded heart failure diagnosis is about 48% [21, 22]. A survival rate as low as several common cancer diseases [23].

The financial burden of heart failure is immense for the healthcare systems owing to the high amount of hospitalizations, rehospitalizations and polyclinic visits. In developed countries the costs for heart failure care is estimated to about 1-3% of the total healthcare budget [18]. In Sweden, the annual cost for managing patients with heart failure is estimated to 5.0-6.7 billion Swedish krona [24].

Definition of heart failure

Heart failure is a serious condition in which the heart is unable to supply the peripheral tissues with enough blood and oxygen to meet their metabolic demands at normal filling pressures [25]. The diagnosis is defined as a clinical syndrome with typical symptoms and signs caused by cardiac dysfunction, resulting in a reduced cardiac output and/or increased intracardiac pressures [26-28]. The diagnosis is established through symptoms and signs (see Figure 1), as well as echocardiography examination of any underlying cardiac cause. In cases where the diagnosis is in doubt, it is confirmed with a favorable effect of evidence-based heart failure medications.

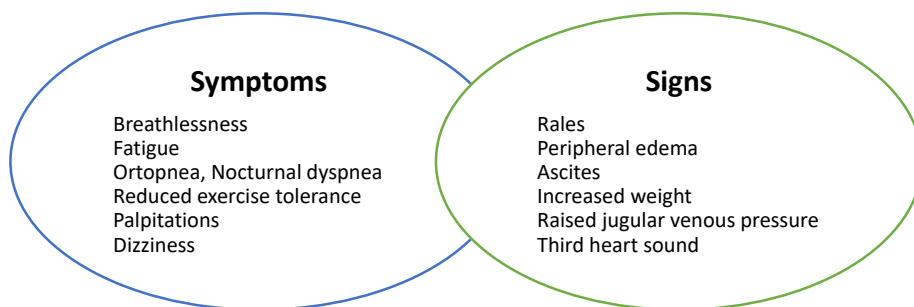


Figure 1. Typical symptoms and signs in heart failure.

Aetiology and classification of heart failure

Heart failure is an end stage syndrome caused by one or several underlying serious cardiovascular and/or non-cardiovascular diseases. The most frequent causes for heart failure in developed countries are ischemic heart disease, atrial fibrillation, and hypertension [25, 26, 29, 30]. In addition, cardiomyopathies, valvular heart diseases, and diabetes mellitus are common etiologic factors.

Heart failure can be classified according to several different aspects [25, 26]. Classification according to ejection fraction (EF) or systolic/diastolic function are the most common distinctions. The syndrome can also appear as an acute or chronic disorder. This thesis focuses mainly on patients with heart failure and reduced ejection fraction (HFrEF) in chronic condition.

Classification according to ejection fraction

EF is defined as the fraction of end-diastolic volume ejected from the left ventricle during each contraction [25]. Normal EF is considered as $\geq 50\%$ [26]. Patients suffering from typical symptoms and signs, yet having normal EF are referred to as heart failure with preserved EF (HFpEF). Patients with reduced EF $< 40\%$ are referred to as heart failure with reduced EF (HFrEF). The remaining patients with EF 40-49% represent a “grey area” defined as heart failure with mid-range EF (HFmrEF) (see Table 1).

Table 1. Classification of heart failure according to ESC guidelines [26].

Type of HF	HFrEF	HFmrEF	HFpEF
	Symptoms \pm Signs ^a	Symptoms \pm Signs ^a	Symptoms \pm Signs ^a
Criteria	EF $< 40\%$	EF 40-49%	EF $\geq 50\%$
	-	1. Elevated NPs ^b 2. Relevant structural heart disease (LVH and/or LAE) and/or diastolic dysfunction	1. Elevated NPs ^b 2. Relevant structural heart disease (LVH and/or LAE) and/or diastolic dysfunction

BNP, B-type natriuretic peptide; EF, ejection fraction; ESC, European Society of Cardiology; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; NPs, Natriuretic peptides; NT-proBNP, N-terminal pro-B type natriuretic peptide.

^aSigns may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics. ^bBNP > 35 pg/ml and/or NT-proBNP > 125 pg/mL.

Systolic versus diastolic heart failure

Systolic heart failure differs from diastolic heart failure in several aspects [25]. In systolic heart failure, the contractility of the left ventricle is impaired, resulting in a reduced EF. When the left ventricle is unable to contract with enough force, remodeling occurs. This causes chamber dilation and volume overload leading to forward failure with increased afterload. Ischemic heart disease, cardiomyopathies, and heart valve diseases are most often responsible for development of systolic heart failure.

In diastolic heart failure on the other hand, EF is normal [25-27]. A diastolic heart has an increased ventricle stiffness due to impairment in the relaxation and filling of the left ventricle. This causes remodeling with ventricular hypertrophy, leading to pressure overload and backward failure with increased pulmonary pressure and lung edema.

Acute versus chronic heart failure

Acute heart failure is recognized as a rapid onset or worsening of heart failure symptoms/signs (within 24 hours) [26, 27]. It requires urgent hospital admission with emergency management. Most often acute heart failure occurs as an acute decompensation of chronic (also called congestive) heart failure but can also occur, *de novo*, as a first occurrence. Acute heart failure can be due to e.g. acute myocardial infarction, dilated cardiomyopathy, and acute pulmonary edema secondary to cardiac dysfunction. In chronic heart failure, the patients are in stable condition.

Functional classes

To describe the severity of heart failure symptoms and to guide patient management the New York Heart Association (NYHA) functional classification is often used (see Table 2) [26]. Higher classification is associated with poorer prognosis.

Table 2. New York Heart Association (NYHA) functional classification [31].

NYHA class	Symptoms
I	No symptoms and no limitation of ordinary physical activity.
II	Mild symptoms (breathlessness, fatigue, or palpitations) and slight limitation during ordinary activity.
III	Marked limitation of physical activity. Comfortably only at rest.
IV	Severe physical limitations with symptoms even at rest.

Diagnosis of heart failure

In patients with suspected heart failure a detailed history and physical examination is essential [26]. Electrocardiography (ECG) and natriuretic peptides (NT-proBNP ≥ 125 pg/mL or BNP ≥ 35 pg/mL) are used to assess any cardiac abnormalities. Patient with normal ECG and natriuretic peptides are unlikely to suffer from heart failure. Patients with abnormalities in ECG or natriuretic peptides should undergo echocardiography.

Echocardiography is an ultrasound technic where a transducer is used to send and receive the reflecting sound [32]. The method is used to assess chamber dimensions, wall thickness, systolic and diastolic function [32, 33]. Systolic function is primarily estimated with EF, while estimation of the diastolic function is more complex. Echocardiography is a widely available, rapid, convenient, low-cost, reproducible and accurate method [33, 34]. However, the variability between investigators can be significant and has to be considered.

Pathophysiology

Development of manifest heart failure is usually a slow process [25, 32, 35, 36]. In the beginning, several complex compensation mechanisms activate the heart, kidneys, blood vessels, muscles and other organs to maintain cardiac output. When stroke volume reduces, the body first activates the neurohormonal system, including the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, and vasoactive peptides (such as antidiuretic hormone and natriuretic peptides). This result in vasoconstriction, sodium and water retention, increased heart rate, increased myocardial contractility and abnormal cell growth. The heart itself tries to compensate through the Frank-Starling law and ventricular remodeling.

All these compensation mechanisms are vital in short-term life-threatening situations, such as major bleeding or severe dehydration [35]. However, when activated over time the increased preload and afterload drive heart failure progression and creates a “vicious cycle” (see Figure 2).

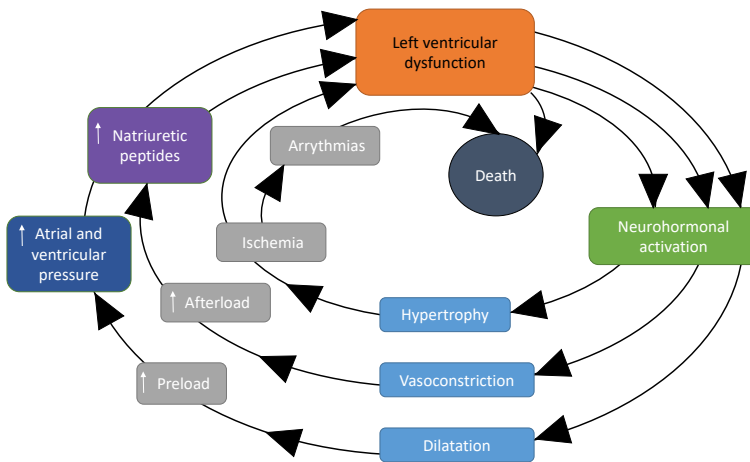


Figure 2. The progression of heart failure.

Frank-Starling mechanism

The Frank-Starling law describes how the heart can maintain the stroke volume during acute injury or compensatory in chronic heart failure [25, 32, 36]. It is defined as the ability of the heart to change its force of contraction and thereby increase stroke volume due to an elevated preload (see Figure 3). The higher contraction force is generated through increased stretch of the myocytes in the left ventricle. The Frank-Starling curve can reach a plateau if the heart reaches its maximum capacity where increased stretch no longer results in increased contractility [25].

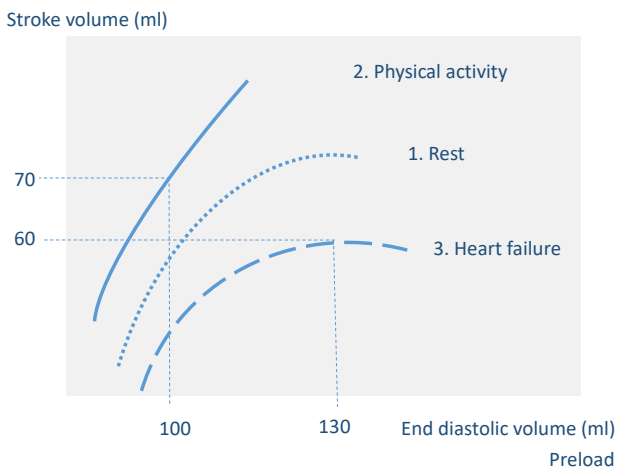


Figure 3. The Frank-Starling curve.

Ventricular remodeling

The heart has the ability to compensate by left ventricle remodeling at increased preload and afterload [25, 36]. Volume overload (e.g. by mitral or aortic insufficiency, or in dilated cardiomyopathy) often cause left ventricular dilatation. In contrast, at pressure overload (e.g. by arterial hypertension or aortic stenosis) the left ventricle develops concentric hypertrophy instead. Like other compensatory mechanisms, hypertrophy is unable to preserve pump function over time [32, 36]. Eventually the oxygen supply becomes insufficient, leading to impaired myocardial function and progression of heart failure.

Sympathetic nervous system

In heart failure, reduced cardiac output and blood pressure activates the sympathetic nervous system, which increase blood volume, myocardial contractility and heart rate [25, 32, 36]. The positive inotropic (increased contractility) and chronotropic (tachycardia) effect cause perfusion redistribution to maintain blood flow to vital organs. The redistribution is controlled by peripheral vasoconstriction and central vasodilatation, which activates RAAS.

Renin-Angiotensin-Aldosterone System

RAAS is activated by a pressure-mediated reflex, caused by reduced stretch of the glomerular afferent arteriole and decreased chloride levels in macula densa [25, 32, 36]. Macula densa is placed in the juxtaglomerular cells of the kidneys, inside the glomerular capillaries, and releases renin into the blood. Renin release can also be stimulated through the sympathetic nervous system, yet the two systems are independently regulated. Plasma renin transforms inactive angiotensinogen (produced in the liver) to angiotensin I, after which angiotensin-converting enzyme (ACE) (mainly released from the pulmonary capillaries) converts angiotensin I to angiotensin II (see Figure 4).

Angiotensin II is a vasoconstrictor and induces salt and water retention both by itself and via aldosterone [25, 36]. Aldosterone is a hormone released from the adrenal cortex, which increases sodium and water reabsorption in the kidneys. In addition, angiotensin II induces noradrenaline excretion from sympathetic nerve terminals and inhibits parasympathetic activity. Angiotensin II also mediates myocardial cell hypertrophy, fibrosis, and myocyte apoptosis, which may contribute to ventricular remodeling and progressive cardiac dysfunction in heart failure.

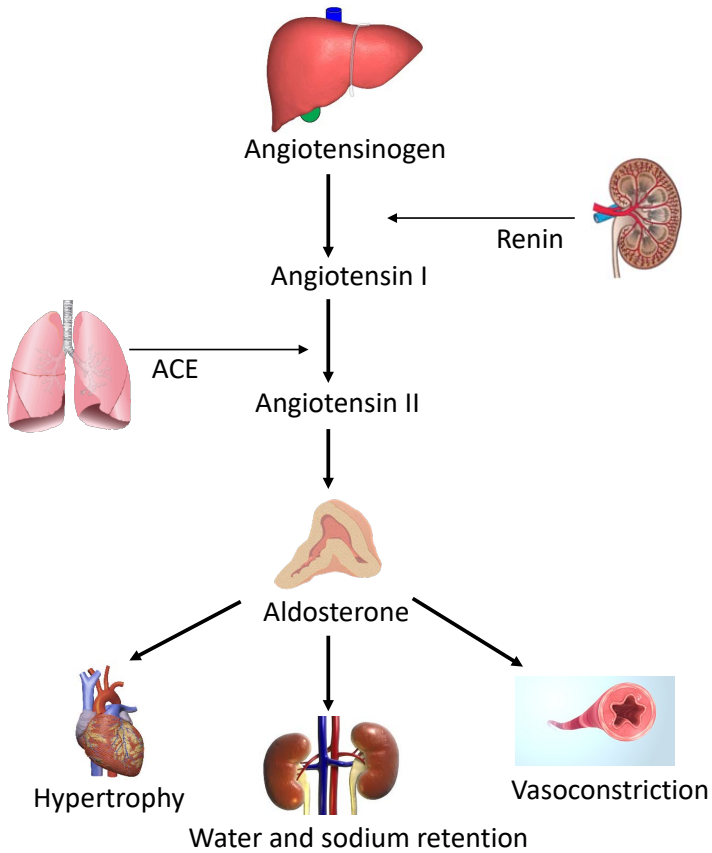


Figure 4. The renin-angiotensin-aldosterone system. ACE, angiotensin-converting enzyme.

Natriuretic peptides

Natriuretic peptides promote the previously described compensatory mechanisms through vasodilatation, natriuresis and diuresis [25, 36]. Natriuretic peptides are endogenous peptide hormones that are released as a response to atrial and ventricle wall stretch due to pressure or volume overload [25, 35, 36]. A-type (atrial) natriuretic peptide (ANP) and B-type (brain) natriuretic peptide (BNP) play a key role in heart failure. C-type natriuretic peptide (CNP) is also involved by enhancing vasodilatation and endothelial permeability. The prohormones proANP and proBNP are cleaved to ANP, BNP, and the biological inactive N-terminal (NT)-proANP and NT-proBNP [37, 38]. ANP is primarily secreted from the atria, while BNP is primarily secreted from the ventricles. Thus, BNP and NT-proBNP are used in diagnosis and prognosis of heart failure.

Natriuretic peptides generate the hypotensive effects (vasodilatation, enhance diuresis with natriuresis) through binding to membrane bound natriuretic peptide receptors (NPR-A, NPR-B) [25, 35, 39]. Stimulation of the NPR-receptors initiates a complex signaling system with synthesis of cyclic guanosine monophosphate (cGMP) and downstream kinases (see Figure 5). Natriuretic peptides reduce cardiac hypertrophy and remodeling, as well as inhibit RAAS, endothelin secretion, antidiuretic hormone and sympathetic tone. All these effects contribute to decreased preload and afterload, and so forth, natriuretic peptides have a protective role in heart failure.

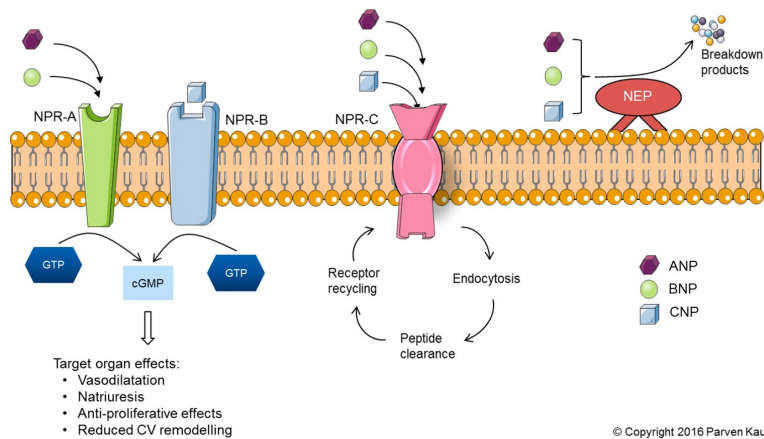


Figure 5. The mechanism of action and pathways of metabolism of ANP, BNP and CNP. Copyright © 2015 Parven Kaur. Reproduced from [40] with permission from BMJ Publishing Group Ltd. ANP, A-type natriuretic peptide; BNP, B-type peptide; cGMP, cyclic guanosine monophosphate; CNP, C-type peptide; CV, cardiovascular; GTP, guanosine triphosphate; NEP, neprilysin; NPR, natriuretic peptide receptor.

Natriuretic peptides are eliminated from the circulation by two pathways. The main pathway in healthy individuals is clearance via NPR-C receptors (see Figure 5) [41-43]. However, in patients with symptomatic heart failure the NPR-C receptors are saturated (or downregulated due to chronic high natriuretic peptides levels) and thus hydrolysis by neprilysin becomes the key degradation pathway. Neprilysin is a membrane-bound metalloproteinase or neutral endopeptidase, mainly presented in the proximal tubular cells in the kidneys but are also found in the brain, eyes, lungs, intestines and fibroblasts [42].

Unfortunately, as chronic heart failure progresses to more severe stages, the compensatory effects of natriuretic peptides are diminished [39]. This is probably due to reduced levels of active forms of BNP, reduced target organ responsiveness and over-activated counter-regulatory hormones of RAAS and the sympathetic

nervous system. When the protective mechanisms of natriuretic peptides have declined to critical levels, the preload and afterload start to increase and the heart deficiency become even more pronounced.

Sex and age-associated differences in heart failure

Sex differences

The overall lifetime risk to develop heart failure is similar between men and women; however, in etiology, pathophysiology, comorbidities, and presence of symptoms there are marked sex differences [44-46]. In general, women with heart failure are older than men, more likely to have poor renal function, be more symptomatic (higher NYHA class), have a history of hypertension and to present with HFpEF [20, 45-56]. Women have less ischemic heart disease, whereas men are more likely to develop HFrEF after a myocardial infarction and hence, develop a more sudden heart failure diagnosis. Further, women report a lower quality of life than men do, with a 10-point difference in median Kansas City Cardiomyopathy Questionnaire Clinical Summary Score despite similar EF and NT-proBNP [57]. Women also experience adverse drug reactions more often and severe than men [58, 59]. For example in heart failure therapy, women have a higher risk of drug-induced torsade de pointes, and cough and elevated creatinine with ACE inhibitors (ACEI) [58, 60].

The most prominent factors that predispose women to HFpEF are sex differences in cardiac structure, function, and metabolism, vascular aging, and immune system response (see Figure 6) [44, 45]. Women have smaller left ventricular chambers and consequently lower stroke volumes, yet with a higher resting heart rate the cardiac output sustains comparable to men. Lower cardiac output in women results in lower hepatic flow and lower glomerular filtration rate (GFR) [61]. Cardiomyocyte hypertrophy and left ventricular remodeling are also more pronounced in women [44, 45]. Hypertension and diabetes pose a higher risk to develop heart failure for women. Many women also suffer from coronary disease. However, women tend to suffer from angina pectoris with microvascular and endothelial dysfunction leading to a higher degree of hypertrophy and fibrosis [44, 46]. Coronary microvascular dysfunction has been assumed associated with HFpEF. Men, on the other hand, are predisposed to macrovascular coronary artery disease and myocardial infarction, which are a well-known precursor to HFrEF. Additionally, inflammation probably play a key role in HFpEF. As women have stronger immune responses, higher levels of C-reactive protein, and enhanced inflammatory pathways in the myocardium, female patients are predisposed to HFpEF. Women are also more likely to have comorbidities that are involved in inflammation, such as hypertension, diabetes, chronic kidney disease, obesity, iron deficiency, and preeclampsia.

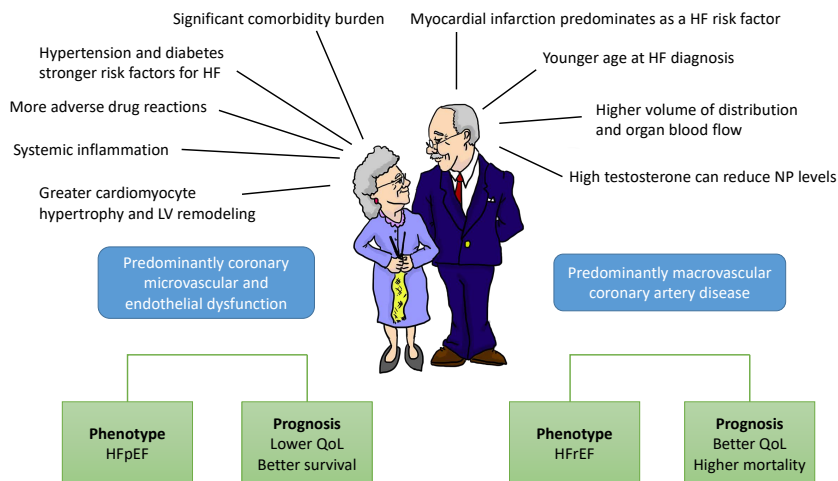


Figure 6. Sex differences in heart failure. HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; NP, natriuretic peptide; QoL, quality of life.

Sex differences affect the pharmacokinetics of drugs [58, 59, 62, 63]. Women have for example different body composition with higher proportion of body fat, lower body weight, organ blood flow, and renal function, longer gut transit time, and higher cytochrome P450 3A4 enzyme activity than men. This explains the longer effect duration of lipophilic drugs (e.g. amiodarone, diazepam, metoprolol) due to the increased volume of distribution in female patients. For hydrophilic drugs (e.g. aspirin, enalapril, atenolol, digoxin, metformin) the volume of distribution is smaller, with higher plasma concentrations and stronger effects in women compared with men.

The effect of sex hormones are not entirely understood, however, oestrogens have been assumed to play a protective role against cardiovascular disease in women [46]. In patients with heart failure, high levels of testosterone (in men and post-menopausal women) can reduce the level of natriuretic peptides.

The mortality risk differs between the sexes, with higher age-adjusted mortality in men than in women with heart failure. Previous studies have shown 20-30% higher all-cause mortality risk in men versus women with HFrEF [53-56, 64]. Mortality has declined over time for both sexes, with a greater decline in male compared with female heart failure patients [64-66]. Further, the Framingham Heart Study showed a 36% lower age-adjusted mortality in women than in men [67]. Median survival was longer in women than in men (3.2 vs. 1.7 years, respectively). Worse prognosis was shown in both men and women with ischemic cause of heart failure compared with non-ischemic etiology, yet women had lower all-cause mortality in both etiologic groups.

Women receive less guideline-recommended heart failure medications and in lower doses compared with men, as well as fewer diagnostic procedures, such as echocardiography and EF measurements [51-53]. Sex differences in prescription of heart failure treatment can be influenced by gender of physicians and patients. In a German cross-sectional study, male physicians prescribed significantly less heart failure medications and in lower doses to female patients, while female physicians had no significant treatment differences [68].

Age-related changes

The prevalence and incidence of heart failure increases with age [20]. This is due to that we live longer, better management of acute coronary syndrome and other co-morbidities, as well as physiological and structural changes caused by aging [69-71]. The age-related changes enhance the risk of multimorbidity, which in turn drives the development of heart failure. Elderly also have higher risk for adverse drug reactions, due to age-associated changes and polypharmacy [70, 72]. HFpEF is more common among the elderly compared to younger patients [73, 74].

The foremost pharmacokinetic change in the elderly is impaired renal function [72, 75]. A significant decrease in GFR, tubular secretion, renal mass, and renal blood flow cause reduced elimination of hydrophilic drugs (e.g. aspirin, enalapril, atenolol, digoxin, metformin), leading to elevated plasma concentrations. Elderly also have less total body water and more body fat compared to younger adults. This alters the volume of distribution, causing elevated plasma concentrations of hydrophilic drugs and prolonged elimination of lipophilic drugs (e.g. amiodarone, diazepam, metoprolol). In addition, very old adults often lose weight and become frail. Hence, patients with low body weight receive higher doses per unit body weight compared to heavier patients, which reduces drug tolerance.

Pharmacodynamical changes in the elderly can occur at either receptor level or by altered homeostasis [72, 75]. Diminished response in β -adrenoreceptor activity has been shown in elderly, probably caused by increased levels of serum noradrenaline, which mediates downregulation of the receptors. The decreased effect of beta-blockers, however, is probably associated with lower renin levels in older patients. Further, elderly have a reduced cardiovascular response to postural changes, which increase the risk of orthostatic hypotension after standing up, due to a reduction in blood pressure homeostasis. Unlike younger adults that increase the heart rate to compensate for postural changes, elderly tend to increase stroke volume instead [76]. This increases the risk of orthostatic hypotension, also during antihypertensive drug treatment.

Changes in cardiac structure and function also have a significant role in elderly patients with heart failure [71]. Among the most important changes are impaired elasticity of the aorta and arterial system, resulting in higher systolic blood pressure and left ventricular hypertrophy [70, 76]. Heart rate and sinoatrial node transmission decreases with age. Further, calcium metabolism and regulation are reduced in elderly, which result in impaired myocardial relaxation and diastolic dysfunction [71]. In summary, age-related changes are involved in heart failure progression and affects how elderly tolerate heart failure drugs.

Under-representation of women and elderly in clinical trials

Women and elderly are underrepresented in heart failure studies. Two recent systematic reviews confirmed that HFREF trials conducted between 2001-2016 only included about 24% women or 0.5-0.6 of prevalence-corrected participation, respectively [14, 15]. This should be compared with the real-world prevalence of women with heart failure, which is generally between 47-53 % in patients with heart failure and 36-42% in HFREF [21, 51, 77-79]. Depending on the inclusion criteria, surveys and registries often show a more selected and homogenous patient population with 28-37% women with heart failure and 21-29% with HFREF [13, 56, 80]. An overview of landmark heart failure trials and their proportion of women and elderly is shown in Table 3.

Regarding age, several heart failure studies have focused explicitly on the therapeutic effects in the elderly [81-85]. However, most landmark heart failure trials that current treatment guidelines are based upon mainly include younger patients (see Table 3). The average age in heart failure trials is 65 years [15], while the mean age at first heart failure diagnosis in clinical practice is 12 years older (overall 77 ± 12 years; women 80 ± 10 years vs. men 75 ± 11 years, $P < 0.001$) [20, 21, 65]. This discrepancy between patients included in clinical trials and real-world patients were also highlighted in a review from 2012 where four widely prescribed drugs (pioglitazone, rosuvastatin, risedronate, and valsartan) were investigated [86]. The majority of included randomized controlled trials had included less than half the expected real-world population of patients aged 65 years and older.

Strict inclusion criteria in clinical trials often result in fewer women and elderly patients being eligible, which limit the external validity [87]. Strict criteria may cause either direct (upper age limit) or indirect exclusion (comorbidities, polypharmacy, or reduced life expectancy) of women and elderly [87, 88]. Exclusion due to reduced life expectancy is always justified but other criteria can be questioned. To exclude due to an upper age limit, physical disabilities, drug use (other than drugs interfering with the study drug), or comorbidities not related to a reduced life expectancy, creates a more homogenous study population

and limits the generalizability [88]. Therefore, older patients who manage to fulfill all inclusion criteria in clinical trials are often not representative of patients treated in routine care [89].

Table 3. Selected landmark heart failure trials and their representation of elderly and women.

Trial	Year	Study treatment^a	N	Mean age (years)^b	Key age-related inclusion	Women (%)
SOLVD	1991	Enalapril	2569	61	Age <80; EF ≤ 35%	20
CIBIS II	1999	Bisoprolol	2647	61 ± 11	Age 18–80; EF ≤35%	19
MERIT-HF	1999	Metoprolol	3991	64 ± 10	Age 40-80; EF ≤40%	22
RALES	1999	Spironolactone	1663	65 ± 12	EF ≤35%	27
ATLAS	1999	Low-dose vs. high-dose lisinopril	3793	64 ± 10	EF ≤30%	20
COPERNICUS	2001	Carvedilol	2289	63 ± 12	EF ≤25%	21
Val-HeFT	2002	Valsartan	5010	62 ± 11 ACEI, 67 ± 10 no ACEI	EF ≤40%	20
EPHESUS	2003	Eplerenone	6632	64 ± 11	EF ≤40%	28
CHARM-Alternative	2003	Candesartan	2028	66 ± 11	EF ≤40%	32
SHIFT	2010	Ivabradine	6558	60 ± 11	EF ≤35%	24
EMPHASIS-HF	2011	Eplerenone	2737	69 ± 8	EF ≤35%	22
PARADIGM-HF	2014	Sacubitril-valsartan vs. Enalapril	8442	64 ± 12	Run-in with Sacubitril-valsartan/Enalapril in target dose; EF ≤35%	22

ACEI, angiotensin-converting enzyme inhibitor; ATLAS, Assessment of Treatment with Lisinopril and Survival study; CIBIS-II, Cardiac Insufficiency Bisoprolol Trial II; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study; EF, ejection fraction; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; MERIT-HF, Metoprolol Randomized Intervention Trial in Congestive Heart Failure; PARADIGM-HF, Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; RALES, Randomized Aldactone Evaluation Study; SHIFT, Systolic Heart failure treatment with the If inhibitor ivabradine Trial; SOLVD, Studies Of Left Ventricular Dysfunction; Val-HeFT, Valsartan Heart Failure Trial.

^aVersus placebo if not otherwise specified.

^bMean ± standard deviation, if not otherwise specified.

Some heart failure studies, such as the PARADIGM-HF (Prospective Comparison of Angiotensin Receptor–Nepriylsin Inhibitor (ARNI) with ACE inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure), required that eligible patients should tolerate a fixed target dose of the study drugs before inclusion, which resulted in a low frequency of women (22%) and a relatively young patient population (mean age 64 years) [90]. Hence, women included in clinical trials with strict entry criteria are also not representative for the typical female patients in clinical practice.

Moreover, women face several barriers for full participation in clinical trials. The U.S. Food and Drug Administration (FDA) has identified barriers for inclusion in their work for women’s health [91], such as

- i)* unintentionally exclusion of women due to enrolment criteria potentially not needed to define the study population - e.g. upper age limit,
- ii)* knowledge gap in differences in disease aetiology and pathophysiology,
- iii)* investigator and sponsor avoidance of female patients due to the perception that it will take more time and money to recruit them,
- iv)* family responsibilities limiting women’s ability to commit to study follow-up.

Considerations of how to achieve an appropriate enrolment in clinical trials would be preferred already in the study design and early enrolment stages. Federal agencies and institutes, such as FDA, European Medicines Agency (EMA) and National Institutes of Health, have adopted guidelines and strategies to increase the inclusion of women and other minorities in clinical studies [92-95]. Hopefully efforts like these will enhance female and elderly participation in clinical trials.

In summary, the underrepresentation of women and elderly in clinical trials creates a knowledge gap of how to treat these patients with the best quality of care. Biological sex differences, such as body composition, blood flow, cytochrome P450 enzyme activity, sex hormonal fluctuations, as well as age-related changes might lead to different efficacy and safety of the same drug. Women and elderly need to be included in clinical trials in a more representative proportion that reflect the underlying disease distribution in clinical practice.

Development of standard heart failure medications

The last three decades ACEI, angiotensin receptor blockers (ARB), beta-blockers and mineralocorticoid receptor antagonists (MRA) have been developed and implemented as standard of care in patients with HFrEF [26, 96, 97]. Multiple large-scale randomized controlled trials have shown beneficial treatment outcomes in reducing mortality and morbidity in patients with HFrEF and have transformed the management of heart failure from previously available treatment with digitalis, vasodilator drugs and diuretics. Decrease in all-cause mortality for all four groups of standard heart failure medications is shown in Figure 7.

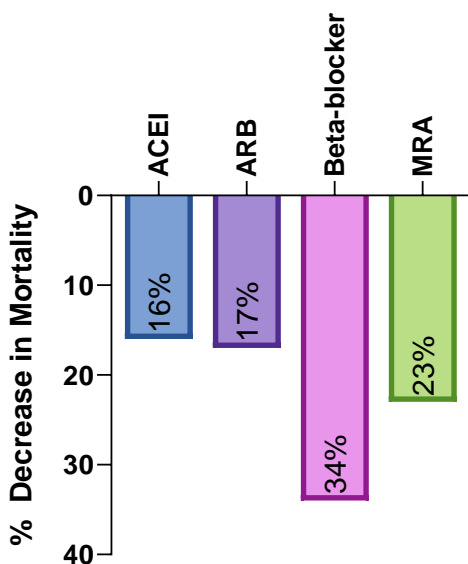


Figure 7. Drugs that reduce mortality in patients with heart failure and reduced ejection fraction. Based on results from SOLVD-Treatment, CHARM-Alternative, CIBIS II, MERIT-HF, COPERNICUS, RALES, EPHESUS, EMPHASIS-HF [98-105]. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

ACE inhibitors/Angiotensin receptor blockers

The first ACEI study that showed prognostic enhancement in HFrEF was CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) in 1987 [106]. Enalapril was compared with placebo in patients with NYHA class IV, where enalapril presented a 40% risk reduction in mortality. In the following SOLVD-Treatment (The Studies Of Left Ventricular Dysfunction–Treatment) trial in 1991, enalapril was compared with placebo in patients with NYHA class II-III [98]. Enalapril showed a 16% risk reduction in all-cause death and 26% risk reduction in the combined endpoint death or hospitalizations for chronic heart failure.

A common side effect of ACEI is dry cough in 5-20% of patients, as well as hypotension, renal impairment and hyperkalemia [60, 107]. The cough may be caused by elevated levels of bradykinin and substance P when their degradation by ACE is inhibited [96]. ARBs do not alter ACE activity and have shown lower rates of cough and other adverse events, as well as similar mortality and morbidity reduction compared with placebo or ACEI [26, 81, 96, 99, 108-110]. ARBs are recommended in HFrEF patients who do not tolerate ACEI [26]. In addition, concomitant use of ACEI and ARBs increase the risk of hyperkalemia and have not persistently shown reduced mortality in HFrEF [108, 111, 112]. ACEI plus ARBs in combination are therefore only recommended to patients with symptomatic HFrEF receiving a beta-blocker but unable to tolerate MRA, and must be followed-up closely [26].

Beta-blockers

Beta-blockers improve survival and reduce morbidity in chronic heart failure [26]. The mechanism of beneficial effects from beta-blockers in HFrEF is reduction of the sympathetic nervous system activity through decreased levels of catecholamines [96]. Presently, beta-blockers are recommended to all patients with symptomatic HFrEF and accepted as a standard care medication in stable heart failure [26, 97]. The implementation of beta-blockers in heart failure therapy, however, took about 20 years from the first observations of survival in 1979 before it was approved as treatment for heart failure in 1997 [113]. The slow adoption was due to the negative inotropic effect, which in turn increase the risk of heart failure decompensation. In 1995, Hall et al. [114] showed that the negative effects on ventricular function during metoprolol treatment were focused to the initial month of treatment. The beneficial effects were presented during long-term therapy - 18 months - and resulted in reduced heart rate, improved EF, regression of left ventricular mass, reduced ventricular remodeling, and improved ventricular geometry with less spherical form of the left ventricle. Hence, beta-blockers are recommended to be introduced in clinically stable heart failure patients and to apply a “start low, go slow” management until the target dose, or maximum tolerated dose, is achieved [26].

Beta-blockers differ between substances and the ones with proven effects in HFrEF are bisoprolol, metoprolol controlled release/extended release (CR/XL), and carvedilol [113]. In 1999, two large randomized controlled trials investigated bisoprolol and metoprolol CR/XL versus placebo [100, 101]. The CIBIS II (Cardiac Insufficiency Bisoprolol Study II) was performed in patients with NYHA class III-IV, EF 35% or less, receiving standard therapy with diuretics and ACEI [100]. Bisoprolol showed a 34% risk reduction on all-cause mortality and 20% risk reduction on all-cause hospitalization compared with placebo. In MERIT-HF (Metoprolol CR/XL Randomized Trial In congestive heart failure) metoprolol

was compared with placebo in patients with NYHA class II-III, EF 40% or less and optimal standard therapy including diuretics and ACEI [101]. The trial was stopped early because metoprolol showed a 34% risk reduction in total mortality compared with placebo. Further, in 2001 COPERNICUS (Carvedilol Prospective RaNdomIzed CUmulative Survival trial) studied carvedilol versus placebo in patients with severe chronic heart failure and EF less than 25% and appropriate conventional therapy with diuretics and ACEI/ARB [102]. The carvedilol group showed a 35% decrease in the risk of death compared with the placebo group.

Mineralocorticoid receptor antagonists

When ACEI were approved, it was first assumed that their mechanism of action would be enough to inhibit RAAS and the harmful effects of aldosterone in heart failure [103]. Unfortunately, the plasma aldosterone level has been observed to return to baseline during long-term angiotensin II suppression. For that reason, in 1999, the RALES (Randomized Aldactone Evaluation Study) trial aimed to investigate if the MRA spironolactone would significantly reduce all-cause mortality in patients with severe heart failure in addition to an ACEI [103]. Patients were included if they were in NYHA class IV, had EF 35% or less, were being treated with an ACEI and a loop diuretic. Eligible patients were randomized to either spironolactone or placebo. Spironolactone showed a 30% risk reduction in all-cause death and a 30% reduction in the risk of hospitalization for cardiac causes compared with placebo. Further, in 2003, the EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) trial evaluated the effects of eplerenone on morbidity and mortality in patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure [105]. Patients were randomized to either eplerenone or placebo. Inclusion criteria were acute myocardial infarction within 3 to 14 days, EF 40% or less, and heart failure. The eplerenone group had a 15% risk reduction in death from any cause compared with placebo. Later in 2011, the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) trial assessed the effects of the MRA eplerenone in patients with HFrEF, EF 35% or less, and milder symptoms with NYHA class II [104]. Patients were randomized to either eplerenone or placebo, in addition to standard therapy. The primary endpoint, cardiovascular death or hospitalization for heart failure, showed a 37% risk reduction in the eplerenone group compared with placebo. The eplerenone group also showed a 23% lower risk of cardiovascular death. So forth, heart failure guidelines recommend an MRA to patients with HFrEF who are still symptomatic despite treatment with an ACEI and a beta-blocker [26, 97].

Development of neprilysin inhibitors

Despite the effective standard heart failure treatments described above mortality is still high in heart failure and new effective medications are needed. Another interesting compensatory system to explore for possible therapeutic targets has been the natriuretic peptides. Two strategies have been tested to try to moderate the protective effects of natriuretic peptides in patients with HFrEF [115]. First, administration of exogenous natriuretic peptides were conducted with nesiritide (human recombinant BNP) but without outcome improvements [116]. The second approach was to inhibit the catabolic enzyme, neprilysin, which is the main degradation pathway of ANP, BNP and CNP in patients with heart failure [115]. Other vasoactive peptides that are substrates for neprilysin are for example angiotensin I and II, bradykinin, substance P, and endothelin-1.

The first neprilysin inhibitor that was tested in humans was candoxatril [117]. First patients with essential hypertension were investigated [118]. Forty patients were treated with candoxatril or placebo in 28 days. No significant effect on blood pressure was observed even though natriuretic peptide levels increased significantly. A possible explanation was elevated angiotensin II levels due to neprilysin inhibition that may counteract the vasodilating effects of ANP and BNP.

The next step was to combine a neprilysin inhibitor with RAAS inhibition to suppress angiotensin II elevation and aldosterone release [117]. Omapatrilat, a vasopeptidase inhibitor that inhibit both neprilysin and ACE, was first developed. In early studies omapatrilat showed some improvements in composite endpoints of death and hospitalization, such as IMPRESS (Inhibition of MetalloProtease by BMS-186716 in a Randomized Exercise and Symptoms Study) where omapatrilat was compared with lisinopril in patients with HFrEF [119]. However, later and larger studies did not confirm these results. The OVERTURE (The Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) trial, randomized patients with NYHA class II-IV to either enalapril or omapatrilat [120]. Omapatrilat showed non-inferiority in reducing the primary endpoint death or heart failure hospitalization compared with enalapril. Finally, in the hypertension trial, OCTAVE (Omapatrilat Cardiovascular Treatment vs. Enalapril), omapatrilat was found to more than 3-fold the incidence of angioedema compared with enalapril [117, 121]. Consequently, the development of omapatrilat was disrupted.

To reduce the risk of angioedema the solution became to switch the ACEI to an ARB instead [122]. The angioedema was probably caused by elevated levels of bradykinin and substance P during ACE and neprilysin inhibition with omapatrilat. By using an ARB, bradykinin and substance P can still be metabolized by ACE and the risk of angioedema is minimized. The first substance to accomplish the combination of a neprilysin inhibitor and an ARB was LCZ 696, later renamed sacubitril-valsartan. An overview of the mechanisms and effects of drugs acting on the natriuretic peptide system is shown in Figure 8.

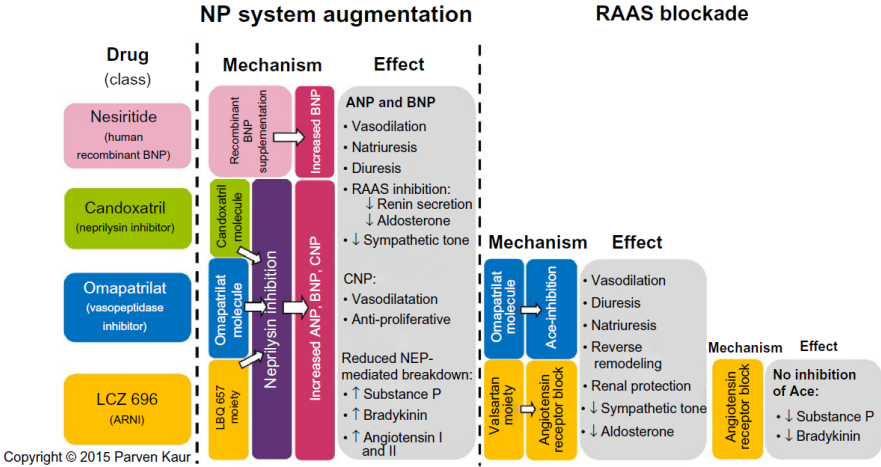


Figure 8. Overview of the mechanisms and effects of nesiritide, candoxatril, omapatrilat, and sacubitril-valsartan. Nesiritide and candoxatril only augment the NP system, with candoxatril increasing ANP, BNP, and CNP compared with isolated BNP augmentation by nesiritide. Omapatrilat and sacubitril-valsartan have dual system activity (NP and RAAS), noting the additional benefit of sacubitril-valsartan in preventing accumulation of substance P and bradykinin because it has no effect on ACE. Downward arrows indicate reduction. Upward arrows indicate increase. Copyright © 2015 Parven Kaur. Reproduced from [123], licensed under CC-BY-NC 3.0, <http://creativecommons.org/licenses/by-nc/3.0/>. ACE, angiotensin-converting enzyme; ANP, A-type natriuretic peptide; ARNI, angiotensin receptor-neprilysin inhibitor; BNP, B-type natriuretic peptide; CNP, C-type natriuretic peptide; LCZ 696, sacubitril-valsartan; NEP, neprilysin; NP, natriuretic peptide; RAAS, renin-angiotensin-aldosterone system.

Sacubitril-valsartan

Sacubitril-valsartan is a first-in-class dual-acting ARNI. The FDA and EMA approved sacubitril-valsartan in 2015, for the treatment of chronic HFrEF.

Pharmacodynamics

Sacubitril-valsartan is a supramolecular sodium salt complex of the neprilysin inhibitor prodrug sacubitril and the ARB valsartan, with a 1:1 molar ratio [124, 125]. The chemical structure is shown in Figure 9.

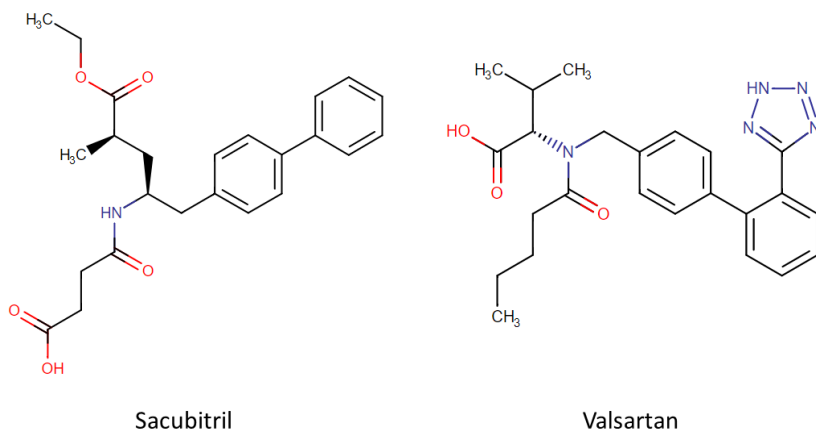


Figure 9. Chemical structure of sacubitril-valsartan.

The crystalline structure is stable and highly water-soluble and dissociates after oral administration into sacubitril and valsartan [124, 125]. Sacubitril is metabolized (by enzymatic cleavage of its ethyl ester) to the active neprilysin inhibitor LBQ 657 (sacubitrilat). Since neprilysin play a key role in degradation of natriuretic peptides in patients with heart failure, inhibition of the enzyme increases natriuretic peptide levels [126]. Increased ANP and BNP levels generate vasodilatation, natriuresis and diuresis, as well as decreases sympathetic tone, aldosterone levels, cardiac hypertrophy and fibrosis. As previously known, valsartan binds to the angiotensin II type-1 receptor and inhibits aldosterone release and further RAAS activity (see Figure 10).

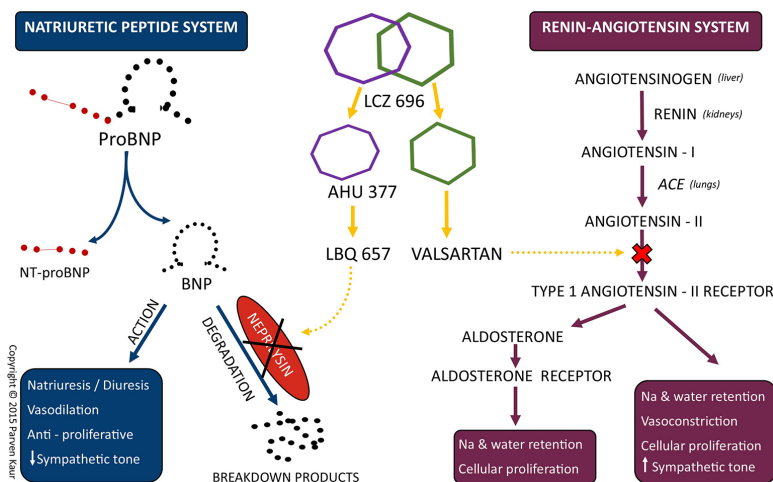


Figure 10. Schematic representation of the mechanism of action of sacubitril-valsartan on the natriuretic peptide and renin–angiotensin–aldosterone system. Copyright © 2015 Parven Kaur. Reproduced from [127] with permission from BMJ Publishing Group Ltd. ACE, angiotensin-converting enzyme; AHU 377, sacubitril; BNP, B-type natriuretic peptide; LBQ 657, sacubitrilat; LCZ 696, sacubitril-valsartan; Na, sodium; NT-proBNP, N-terminal pro B-type natriuretic peptide.

Pharmacokinetics

The pharmacokinetic parameters for sacubitril-valsartan and its active metabolite sacubitrilat are summarized in Table 4. Sacubitril-valsartan is rapidly absorbed after oral administration [125, 128, 129]. The bioavailability is over 60% for sacubitril and 23% for valsartan. However, one important aspect is that the valsartan in sacubitril-valsartan is about 40% more bioavailable than the valsartan in other marketed tablets. In sacubitril-valsartan 97/103 mg twice daily, the ARB component is equivalent to 160 mg valsartan alone. Steady state is reached in three days following twice-daily dosing of sacubitril-valsartan. Food intake does not affect the therapeutic effect of sacubitril-valsartan. The active metabolite sacubitrilat has limited ability to cross the blood brain barrier (0.28%).

Table 4. Summary of pharmacokinetics of sacubitril-valsartan.

	Sacubitril	Sacubitrilat	Valsartan
Bioavailability	>60%		>23%
Time to peak	0.5 h	2 h	1.5 h
Protein binding	94-97%	94-97%	94-97%
Distribution	103 L		75 L
Metabolism	Metabolized to sacubitrilat	No significant metabolism	20%
Elimination	Primarily as sacubitrilat	Kidney 52-68%, Feces 37-48%	Kidney 13 %, Feces 86 %
Half-life elimination	1.4 h	11.5 h	9.9 h

Special populations

Patients with only mild renal impairment (estimated glomerular filtration rate [eGFR] 60-90 ml/min/1.73 m²) do not require any dose adjustments of sacubitril-valsartan [128, 129]. In patients with eGFR 30-60 ml/min/1.73 m², a starting dose of 24 mg/26 mg twice daily is recommended. For patients with eGFR <30 ml/min/1.73 m², caution is advised due to very limited clinical experiences.

Mild hepatic impairment do not require any dose adjustments of sacubitril-valsartan [128, 129]. However, there is so far limited clinical experiences in patients with moderate hepatic impairment. Caution and a starting dose of 24 mg/26 mg twice daily is recommended. Sacubitril-valsartan is contraindicated in severe hepatic impairment, biliary cirrhosis and cholestasis.

In a small, open-label, single oral dose (400 mg) in 36 healthy participants, the effect of age and sex on the pharmacokinetics of sacubitril-valsartan was investigated [130]. Elderly patients (>65 years) had an increased exposure (area under the curve) to both sacubitrilat and valsartan by 42% and 30%, respectively. The elimination half-lives were prolonged with about 3-4 hours for both substances. The pharmacokinetic differences of sacubitril-valsartan are probably associated with lower renal function in the elderly. Further, no differences in pharmacokinetic parameters were shown between male and female patients. In a post-hoc analysis of the PARADIGM-HF trial, efficacy and safety was superior in the sacubitril-valsartan group compared with the enalapril group across all age categories [131]. In summary, no dose adjustments are recommended due to age or sex [26, 97].

Sacubitril-valsartan in clinical trials

Sacubitril-valsartan has been studied in a number of clinical trials. Trials have been performed, or are ongoing, in patients with hypertension [132, 133], HFpEF [134, 135], acute heart failure [136, 137], heart failure after myocardial infarction [138], but the so far most guideline-changing results have been shown in patients with HFrEF and NYHA class II-III in the landmark trial, PARADIGM-HF [90].

PARADIGM-HF

PARADIGM-HF aimed to investigate whether sacubitril-valsartan or enalapril had superior long-term effects on morbidity and mortality in patients with chronic HFrEF [90]. The primary composite endpoint was cardiovascular death or hospitalization for heart failure.

This randomized, double-blind, multicenter trial is one of the largest heart failure trials performed so far, involving 1043 centers in 47 countries. In total, 10,513 patients entered the run-in phase and 8442 underwent randomization. Eligible patients were at least 18 years old, NYHA class II-IV, EF 40% or less (which was changed to 35% or less in Dec 2010). Patients were also required to have BNP >150 pg/mL (or NT-proBNP ≥600 pg/mL) or, if they had a heart failure hospitalization within the previous 12 months, a BNP >100 pg/mL (or NT-proBNP ≥400 pg/mL). Before the run-in phase, patients had to tolerate a stable dose of a beta-blocker and an ACEI/ARB equivalent to at least 10 mg of enalapril daily.

Patients were excluded if they had symptomatic hypotension, a systolic blood pressure <100 mm Hg at screening (or 95 mm Hg at randomization), an eGFR <30 ml/min/1.73 m², a serum potassium level >5.2 mmol/L at screening (or >5.4 mmol/L at randomization), or a history of angioedema or unacceptable side effects during treatment with ACEI/ARB.

The run-in phase started with a switch from the patients' ordinary ACEI/ARB to enalapril in target dose, 10 mg twice daily. Patients who tolerated this regimen were switched to sacubitril-valsartan for an additional 4-6 weeks (initially at 100 mg twice daily, which was increased to 200 mg twice daily). Patients without unacceptable side effects during the two run-in periods were randomized in a 1:1 ratio to receive either sacubitril-valsartan (200 mg twice daily) or enalapril (10 mg twice daily). To reduce the risk of angioedema due to overlapping ACE and neprilysin inhibition, enalapril was discontinued one day before sacubitril-valsartan initiation and sacubitril-valsartan was discontinued one day before randomization.

Out of the initially 10,513 patients, 1102 patients discontinued the enalapril run-in phase and 977 patients discontinued the sacubitril-valsartan phase. Finally, 4187 patients were randomized to the sacubitril-valsartan group, while 4212 patients were randomized to the enalapril group. Baseline characteristics were balanced between the study groups. Mean age was 64±11 years, 21 % were female, 66% were white, 60% had a history of ischemic cardiomyopathy, median NT-proBNP was about 1600 pg/mL, the majority had NYHA class II or III (70% and 24%, respectively). Mean doses of sacubitril-valsartan and enalapril at the last follow-up were 375±71 mg and 18.9±3.4 mg, respectively.

The primary endpoint, cardiovascular death and hospitalization for heart failure, was reduced with 20% in the sacubitril-valsartan group compared with the enalapril group (hazard ratio [HR] 0.80; 95% confidence interval [CI], 0.73-0.87; $P<0.001$). The number needed to treat to prevent one primary event was 21. Further, the secondary outcome death from any cause was reduced with 16% (HR 0.84; 95% CI, 0.76-0.93; $P<0.001$). The trial was stopped early, after a median follow-up of 27 months, due to overwhelming benefit with sacubitril-valsartan.

Regarding safety, 12% of the patients discontinued treatment because an adverse event during the run-in phase, with a higher withdrawal rate in the enalapril group compared with the sacubitril-valsartan group. Patients in the sacubitril-valsartan group reported symptomatic hypotension more frequently than the enalapril group. On the other hand, the enalapril group was more likely to have cough, elevated serum creatinine (≥ 221 $\mu\text{mol/L}$), and serum potassium (>6 mmol/L). No difference in risk of angioedema was shown between the treatment arms (sacubitril-valsartan 0.2% vs. enalapril 0.1%, $P=0.13$).

Sacubitril-valsartan in heart failure guidelines

Based on PARADIGM-HF, sacubitril-valsartan was rapidly included in European and American heart failure guidelines after regulatory approval. The European Society of Cardiology (ESC) and American Heart Association guidelines, recommend sacubitril-valsartan as a replacement for an ACEI in patients with chronic HFrEF who remain symptomatic and have EF $\leq 35\%$ despite optimal treatment with maximum tolerated evidence-based doses of an ACEI, a beta-blocker, and a MRA [26, 97].

Patients who tolerate an ACEI/ARB in doses equivalent to enalapril 10 mg twice daily can be switched to sacubitril-valsartan [26]. A starting dose of 49/51 mg twice daily is recommended in 2-4 week, before the dose is doubled to 97/103 mg twice daily as tolerated by the patient [128, 129].

Sacubitril-valsartan should not be co-administered with an ACEI/ARB [26, 97, 128, 129]. Due to the rare but potential risk of angioedema, the ACEI should be withheld for at least 36 hours before sacubitril-valsartan is initiated. Sacubitril-valsartan is contraindicated to patients with a history of angioedema. Further, treatment should not be initiated to patients with high risk of hyperkalemia (serum potassium >5.4 mmol/l) or hypotension (systolic blood pressure <100 mm Hg).

Safety monitoring: post-authorisation

When novel drugs attain regulatory approval and clinicians start to prescribe them in routine care, there is still limited data on effectiveness and safety in real-world settings. Safety monitoring systems for post-authorisation evaluation has therefore been developed.

To receive marketing approval for a novel drug, EMA performs a careful assessment that the benefits outweigh their risks [139]. This is to ensure that patients can use the medicine they need without being exposed to unacceptable side effects. The assessments are based on results from clinical trials where patients are often carefully selected and efficacy and safety have only been able to study for a limited time. After authorisation, the drug is prescribed to a large number of patients with other comorbidities and concomitant medicines. Rare or unexpected side effects may emerge in these new settings. Therefore, it is vital to monitor the safety of all drugs on the market. The European Union (EU) legislation from 2012 requires that pharmaceutical companies, national regulatory authorities and EMA perform a number of post-authorisation safety monitoring processes after a drug has been authorized for use. The post-authorisation system run by EMA is explained in further details on their website [140].

Pharmacovigilance

To monitor the safety of a medicine once it is on the market is called pharmacovigilance [139, 140]. Pharmacovigilance is defined as the science and activities to detect, assess, understand and prevent adverse effects or any other medicine-related problem. EMA is responsible for the EU pharmacovigilance system and cooperates with the EU Member States and the European Commission. To assess and monitor the safety of human medicines, EMA has a dedicated committee called the Pharmacovigilance Risk Assessment Committee (PRAC).

Reporting side effects

Healthcare professionals and patients are encouraged to report suspected side effects with any medicine on the market [141, 142]. The reports give vital information on medicines used in clinical practice. Regulatory authorities analyse the reports together with all other available information of the medicine to make sure that the benefits remain greater than their risks. If necessary, the regulatory authorities take action for restrictions or, in worst case, withdrawal of the medicine.

Medicines under additional monitoring

After regulatory approval in the EU, all medicines are closely monitored. However, some medicines are labelled with a black inverted triangle (▼) in the product information, which means that the medicine is subject to additional monitoring [142]. The goal with additional monitoring is to enhance reporting of suspected side effects for medicines for which the clinical evidence is still limited. Patients and healthcare professionals are strongly encouraged to report any suspected side effects with these medicines. By collecting information of the use of medicines in an early stage, it is possible to evaluate their benefit-risk profiles in routine care. Additional monitoring status is always given to drugs that contain:

- i) a new active substance,
- ii) biological drug (such as vaccine or a medicine derived from blood plasma),
- iii) if it has received conditional approval,
- iv) if the pharmaceutical company is required to perform additional studies (e.g. to provide data on long-term use or rare side effects seen during clinical trials),
- v) if it is authorised with specific obligations to record suspected adverse drug reactions.

Other drugs can also be given additional monitoring labelling if advised from PRAC.

Post-authorisation safety studies

Another example of a safety-monitoring tool in the EMA pharmacovigilance system is post-authorisation safety studies (PASS) [143]. PASSs are studies performed after a drug has received regulatory approval. They are conducted to evaluate a drug's safety and benefit-risk profile, assess the effectiveness of risk-management measures, and support regulatory decision-making. PASSs can be either clinical studies or non-interventional studies.

PASSs can be imposed or voluntary [143]. Imposed PASSs must be performed by the pharmaceutical company if the drug authorization is granted with specific obligations or other studies that PRAC requests the company to perform. PRAC is responsible for assessing the protocols and results of imposed PASSs.

Comparative Effectiveness Research

A research field for real-time post-marketing evaluation of new drugs, that has become more important with the increasing number of available drugs, is Comparative Effectiveness Research (CER). CER compares benefits and/or harms of two active forms of health interventions in real-world settings under routine clinical conditions [144-146]. Traditionally, CER is performed after completion of a phase III placebo controlled trial [145]. Different methods can be used in CER studies [147, 148], such as;

- Systematic review or Meta-analysis - analyse published studies,
- Decision analysis - mathematical simulation using published evidence,
- Observational cohort, cross-sectional or case-control studies - analyse clinical data, and
- CER-focused randomized controlled trials or ‘practical clinical trials’ - compare intervention to standard-of-care in representative population randomized to control and intervention groups.

The possibilities to use medical records, registry data or already published evidence in CER are both cost-effective and less time-consuming than performing interventional studies [147]. Except that CER have a key role in head-to-head comparative studies, they also offer a second chance to conduct studies that include women, elderly, and/or patients with multiple morbidities, that are usually under-represented in clinical trials, despite that these patients are the primary drug users [146].

Sweden provides unique opportunities to perform observational CER due to the civic registration system involving a 12-digit personal identity number, unique to all Swedish citizens, as well as the many nationwide health registers and use of electronic medical records [149]. Several frameworks for CER methodology have been published; one example is a recent study of how to monitor new drugs in Sweden [149]. The authors promote a model using data collected in routine care to continuously monitor effectiveness, safety and cost-effectiveness of novel drugs. The framework involves a prospectively determined protocol, preferably conducted in cooperation between regulators, payers and pharmaceutical companies. In each recruitment cycle, new users are included and added to the cohort, to continuously increase the study sample size. The data are sequentially analysed according to a pre-specified statistical analysis plan.

Implementation of novel treatments in Swedish healthcare

Parallel with the EMA safety monitoring and CER, the novel medicine needs to be efficiently implemented to eligible patients in routine care before patients can gain benefit. Different countries have developed different implementation processes. A short summary of the Swedish process for managed introduction of new medicines and local implementation process is presented below.

National process for managed introduction

In Sweden, a national process for managed introduction of new medicines is used to attain an equal, cost-effective and safe use of novel therapies for all patients in the country. The national process derives from an initiative by the regional drug and therapeutics committee (DTC) in Region Stockholm due to the exponential development and costs of novel medicines during the last decades [150, 151]. The national model has been refined and is now managed by the Swedish Association of Local Authorities and Regions. The DTCs, several governmental agencies and the pharmaceutical industry collaborate in this process. Not all new medicines are included in the national process for managed introduction. The national process is applied for specialist medicines and medicines intended for use in large patient populations, which is believed to have a major impact on healthcare. The process is explained in further details on a dedicated website [152].

The first step of the national process for managed introduction of new medicines is horizon scanning [153, 154]. The horizon scanning working group continuously search available data for novel treatments about 1-2 years before expected regulatory approval. The group prioritize the most interesting medicines and summarize current knowledge in early assessment reports.

The reports are sent to the DTCs and to the New Therapies (NT) Council about six months before estimated regulatory approval. The NT Council decide whether the medicine should be included in the national managed introduction process.

When the medicine has received marketing authorization (by EMA or the Swedish Medical Product Agency), the NT Council asks the Dental and Pharmaceuticals Benefits Agency (TLV) to perform a health economic evaluation. TLV conclude whether the treatment is cost-effective and provides the NT Council with an evaluation report. In certain cases, negotiations between the county councils and the pharmaceutical company are held regarding pricing. The NT Council then decides on recommendations for use to the DTCs.

Local implementation process

Based on the NT Council recommendation, the DTCs conduct local routines to implement the novel treatment in each county council. The DTCs and the specialists responsible for medical treatment implementation at the concerned clinics discuss budget allocations and designate details of which drugs to introduce and how to manage the implementation.

To gain real-world experience of management and safety in clinical practice, local guidelines usually first recommend merely specialists at the hospital to prescribe the novel drug. After a few years, general practitioners are encouraged to prescribe the drug also in primary care, with the possibility to ask for specialist consultation.

More effective implementation needed in clinical practice

Efforts have been made during the last decades to develop and refine the national and local implementation processes in Swedish healthcare. However, in clinical practice, in Sweden as in other countries, the implementation of novel treatments to all eligible patients within a population still takes several years [1-13]. One reason might be the organization of local implementation at the clinics.

The local implementation in routine care are commonly organized as follows: patients with chronic diseases have to visit their physician - on a planned re-visit, book an appointment initiated by themselves, or become hospitalized due to worsening symptoms or an emergency event - before they have a chance to be evaluated for the novel therapy. This means that patients are dependent on their physician's updated knowledge and interests in trying new therapies. The consequence is often a long passive waiting period before all eligible patients have received the novel treatment, also referred to as clinical inertia [8]. Problems with clinical inertia, where patients do not receive proper diagnostics and/or guideline-recommended therapy within a reasonable time, have been reported in a variety of diagnoses, such as diabetes, hypertension, dyslipidemia, asthma [8], as well as osteoporosis [9] and heart failure [1, 6, 10, 11].

Further, newly approved drugs are often heavily marketed for being more effective than conventional therapies or reducing the risk of major safety concerns [146, 155, 156]. Since patients in routine care tend to be older with more comorbidities compared with patients included in clinical trials, there is a risk that interested physicians prescribe novel therapies to patients slightly outside approved indication. In clinical practice this may underestimate the benefits of new medicines and overestimate the risks, which is neither cost-effective nor offers the best quality of care. Consequently, novel medicines with potential to reduce mortality and morbidity need to be implemented more efficiently [157].

Aims

The overall aims of this thesis were to investigate obstacles to implement sacubitril-valsartan in a real-world heart failure population and to develop a systematic and effective method to implement novel treatments in patients with chronic disease.

Specific aims in the papers I-IV are as follows:

- I. To investigate if the PARADIGM-HF population is a fair representation of a real-world HFREF population.
- II. To examine sex differences in a heart failure population with regards to treatment and patient characteristics and to investigate the impact of sex on achieved doses of heart failure medications.
- III. To investigate the safety and tolerability in switching patients on target dose renin-angiotensin system inhibitors directly to maximum-dose sacubitril-valsartan.
- IV. To develop a model for a systematic introduction and to test the feasibility of this model on a new treatment of a chronic disease. Further, to investigate how such an approach would be received by the patients.

Methods

Study population

The thesis is based on medical record data from the Umeå University Hospital, Sweden. All patients alive at March 2016, were retrospectively included if they had a heart failure diagnosis, were living within the hospital catchment area, and had at least one specialist clinic visit at the Heart Centre or Department of internal medicine between 1 January 2010 and 31 March 2016.

The heart failure diagnosis was obtained from medical records as primary or contributory diagnosis according to the *International Classification of Diseases, 10th revision* codes I50.X, I42.X, and I11.0. All heart failure diagnosis had been signed or countersigned by a specialist in cardiology or internal medicine. To be recorded with an HFrEF diagnosis, patients also needed to have a EF of $\leq 40\%$ or $\leq 35\%$. Study populations in paper I-IV are presented in Figure 11.

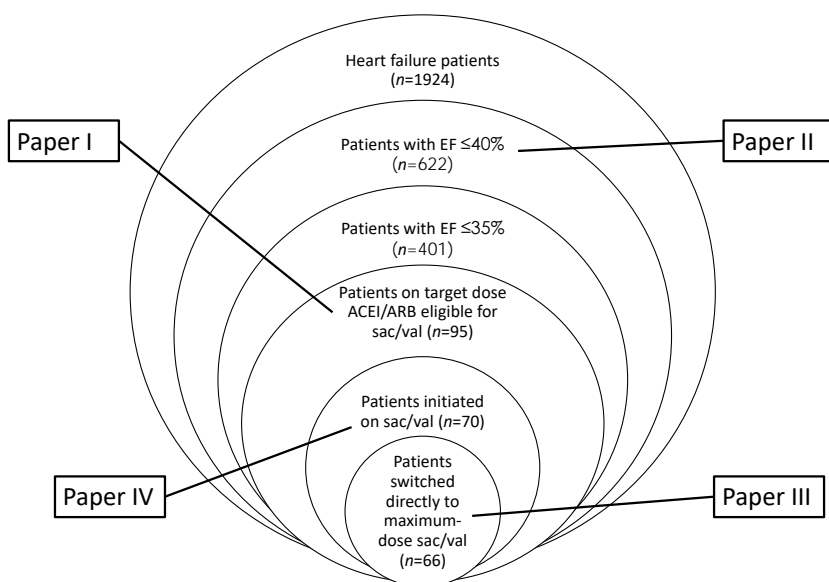


Figure 11. Venn diagram showing the study populations in Paper I-IV. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; EF, ejection fraction; Sac/val, sacubitril-valsartan.

A specialist in cardiology reassessed the echocardiography examination results for patients with EF 30-40% to validate the borderline heart failure diagnosis. The diagnosis with mid-range or preserved EF was not further validated. Data from patients with HFmrEF and HFpEF was only included in the patient characteristics for the total heart failure population in Paper II.

Settings

Umeå University Hospital serves around 150,000 residents with a mixed urban and rural population in Northern Sweden. The hospital comprises the only cardiology clinic in the region. As stated by local guidelines, all patients with suspected heart failure should be referred to the cardiology clinic for diagnosis and up titration of heart failure medications.

Data collection

The data was manually collected from the hospital's electronic medical records system (NCS Cross), between 1 June 2015 and 31 March 2016. A standardized protocol was applied, including clinical characteristics, laboratory data, medications, use of devices, and echocardiography and electrocardiography parameters.

To validate the collected data we performed validity assessments on a sample of the collected data. One researcher performed an additional data collection according to the standardized protocol on a minor proportion of medical records.

Study design

Patients were considered eligible for sacubitril-valsartan in all papers if they fulfilled the main PARADIGM-HF study criteria [90]:

- 18 years and older,
- EF \leq 35%,
- ACEI/ARB in target dose (equivalent to enalapril 20 mg daily),
- NT-proBNP \geq 600 pg/ml,
- eGFR \geq 30 mL/min,
- systolic blood pressure \geq 95 mm Hg,
- serum potassium level $<$ 5.4 mmol/L.

The Cockcroft-Gault equation was used to calculate eGFR in all papers.

In Paper I, a second selection process was performed with the above-described PARADIGM-HF criteria except with EF \leq 40% and at least half dose ACEI/ARB (equivalent to enalapril 10 mg daily) to assess the eligibility before the enrolment criteria were made stricter.

In paper II, sex differences in the total heart failure population and HFrEF population (EF \leq 40%) were analysed. To assess if sex was an independent predictor for achieved doses of heart failure medications - ACEI/ARB, beta-blockers, and MRA - patients with HFrEF were included in a multivariable linear regression analysis.

Paper III was a prospective cohort study with patients eligible for sacubitril-valsartan. Inclusion of patients were performed between April 2016 and November 2017. Patients were identified either through screening by the systematic introduction approach or in routine care during the study period. Identified patients were switched directly from target dose ACEI/ARB to maximum-dose sacubitril-valsartan (200 mg twice daily). Patients were instructed to wait 24 hours between the last ACEI/ARB dose until the first sacubitril-valsartan dose. Patients were followed up with blood pressure measurements after 2 weeks if systolic blood pressure was 110 mm Hg or less at baseline visit. Further, follow-up for tolerability and safety was performed after 3 and 12 months. Tolerability was assessed as patient-reported adverse events, need of dose reduction, and drug discontinuation. Safety was assessed as hospitalization or emergency room visits within 14 days of initiation or development of angioedema within 12-months follow-up.

Systematic introduction approach

The systematic introduction approach is a process of seven steps, presented in Paper IV. The procedure is summarized in Figure 12.

Step 1: Define which criteria to use for the specific treatment. This requires discussion with hospital administrators responsible for budget allocation. We recommend keeping the criteria as strict as possible to optimize cost-effectiveness, especially when the treatment has not been widespread. Large-scale clinical studies as well as established guidelines should be the foundation of the criteria.

Step 2: Start with the one or two main criteria and perform a primary scan to identify patients. Use computerized medical records, databases or clinical registries for this step.

Step 3: Perform a careful examination of the medical records of the identified patients to apply the other predefined criteria and sort out the patients who have contraindications to the treatment or are clearly not suited for other reasons.

Step 4: Evaluate if any examinations or laboratory test updates are required.

Step 5: Summon the identified patients with an information letter. The letter should contain short information about the new therapy and why they are summoned to the clinic.

Step 6: Discuss the new treatment option with the patient. Explain risks and benefits with the therapy and involve the patient in the treatment decision. Initiate treatment to appropriate patients.

Step 7: Follow-up regarding adverse events, dose adjustments and other aspects depending on the introduced therapy. Evaluate the process itself, whether-or-not, the prespecified criteria were useful in identifying the correct patients or if there would have been an easier way of identifying the patients.

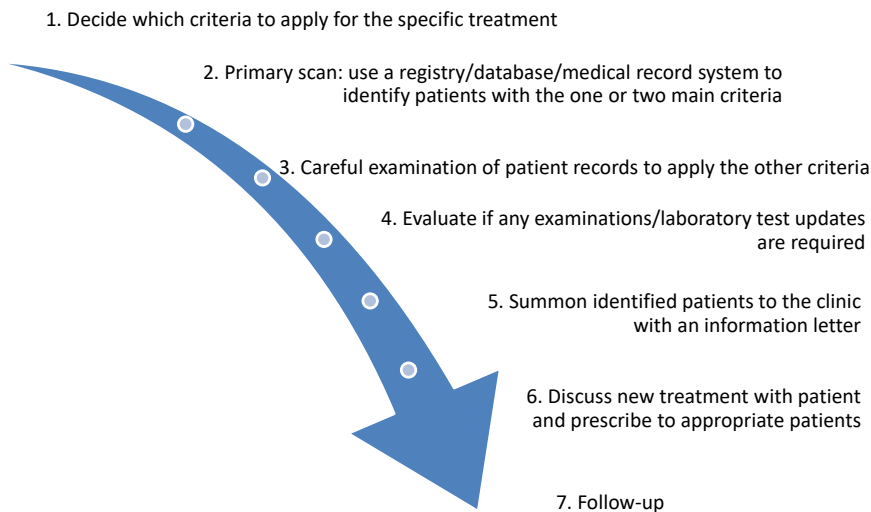


Figure 12. Workflow in the Systematic introduction approach.

In Paper IV, the systematic approach was evaluated with a mixed method, including both a case study of the implementation of sacubitril-valsartan and a qualitative interview study.

Case study: Implementation of Sacubitril-Valsartan

In the case study, the main PARADIGM-HF criteria were applied as predefined criteria in the systematic patient selection in Step 1 to 3. In Step 4, patients with an echocardiogram older than 18 months were reexamined. In Step 5, the information letter was written and signed by the heart failure cardiologist in charge of the program. A research nurse sent the letters. In Step 6, a heart failure cardiologist evaluated other therapies and discussed pros and cons of sacubitril-valsartan with the patients and prescribed the medicine if both physician and patient agreed. In Step 7, follow-up was performed at 3 (by telephone) and 12 months (outpatient visit). Patients with systolic blood pressure of 110 mm Hg or less at the baseline visit had an additional 2-week follow-up of blood pressure.

Qualitative study

An interview study was performed to investigate patients' experiences with the systematic introduction approach. Patients were invited consecutively to participate in an interview at the baseline visit of the sacubitril-valsartan case study. In total, 24 interviews were conducted (22 male and 2 female patients) by one member of the research team trained to do semi-structured interviews. The interviews were transcribed verbatim and analysed with a general inductive and manifest approach with qualitative content analysis, inspired by Graneheim and Lundman [158]. Text segments that corresponded to the aim of the interview study were labelled with codes and further sorted into categories. Two members of the research team performed the coding separately and subsequently discussed coding discrepancies to reach consensus of the final coding.

Statistics

All statistical analyses were performed with IBM SPSS Statistics, version 24 (Paper I) or 25 (Paper II and III) (Armonk, NY, USA.). The level of significance was set as 0.05.

Descriptive statistics

Statistical analyses of patient characteristics were performed with t-, chi-square, and Mann Whitney U tests for continuous, categorical and non-normally distributed continuous variables, respectively. Descriptive data for continuous variables are presented as means with standard deviations, or, as medians with interquartile range if non-normally distributed. Categorical variables are described as frequencies with proportions. In Paper III, paired t-test was used for comparisons between baseline and follow-up.

Regression analysis

In Paper II, factors predicting the percentage of achieved target dose of ACEI/ARB, beta-blockers, and MRA in patients with HFrEF (EF \leq 40%), were determined using a manual stepwise backward multivariable linear regression model. Percentage of achieved target doses was calculated as the latest prescribed dose divided by the target dose of the individual substance, according to ESC guidelines [26], for each patient separately as a continuous variable. Target doses are defined in Table 5. For example, if a patient is prescribed enalapril 5 mg twice daily (target dose 10 mg twice daily), the percentage of achieved target dose is 50%. The selected target doses were in strict accordance to the guidelines and did not consider individual decisions for lower target doses due to renal function, body weight or other reasons.

Table 5. Target doses of heart failure medications [26].

Heart failure medications	Target doses
<i>Angiotensin-converting enzyme inhibitors (ACEI)</i>	
Captopril	150 mg
Enalapril	20 mg
Lisinopril	20 mg
Ramipril	10 mg
<i>Angiotensin receptor blockers (ARB)</i>	
Candesartan	32 mg
Irbesartan	150 mg
Losartan	150 mg
Telmisartan	80 mg
Valsartan	320 mg
<i>Beta-blockers</i>	
Bisoprolol	10 mg
Carvedilol	50 mg
Metoprolol	200 mg
<i>Mineralocorticoid receptor antagonists (MRA)</i>	
Eplerenone	50 mg
Spironolactone	50 mg

Separate analyses were performed for each group of heart failure medication: ACEI/ARB, beta-blockers, and MRA. First, bivariate models were performed with the most relevant patient characteristics; age, sex, body weight, eGFR, systolic blood pressure, heart rate, EF, NT-proBNP, serum potassium, atrial fibrillation, coronary artery disease, diabetes and hypertension. Variables were reviewed to explore distribution, outliers and dependency. Since 5% of eGFR values were outliers (>130 ml/min) due to extreme body weight or muscle mass, these were truncated to 130 ml/min to reduce the statistical impact in the multivariable analysis. Variables with a *P* value less than 0.25 were later included in a manual stepwise backward multivariable linear regression analysis to determine the final prediction models. Further, interaction terms for sex*age, sex*body weight and sex*eGFR were included in the multivariable analyses. Sex was kept in the backward analysis, even if not significant, since it was central to our aims. *P* values less than 0.05 were considered significant in the final models.

Kaplan-Meier

In paper III, persistence on sacubitril-valsartan therapy during the first year was summarized in a Kaplan-Meier curve.

Ethics

The studies in this thesis were conducted in accordance with the Declaration of Helsinki and were approved by the Regional Ethical Review Board in Umeå, Sweden, registration numbers 2015-419-31 and 2016-233-32M.

Medical records data is, according to law, under secrecy but can be made available for research purposes with an approval from an Ethical Review Board. Health-related data is classified as especially sensitive information, and because research on medical record data/health data registries are not optional and the patient cannot give consent to participate, the responsibility for non-disclosure should be emphasized. The manually collected medical record data for this thesis is stored on a computer protected by the firewall of Umeå University Hospital. The responsible researcher coded the personal identification numbers and all statistical analyses were performed on anonymous data sets. All analyses were performed on group level and no lone individual is possible to identify.

Participants in Paper III and IV gave written consent to participate in the studies after given written and oral information at the baseline visit. They were informed about confidentiality and data protection, that participation in the study is voluntary and would not affect future care. The participants were also informed that they could request individual extracts from study data and that they could withdraw from the study at any time.

Results

Study population and data validity

In total, 1924 patients with heart failure were included in this thesis. Of these, 622 patients had an EF of 40% or less and 401 patients 35% or less at the latest echocardiography. Women represented about a third of these HFrEF populations (30% vs. 28% women, respectively).

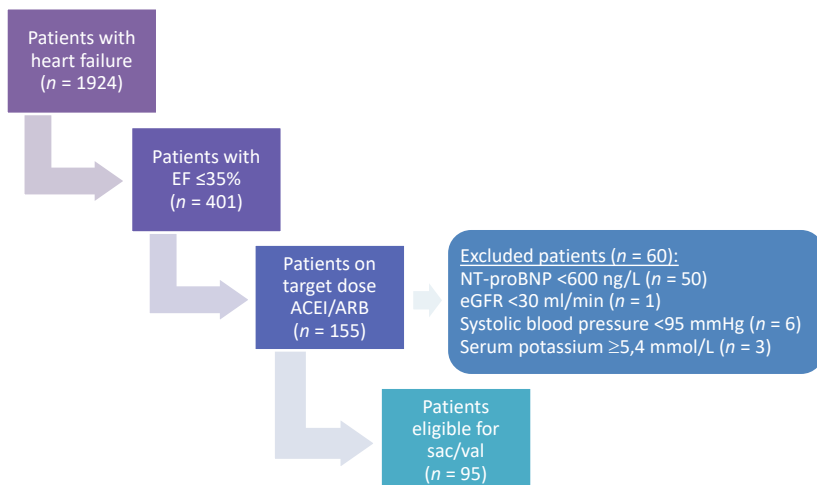
The reassessment of a minor sample of the collected data from the electronic medical records showed high compliance with the original data collection.

Eligibility for Sacubitril-Valsartan

The eligibility for sacubitril-valsartan in the Umeå heart failure population was investigated according to the PARADIGM-HF criteria; by applying the first two steps of the systematic introduction approach (see Figure 13A). After all criteria had been applied, 95 patients (16% women) fulfilled all criteria and were eligible for sacubitril-valsartan. This corresponds to 24% of the HFrEF population (EF \leq 35%) and 5% of the total Umeå heart failure population.

As PARADIGM-HF initially used less strict inclusion criteria, with EF \leq 40% and a pre-study dose of at least half target dose ACEI/ARB, a second selection was performed with these criteria (see Figure 13B). This resulted in 250 patients (22% women) eligible for sacubitril-valsartan, which corresponds to 40% of the HFrEF population (EF \leq 40%) and 13% of the total Umeå heart failure population.

A



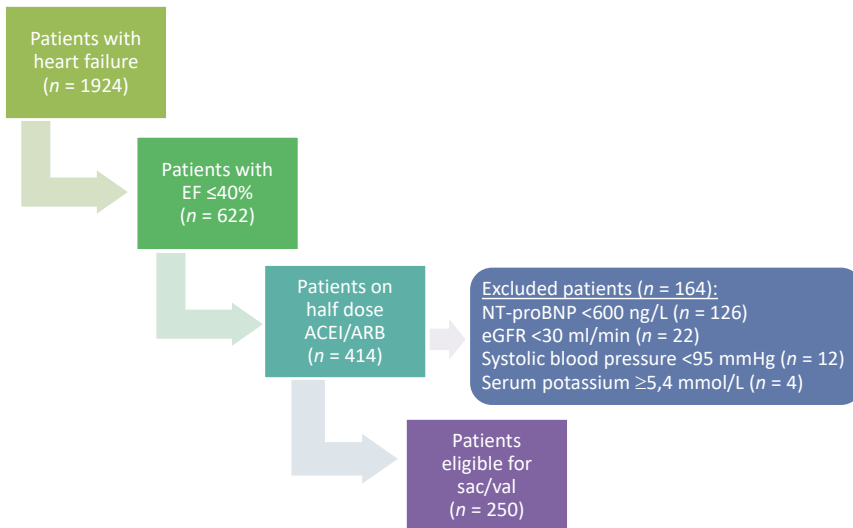
B

Figure 13. Selection of patients eligible for sacubitril–valsartan in the Umeå heart failure population when applying main enrollment criteria from the PARADIGM-HF trial. (A) First selection including EF $\leq 35\%$ and ACE inhibitor or ARB in target dose. (B) Second selection including EF $\leq 40\%$ and ACE inhibitor or ARB in half dose. In both (A) and (B) the following exclusion criteria were applied; NTproBNP < 600 pg/mL, eGFR < 30 mL/min, systolic blood pressure < 95 mmHg, and serum potassium level ≥ 5.4 mmol/L. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; EF, ejection fraction; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PARADIGM-HF, Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor (ARNI) with ACE inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure; Sac/val, sacubitril-valsartan.

Real-world cohort versus PARADIGM-HF population

Patient characteristics were compared between the Umeå HFREF (EF $\leq 35\%$) population and the PARADIGM-HF population in Table 6. The most prominent difference was that patients in the real-world Umeå population were 10 years older (73.2 ± 10.3 vs. 63.8 ± 11.5 years, $P < 0.001$) than the phase III study population. Other differences were higher systolic blood pressure (128 ± 17 vs. 122 ± 15 mmHg, $P < 0.001$) and higher heart rate (77 ± 17 vs. 72 ± 12 b.p.m., $P < 0.001$) in the real-world cohort compared with the PARADIGM-HF population. The real-world patients were also more likely to have a history of atrial fibrillation (51.6% vs. 36.2%, $P = 0.002$), MRA treatment (70.5% vs. 54.2%, $P = 0.002$), and devices, such as implantable cardioverter–defibrillator (23.3% vs. 14.9%, $P = 0.04$) and cardiac resynchronization therapy (18.9% vs. 7.0%, $P < 0.001$).

Table 6. Patient characteristics in the Umeå cohort versus the PARADIGM-HF population.

Characteristics ^a	Umeå cohort (n = 95)	PARADIGM-HF (n = 4187)	P value
Age – yr	73.2 ± 10.3	63.8 ± 11.5	<0.001
Female sex - no. (%)	15 (15.8)	879 (21.0)	0.27
Systolic blood pressure – mmHg	128 ± 17	122 ± 15	<0.001
Heart rate – b.p.m.	77 ± 17	72 ± 12	<0.001
BMI – kg/m ²	28.4 ± 5.8	28.1 ± 5.5	0.62
Serum creatinine - mg/dl ^b	1.09 ± 0.3	1.13 ± 0.3	0.20
Ejection fraction - %	29.8 ± 5.4	29.6 ± 6.1	0.72
NT-proBNP (IQR) - pg/ml	1681 (1074-3337)	1631 (885-3154)	^c
Medical history - no. (%)			
Hypertension	66 (69.5)	2969 (70.9)	0.85
Diabetes	25 (26.3)	1451 (34.7)	0.11
Atrial fibrillation	49 (51.6)	1517 (36.2)	0.002
Myocardial infarction	42 (44.2)	1818 (43.4)	0.96
Pretrial use of ACEI	65 (68.4)	3266 (78.0)	0.04
Pretrial use of ARB	32 (33.7)	929 (22.2)	0.01
Treatment at randomization – no. (%)			
Beta-blocker	91 (95.8)	3899 (93.1)	0.42
MRA	67 (70.5)	2271 (54.2)	0.002
Diuretic	64 (67.4)	3363 (80.3)	0.002
Digitalis	17 (17.9)	1223 (29.2)	0.02
ICD ^d	22 (23.2)	623 (14.9)	0.04
CRT ^d	18 (18.9)	292 (7.0)	<0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PARADIGM-HF, Prospective Comparison of Angiotensin Receptor–Nepilysin Inhibitor (ARNI) with ACE inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure.

^aPlus–minus values are means ± standard deviation. Statistical significance level P <0.05.

^bTo convert the values for creatinine to micromoles per liter, multiply by 88.4.

^cStandard deviation is missing.

^dIncluding patients with cardiac resynchronization therapy defibrillator (CRT-D).

Sex differences in heart failure

In Paper I, many women were excluded during the selection process. Figure 14 shows the proportion of women in each selection step. From 830 (43%) female patients in the total Umeå cohort to 15 (16%) female patients among the eligible patients. The most notable loss of eligible female patients was when the criterion of ACEI/ARB in target dose was applied, after which only 29 (19%) female patients remained. Paper II was designed to investigate the reasons behind this unexplained sex difference regarding patient characteristics and heart failure treatment.

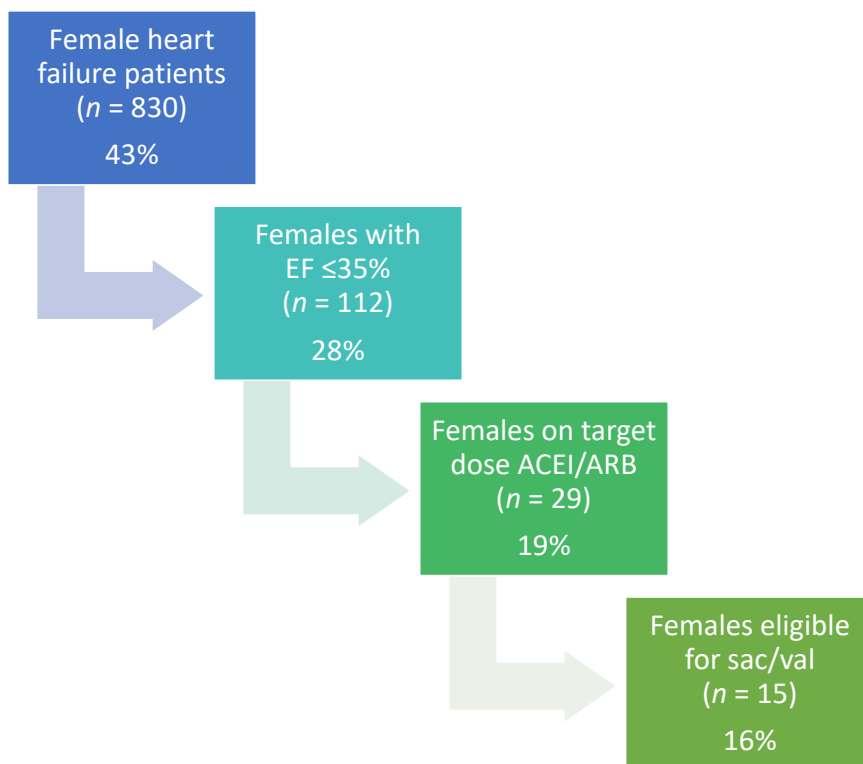


Figure 14. Proportion of female patients during patient selection, according to PARADIGM-HF criteria including EF ≤ 35% and ACEI or ARB in target dose. Between step 3 and 4, the following exclusion criteria were applied for eligible patients; NT-proBNP < 600 pg/mL, eGFR < 30 mL/min, systolic blood pressure < 95 mmHg, and serum potassium level ≥ 5.4 mmol/L. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; EF, ejection fraction; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PARADIGM-HF, Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor (ARNI) with ACE inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure; Sac/val, sacubitril-valsartan.

Patient characteristics

Patient characteristics were compared between women and men in the total heart failure population, as well as in patients with HFrEF (EF \leq 40%). Table 7 shows the HFrEF population. Among patients with HFrEF, 29 patients had a recent diagnosis, set within three months of data collection, and possibly did not have sufficient time for complete up titration. Seven of these had received maximum target dose ACEI/ARB, and nine had received maximum dose beta-blockers.

Women were significantly older, had lower body weight, lower eGFR, higher systolic blood pressure, less coronary artery disease, and received less heart failure medications and devices, in both the HFrEF and total heart failure population. Women in the total heart failure population also had significantly higher EF and heart rate compared with men, which were not shown in patients with HFrEF.

Table 7. Patient characteristics by sex in patients with HFrEF (EF \leq 40%).

Characteristics	Women (n = 188)	Men (n = 434)	P value
Age – years	79.1 \pm 11.1	74.3 \pm 11.7	<0.001
Body weight – kg	69.6 \pm 16.5	85.5 \pm 17.6	<0.001
Height – cm	161.0 \pm 6.5	175.4 \pm 7.4	<0.001
BMI - kg/m ²	26.8 \pm 5.8	27.7 \pm 5.1	0.047
eGFR - ml/min	49.2 \pm 24.4	70.8 \pm 30.4	<0.001
Systolic blood pressure – mmHg	129 \pm 20	124 \pm 18	0.001
Heart rate – beats/min	77 \pm 15	75 \pm 16	0.12
Ejection fraction - %	34.4 \pm 5.9	33.3 \pm 6.3	0.04
NT-proBNP, median (IQR) - pg/ml	1884 (578-4080)	1401 (579-3119)	0.10

Table 7. Continued

Medical history, n (%)	Women (n = 188)	Men (n = 434)	P value
Atrial fibrillation	88 (47)	213 (49)	0.60
Coronary artery disease	72 (38)	243 (56)	<0.001
Diabetes	43 (23)	107 (25)	0.63
Hypertension	126 (67)	297 (68)	0.73
Medications and devices, n (%)			
ACEI or ARB	164 (87)	403 (93)	0.02
Beta-blocker	169 (90)	395 (91)	0.66
MRA	76 (40)	219 (51)	0.02
Loop-diuretics	138 (73)	259 (60)	0.001
ICD [†]	14 (7)	78 (18)	0.001
CRT [†]	19 (10)	71 (16)	0.04

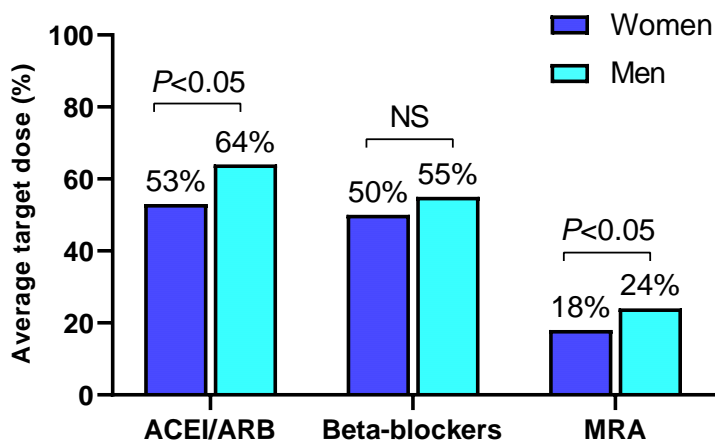
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

[†]Including patients with cardiac resynchronization therapy defibrillator (CRT-D).

Heart failure treatment

In the HFrEF (EF ≤40%) population, approximately 90% of the patients had an ACEI/ARB and a beta-blocker, while 47% had a MRA. Women were prescribed significantly lower doses of ACEI/ARB and MRA, but no significant differences were shown in beta-blocker dose (see Figure 15A). Target doses of ACEI/ARB, beta-blockers, and MRA were prescribed in 37%, 29% and 4%, respectively (see Figure 15B). The distribution of patients according to target dose levels are presented in Figure 16.

A



B

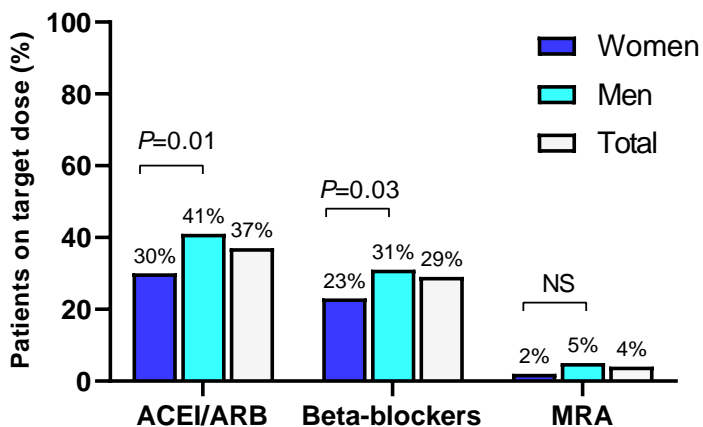


Figure 15. Patients with heart failure and ejection fraction $\leq 40\%$ with A) Average proportion of target dose of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), beta-blockers and mineralocorticoid receptor antagonists (MRA), and B) Total proportion of patients on target dose of ACEI/ARB, beta-blockers and MRA, according to sex. *P* values refer to differences between men and women. NS; Not significant.

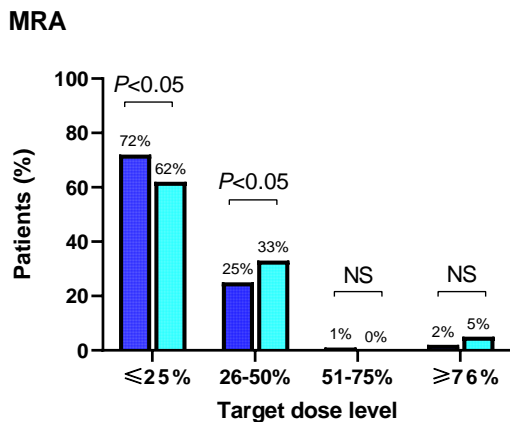
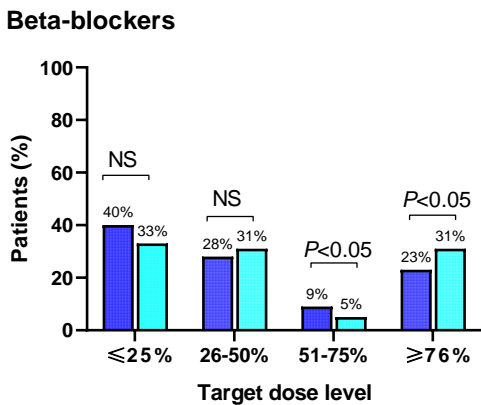
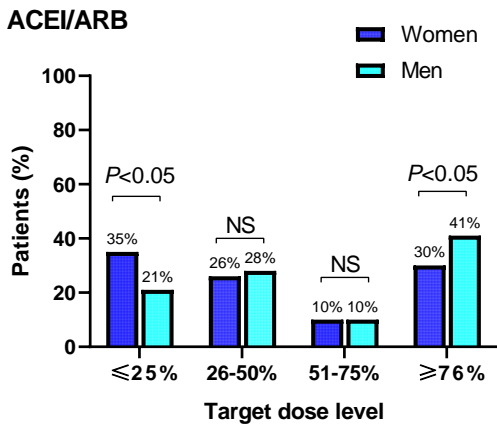


Figure 16. Proportion of patients with heart failure and ejection fraction $\leq 40\%$ according to target dose level of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), beta-blockers and mineralocorticoid receptor blockers (MRA). NS, Not significant.

Factors affecting achieved target dose of heart failure medications

The bivariate models for ACEI/ARB, beta-blockers and MRA in patients with HFrEF (EF \leq 40%) are shown in Table 2 in Paper II. The final multivariable regression models are shown in Table 8. Sex was not an independent predictor for achieved proportion of target dose heart failure medications. However, age was negatively associated with higher target dose for all heart failure medications, which shows that younger patients received (or tolerated) higher doses. eGFR was independently associated with higher proportion target dose for ACEI/ARB and MRA, while body weight and atrial fibrillation were independently associated with higher beta-blocker dose. These results show that the better renal function (higher eGFR) the higher doses of ACEI/ARB and MRA were prescribed. Further, the higher body weight the higher beta-blocker dose was prescribed and patients with atrial fibrillation received higher doses of beta-blockers. Heart rate, systolic blood pressure, and EF were associated factors for both ACEI/ARB and MRA, but not for beta-blockers. Non-significant results were shown for the interaction terms for sex*age, sex*body weight and sex*eGFR, and these were omitted from the final models.

Table 8. Final regression models regarding percentage of achieved target doses of ACEI/ARB, beta-blockers and MRA in patients with ejection fraction $\leq 40\%$ (n = 622).

ACEI/ARB‡

	B	95% CI	P value
Sex†	-0.002	-0.067 to 0.064	0.959
Age	-0.006	-0.009 to -0.003	<0.001
eGFR	0.003	0.002 to 0.004	<0.001
Systolic blood pressure	0.002	0.000 to 0.003	0.012
Heart rate	-0.002	-0.004 to -0.001	0.006
Ejection fraction	-0.005	-0.009 to -0.001	0.028
<i>Adjusted R² = 0.177</i>			

Beta-blockers‡

	B	95% CI	P value
Sex†	-0.021	-0.085 to 0.043	0.527
Age	-0.007	-0.010 to -0.005	<0.001
Body weight	0.002	0.001 to 0.004	0.002
Atrial fibrillation	0.067	0.012 to 0.123	0.018
<i>Adjusted R² = 0.089</i>			

MRA‡

	B	95% CI	P value
Sex†	-0.040	-0.088 to 0.009	0.108
Age	-0.003	-0.005 to -0.001	0.012
eGFR	0.002	0.001 to 0.003	<0.001
Systolic blood pressure	-0.001	-0.002 to 0.000	0.038
Heart rate	-0.001	-0.003 to 0.000	0.026
Ejection fraction	-0.005	-0.008 to -0.002	0.001
Serum potassium	0.078	0.030 to 0.125	0.001
<i>Adjusted R² = 0.168</i>			

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; B, unstandardized B-coefficients; CI, confidence interval; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MRA, mineralocorticoid receptor blockers.

†Reference female

‡Adjusted for body weight, NT-proBNP, serum potassium, atrial fibrillation, coronary artery disease, diabetes, and hypertension.

Safety and tolerability with the simplified switch to sacubitril-valsartan

In total, 66 patients tolerating target dose ACEI/ARB were switched directly to maximum dose sacubitril-valsartan. The cohort consisted of mainly white (98%), male (92%) patients, with a mean age of 72 ± 10 years, which belonged to NYHA class II or III (29% and 61%, respectively) (see Table 9). Mean systolic blood pressure was 121 ± 17 mm Hg, and four patients had a systolic blood pressure of 95 mm Hg.

Table 9. Baseline characteristics of patients switched directly to maximum-dose sacubitril-valsartan.

Characteristics [†]	Patients (n = 66)
Age, years	72 ± 10
Male sex (n, %)	61 (92)
Systolic blood pressure, mmHg	121 ± 17
Diastolic blood pressure, mmHg	72 ± 11
Ejection fraction, %	30 ± 6
Heart rate, b.p.m.	76 ± 18
Serum potassium, mmol/L	4.4 ± 0.4
eGFR, ml/min	76 ± 32
Body weight, kg	93 ± 21
BMI, kg/m ²	31 ± 10
NT-proBNP, ng/L (median, IQR)	1612 (774-3515)
NYHA class (n, %)	
I	2 (3)
II	19 (29)
III	40 (61)
IV	5 (7)
Medical history (n, %)	
Hypertension	42 (64)
Diabetes	19 (29)
Coronary artery disease	37 (56)
Atrial fibrillation	35 (53)
Medications (n, %)	
ACEI‡	37 (56)
ARB‡	29 (44)
Beta-blocker	63 (95)
MRA	47 (71)
Diuretics	42 (64)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; IQR, Interquartile range; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

[†]All values were reported as mean ± standard deviation unless otherwise indicated.

[‡]All patients were prescribed ACEI or ARBs in doses equivalent to enalapril 20 mg daily.

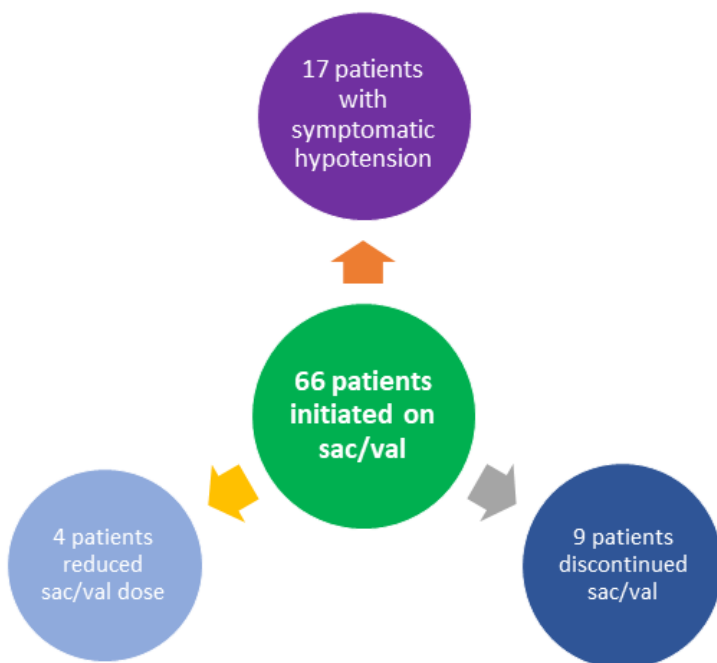


Figure 17. Overview of patients initiated on sacubitril-valsartan (sac/val).

Of the 66 patients initiated on sacubitril-valsartan, four patients (6%) had to reduce the dose within the first year (see Figure 17). Nine patients (14%) discontinued treatment, eight of them (12%) due to adverse events. All reasons for discontinuation within the first year are shown in Table 10. The most common reasons were a slowly developing itching rash during the first weeks after initiation ($n = 3$) and progressive renal impairment ($n = 2$). Symptomatic hypotension was reported in 17 patients (26%) during the first year, of which one patient discontinued sacubitril-valsartan and three patients reduced the dose. The 13 remaining patients with symptomatic hypotension managed to remain on the maximum dose. Persistence on sacubitril-valsartan treatment is shown in Figure 18. The earliest treatment discontinuation was after 10 days; otherwise, treatment was terminated after a median of three months.

Table 10. Reasons for discontinuation of sacubitril-valsartan within first year.

Number	Patient	Reason for discontinuation
1	87-year old man	Dizziness, syncope and a slowly developing itching rash
2	82-year old woman	Irritated bowels
3	81-year old man	Slowly developing itching rash
4	80-year old man	Progressive kidney failure
5	79-year old man	Orthostatic hypotension, even after dose reduction
6	76-year old man	Coughing
7	77-year old man	Progressive kidney failure
8	76-year old man	Slowly developing itching rash
9	69-year old man	Decided he did not want to continue with medication that is not currently endorsed by national guidelines

Regarding safety, no hospitalizations or emergency room visits occurred within the first 14 days. No angioedema was observed during the one-year follow-up. Three patients died during follow-up, none of them within the first three months. Systolic blood pressure was measured at baseline and 12-months follow-up and was significantly reduced at 12-months follow-up (121 ± 17 mm Hg at baseline vs. 115 ± 15 mm Hg at 12-months, paired t-test $P < 0.05$). Otherwise, there were no significant differences between baseline, three month and 12 months follow-up regarding serum creatinine, serum potassium, and NT-proBNP. Of the 37 patients previously on ACEI, 36 patients waited 24 hours between last-dose ACEI and first-dose sacubitril-valsartan and one patient waited 48 hours.

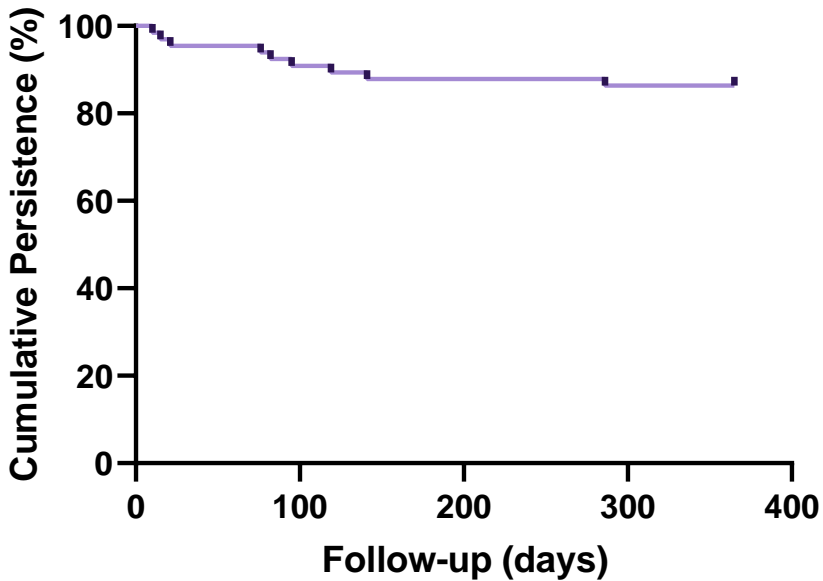


Figure 18. Kaplan-Meier curve of persistence on sacubitril-valsartan.

Systematic introduction approach

Implementation of sacubitril-valsartan in clinical practice

By applying the systematic introduction approach for the implementation of sacubitril-valsartan, the feasibility of the model was tested in clinical practice. The results from this case study is presented in Figure 19. Step 1 shows the entry criteria based on PARADIGM-HF. In Step 2, the total heart failure population of 1924 patients were included, of which 401 patients had EF \leq 35%. Further, 246 patients did not tolerate ACEI/ARB in target dose, 50 patients had NT-proBNP less than 600 ng/L, one patient had eGFR less than 30 mL/min, six patients had systolic blood pressure less than 95 mm Hg, and three patients had serum potassium of 5.4 mmol/L or higher. A total of 95 patients remained for Step 3.

In Step 3, a manual review of medical records was performed on identified patients with exclusion of four patients with other terminal illness or who died before visit. An additional nine patients were no longer eligible due to NYHA class I or NT-proBNP less than 600 ng/L. In Step 4, six additional patients were excluded due to improved EF; hence, 76 patients remained.

In Step 5 and 6, all 76 eligible patients were summoned to the clinic with an information letter and the novel therapy discussed. Finally, 70 patients were initiated on sacubitril-valsartan and followed-up with regards to Step 7.

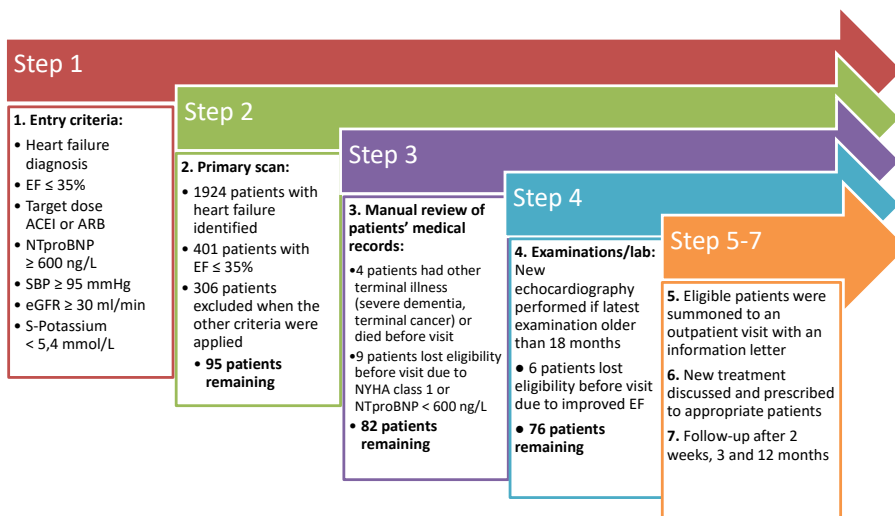


Figure 19. The patient selection process of introducing sacubitril-valsartan to eligible patients. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; EF, ejection fraction; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.

Patient experiences with the systematic introduction approach

The qualitative content analysis resulted in three final categories; *A good approach*, *Role of the information letter*, and *Trust in healthcare*. Table 11 presents the categories in more detail, including the identified codes and supportive quotes.

Patients were overall satisfied with the new approach and thought it felt reassuring to get the information letter in beforehand. The letter gave them an opportunity to consider the treatment offer before meeting the physician. Even though, some patients did not understand that they were summoned to discuss a new therapy, despite the information letter. Patients also expressed a trust in care and thought it felt reassuring with the follow-up procedure.

Table 11. Categories, codes and exemplar quotes from the interview study.

Categories	Codes	Supportive quote(s)
A good approach	It is positive to be summoned	"It feels very good to be summoned."
	Expecting to be summoned	"It is the service that the citizens are expecting from the hospital, when something new is revolutionary in some way, significantly better than what is now on the market, then you have to either summon or send a letter..."
Role of the information letter	Understanding the letter	"Yes, I got a letter...yes a few weeks ago...a month ago...that they wanted to try a new medicine...and...yes, I'd like to put up so that's why I'm here"
	Feeling reassured by being informed before visit	"Then you were a bit warned."
	Requesting more information	"I'm interested in percentages, just weighing the two drugs against each other, short-term, long-term on a paper, because I think many people when visit a doctor, you're nervous...then it's a good idea to get an information letter with easy understandable statistics or percentages. Partly before and also afterwards."
	Not perceiving being summoned for discussion of new treatment	"No...no, it was....it was only that I would take ECG and I'll meet my doctor."
Trust in healthcare	Feeling reassured with follow-up	"Yes, it [the information letter] said that there was phone contact when needed and after some period it was follow-up, so that...it's nothing they're just sending you home with or what to say...eat this and get well but...they will follow-up some time afterwards.... Yes, it feels reassuring, it is nothing you just start with without..."
	Having had good help before	"No, but as I said, I have great confidence in the doctors, I usually say...I have received good help before."
	Grateful that the health-care keeping track of me	"Yes, that's because they'll keep track on me...and I'm grateful for that."

Discussion

Main findings

We studied a real-world heart failure population to investigate obstacles to introduce sacubitril-valsartan in a real-world heart failure population and to implement a systematic introduction of a new treatment. We found in paper I that a real-world heart failure population differed in several major aspects from a landmark heart failure trial and, that only a fraction of the heart failure population would be eligible for treatment if treatment guidelines would be as strict as the study criteria. In paper II, we studied sex differences in heart failure treatment and the results implicate that treatment differences were due to biological differences more than an apparent gender bias. Proceeding to implementation, we showed in paper III that initiating sacubitril-valsartan could be made in a simpler way than recommended in the guidelines, and in paper IV, we implemented a systematic approach for introduction of a new treatment that possibly could be used for introducing other treatments as well.

Methodological considerations

All papers in this thesis are based on a single-center population, which reduces external validity and generalizability to other settings. However, we have studied a representative unselected real-world heart failure population without exclusion of elderly and frail patients with dementia or other comorbidities. This is important when investigating sex differences and implementation of novel treatments in clinical practice. We have tried to include all patients with heart failure within Umeå healthcare region and consequently called it a community-based single-center study in Paper I. In Paper II-IV, however, we realized that some patients might have been missed if they were only treated in primary care, without being referred to the hospital specialist clinics for diagnosis and up-titration of drug therapy. According to clinical experience, patients who are missed in this thesis are primarily patients with mild heart failure and very elderly with other terminal diseases. We are planning to perform a study to investigate the primary care heart failure population in further detail.

A specialist in cardiology or internal medicine countersigned the heart failure diagnosis for patients with HFrEF. For patient with borderline EF (30-40%) and for patients without an exact EF value documented, a specialist in cardiology reassessed echocardiography examination results. The HFpEF diagnosis were not further validated and consequently a minor proportion of the patients might be misdiagnosed. However, we only included patients with HFpEF in Paper II where sex differences in the total heart failure population were analysed with

descriptive statistics. Further, a recent study of heart failure diagnoses set between 2000 and 2012 in western Sweden showed that the overall validity of hospital discharge heart failure diagnoses was high [30]. Since Northern Sweden apply with the same hospital diagnosis routines, it is reasonable to believe that the validity of heart failure diagnoses is equally high in the Umeå University Hospital.

This thesis is primarily based on retrospective review of existing medical records, which have inherent limitations. We were restricted to data already documented, and in some cases, data were missing. Unfortunately, it was not possible to review NYHA class based on the documented medical record data. Another problem with data collection is the validity of collected data. Therefore, we performed validity assessments on a sample of included medical records, which showed a high agreement with the collected data and so forth indicates a high validity. In addition, this thesis is primarily based on patients with HFrEF, where we had echocardiography data that validated the heart failure diagnoses.

We used the Cockcroft-Gault equation to calculate eGFR in all papers. Previous studies have shown Cockcroft-Gault as the most accurate formula to predict mortality risk in heart failure patients and has traditionally been used in heart failure trials [159]. It is also the most common method to estimate GFR in pharmacological studies to assess dose adjustments according to renal impairment level. Even though dose adjustments are made based on Cockcroft-Gault and it might be the most accurate risk assessment formula in heart failure patients, it has been shown as not the most accurate in predicting eGFR in heart failure patients. We performed a study with 146 patients with heart failure (mean EF 45% ± 15) to validate eight creatinine-based equations for estimating GFR against measured GFR (⁵¹Cr-EDTA clearance) [160]. We showed that none of the eight most commonly used eGFR equations was accurate enough. MDRD (Modification of Diet in Renal Disease Study) was the most accurate formula for patients with both heart failure and renal impairment.

In Paper III, we applied a 24-hours washout period instead of the guideline-recommended 36-hours gap from the last ACEI/ARB dose until the first sacubitril-valsartan dose. We did not observe any cases of angioedema during the 12-months follow-up, but all together, we did not have enough power to validate this risk. We had an unexpected low mortality rate with only three death during the one-year follow-up. However, we had a small study population and the eligibility criteria from PARADIGM-HF primarily selected younger patients with relatively mild symptoms.

In Paper IV, we choose qualitative content analysis, with inspiration from Graneheim and Lundman [158], to analyse the interviews. The choice of qualitative method is dependent on the aim of the study. Our aim of the interview study was to describe patient experiences with the new systematic introduction approach, an area that no previous studies have investigated. Since content analysis is a widely used technique in qualitative research and it gives the researcher an opportunity to interpret meaning from the context of data to increase knowledge or provide new insights [161, 162], it fit with our aim. Further, we used an inductive, instead of deductive, analysis since inductive analysis is recommended when no previous studies have investigated the phenomenon or when the knowledge is fragmented [161]. Deductive analysis, on the other hand, is useful if the aim is to test a previous theory in different settings or time periods. Additional, we choose a manifest approach to analyse what the text says in obvious components, in contrast to a latent approach where interpretation of the underlying meaning (also including silence, sighs, laughter, posture etc.) is in focus [158]. Hence, content analysis with an inductive and manifest approach was an appropriate method to explore different patient experiences with our new systematic introduction approach.

To achieve trustworthiness in our qualitative content analysis we have followed the advice from Graneheim and Lundman [158]. We described the analysis process, selected the most appropriate method for data collection and the amount of data, and presented quotes to show the link between the data and the results. To test the reliability of how well codes and categories covers the data, we were two researchers who performed the coding single-handed and afterwards discussed coding discrepancies to reach consensus of the final coding. The transferability (or generalizability) of our results can be reduced due to local routines and settings that are not present in other hospitals or countries. However, as recommended in the literature [158, 161], we have tried to give a description of the context, patient and data selection, as well as the analysis process in order to enable the reader to follow the process and decide if the results are representative to his/hers settings.

Findings and implications

The gap of eligible patients in clinical trials and clinical practice

We found that only a fraction of patients in our single-center heart failure population met all enrollment criteria from PARADIGM-HF. The main reason was that real-world eligible patients were older. With age, several complicating aspects contribute to reduced inclusion in clinical trials, such as renal impairment, comorbidities, physiological and structural changes. In heart failure, several crucial factors are associated with higher age. Older patients are more likely to be women, to present with HFpEF and have an etiology of long-term hypertension.

In more detail, we showed that 24% of the HFREF (EF 35% or less) population were eligible for sacubitril-valsartan according to the PARADIGM-HF criteria. These results are consistent with previous and later studies. Real-world studies on patients with HFREF (EF 40% or less), have shown that between 20% and 26% of the patients fulfilled the PARADIGM-HF randomization criteria [163-165]. Previous ACEI/ARB therapy was one of the main reasons for disqualification in these studies. For example, Pellicori et al. [163] showed that if background medication was ignored, the proportion increased from 21% to 60% eligible patients. We found that sex was not associated with achieved dose of heart failure medications in our real-world population; however, higher age, lower body weight and lower renal function were the most prominent factors for not achieving target doses.

Registry-based studies with more selected patient groups have shown that 12-76% of the included patients are eligible for sacubitril-valsartan depending on which background ACEI/ARB dose that are required [166-170]. Additional studies have analysed eligible patients not only according to PARADIGM-HF criteria but also for the less strict EMA/FDA labels, where 71% and 84% met label criteria [165, 168]. The immense difference in eligibility numbers depending on which criteria are applied highlights a gap between clinical trials and recommended use in clinical practice.

The gap of women and elderly in clinical trials

Women and elderly are often underrepresented in heart failure trials, with no exception in PARADIGM-HF. We showed that strict entry criteria in clinical trial settings result in an even more pronounced under-representation of eligible patients in clinical practice. Consequently, PARADIGM-HF included 22% women, while only 16% women from our real-world population were eligible. Further, our real-world cohort was 10 years older than the PARADIGM-HF population.

Similar results with low eligibility in women and elderly have been reported, not only for sacubitril-valsartan, yet also for standard heart failure medications. A cross-sectional study that included 20,388 heart failure patients from the Medicare program showed that 17%, 13%, and 25% fulfilled all enrollment criteria in the SOLVD (enalapril), MERIT-HF (metoprolol) and RALES (spironolactone) trials, respectively [89]. In patients with HFrEF, the eligible proportions rise to 38%, 25%, and 55%, respectively. Significantly fewer women than men with HFrEF met trial criteria for any of the three trials (35% vs. 40% for SOLVD, 23% vs. 26% for MERIT-HF, and 54% vs. 55% for RALES, $P < 0.01$ for all). The eligibility also markedly decreased with age. Both SOLVD and MERIT-HF had an upper age limit of 80 years, but even when this age limit was ignored, only 35% and 22% of the patients fulfilled all criteria.

Further, we showed that sex differences are the reasons why women were less likely to meet enrollment criteria in PARADIGM-HF. Women with heart failure are in general older, have lower body weight and lower renal function. These biological sex differences are causing higher plasma concentrations in hydrophilic drugs, increased volume of distribution and consequently, prolonged effect durations in lipophilic drugs, as well as enhanced risk of adverse events, which all decreases drug tolerance in women. When a fixed target dose is required for inclusion, disproportionately many women are excluded due to intolerance.

Therefore sex- and age-specific analyses that assess risks and benefits in women and elderly need to be implemented in research more efficiently than today. Women and elderly also need to be included in clinical trials relative to the representation in clinical practice, since extrapolation of results always means a risk. By avoiding enrollment criteria that direct or indirect exclude women and elderly in future studies we can all contribute to close this gap between clinical trials and clinical practice. One step in the right direction is that institutes and regulatory authorities nowadays more often require sex/gender and age pre-specified analysis for funding applications.

The optimal dose of heart failure medications

Our results of low eligibility in clinical practice compared with trial settings and the obstacles to achieve target doses, have drawn our attention to whether there is an optimal dose for heart failure drugs and if sex-differentiated doses would be beneficial. So far, heart failure guidelines recommend the same target doses of heart failure medications to all patients, without distinctions between men and women [26, 97]. Given that the recommended target doses are based on clinical trials with predominantly middle-aged men and that the majority of landmark trials lack subgroup analyses according to sex, many questions remain unanswered. However, some efforts have been made to investigate if target versus

below-target doses are more effective and whether there are sex differences in drug exposure of heart failure treatment.

For ACEI, no significant difference in primary outcome have been shown for patients treated with target dose of enalapril or lisinopril compared with patients treated with below-target doses [171-173]. For beta-blockers, two studies showed no significant difference in all-cause mortality according to beta-blocker dose when target heart rate was reached [174, 175]. In contrast, two additional studies showed that the risk for all-cause death and hospitalization decreased with achieved beta-blocker dose [176] and achievement of target beta-blocker dose was associated with lower mortality [177]. For ARNI, a post-hoc analysis of PARADIGM-HF showed that patients who required a dose reduction during the study period were at higher risk for major cardiovascular events than patients who remained on target dose [178]. Sacubitril-valsartan was still more beneficial than enalapril in patients who required dose reduction.

Regarding sex differences in drug exposure and pharmacodynamic effects of heart failure treatment, a recent post-hoc analysis based on the BIOSTAT-CHF (BIOlogy Study to Tailored Treatment in Chronic Heart Failure) trial showed some interesting results. Among 1710 patients (24% women), a similar proportion of men and women reached target doses of ACEI/ARB and beta-blockers within the first three months of the study [61]. However, men had the lowest hazards of death or heart failure hospitalization at full target dose of ACEI/ARB and beta-blockers, while women had 30% lower risk at only 50% target doses, with no further decrease in risk at higher dose levels. Comparable results were seen in the HEAAL trial, who compared high versus low (150 mg vs. 50 mg) doses of losartan [110]. The highest dose level was more favorable in men, while no significant difference between the two dose levels were seen in women. For MRAs, similar beneficial effects have been shown regardless of sex [179].

Further, pharmacokinetic studies of beta-blockers have shown that women had higher maximum plasma concentration and area under the curve of metoprolol, which resulted in greater reduction in exercise heart rate in women compared with men [180]. For ARNI, similar pharmacokinetic parameters were seen in both sexes [130].

In summary, these studies indicate that - at least for some heart failure medications - there might exist clinically relevant sex differences in the effects and pharmacokinetics and that lower dose levels might already be beneficial in women. This area needs to be further investigated in future studies with sex-specific analysis to be able to conclude whether there is an optimal dose for heart failure medications or not.

Direct switch to target dose sacubitril-valsartan

Heart failure guidelines recommend that evidence-based medications are prescribed according to EF level and symptoms. Each patient is supposed to be up titrated to a specific target dose, or the maximum tolerated dose, for every initiated treatment step. To illustrate, European and American guidelines first recommend initiating an ACEI and a beta-blocker in patients with symptomatic HFrEF [26, 97]. As low starting-doses are preferred to reduce the risk of hypotension and other adverse events, patients need to visit the outpatient clinic several times before the maximum tolerated doses (preferably target doses) are achieved. Patients who do not tolerate ACEI can be switched to ARB, with further up-titration in several steps. In patients who are still symptomatic, despite target doses of ACEI/ARB and beta-blocker, an MRA should be initiated and up titrated, which means a couple of more appointments in the outpatient clinic. Further, patients who are still symptomatic and have EF 35% or less, are recommended to switch from ACEI/ARB to sacubitril-valsartan. According to guidelines, sacubitril-valsartan should be initiated in half dose for 2-4 weeks before up-titration to full target dose, meaning at least two additional visits. Consequently, this guideline-recommended management means multiple up-titration visits for each drug and patient, and there is a risk that clinic resources are stressed or that clinicians and/or patients do not comply with the whole treatment adoption [181, 182]. When medications are not up titrated to target doses, there is a gap between clinical trial and clinical practice. Therefore, studies are needed to investigate simplified initiation managements that remain safe for the patient.

In the case of sacubitril-valsartan, previous studies have reported a slow implementation and that many patients are not properly up titrated to target dose within reasonable time [1, 3, 5, 164, 183-190]. Further, compliance to sacubitril-valsartan treatment often decline within the first six months, yet the compliance was highest among patients who were previous treated with ACEI/ARB, those taking a higher number of total medications, and those initiated on target dose sacubitril-valsartan [3, 189]. We therefore performed a prospective study to investigate a simplified sacubitril-valsartan initiation for both clinicians and patients.

Since sacubitril-valsartan was still a novel treatment with limited post-marketing experiences of real-world safety issues, and because of budget reasons, we chose to focus on the group of patients with so far best evidence. Hence, we only included patients who met the PARADIGM-HF criteria, including tolerating target dose ACEI/ARB. According to previous studies, these patients also have the best opportunities for treatment consistent and adherence.

The direct switch was successful in our real-world population concerning both safety and tolerability, and showed an alternative initiation management to

patients already on maximum RAAS inhibition. This management would probably simplify the initiation process with reduced up-titration visits in clinical practice. It would also avoid a reduced RAAS inhibition during the otherwise 2-4 weeks of sacubitril-valsartan in half dose.

Early experiences of sacubitril-valsartan in clinical practice

Our study with the direct switch to maximum-dose sacubitril-valsartan covers an example of early experience in clinical practice that can help clinicians to make more evidence-based treatment decisions. Real-world data on sacubitril-valsartan use has been scarce for quite a long time, despite inclusion in European and American heart failure guidelines since 2016 and 2017, respectively. However, more and more experiences from routine care are published.

Beneficial effects on symptoms, morbidity and mortality have been shown when patients with HFrEF were treated with sacubitril-valsartan in clinical practice. In a U.S. study, 200 HFrEF patients were treated with sacubitril-valsartan for four months [183]. Patients had a significant reduction in hospitalizations within the follow-up period, as well as significant reductions of fatigue and shortness of breath. In two retrospective Belgian studies, 120 respectively 201 HFrEF patients on sacubitril-valsartan were followed up for a mean time of three and seven months, respectively [188, 191]. The results showed significantly improved NYHA class [188, 191] and reduced left ventricular remodeling, measured as larger increase in EF and larger reduction in left ventricular end systolic volume [191]. Improved NYHA class was also shown in a small prospective study from Switzerland, including 52 HFrEF patients in primary care [190]. Thirty-six percent of the patients achieved target dose of sacubitril-valsartan for over 12 weeks. A reduced proportion of patients in NYHA class III and increase in NYHA class II were shown. Similar to Paper III, a retrospective Irish study of 297 HFrEF patients showed that 13% of the patients discontinued sacubitril-valsartan due to adverse events, most commonly symptomatic hypotension [186]. A reduction in NT-proBNP $\geq 30\%$ was seen in 46% of the patients and 49% had an increase in EF $\geq 5\%$.

Regarding morbidity and mortality, a study from Taiwan compared 466 HFrEF patients on sacubitril-valsartan with 466 HFrEF patients on standard heart failure therapy [192]. The sacubitril-valsartan group had a 34% lower risk of the primary outcome cardiovascular death or first heart failure hospitalization. The primary outcome was also significantly lower in the sacubitril-valsartan group for patients with HFrEF and chronic kidney disease. Further, in a retrospective US study with 279 HFrEF patients on sacubitril-valsartan and 279 matched HFrEF patients on ACEI/ARB, the sacubitril-valsartan group was less likely to be hospitalized [193]. A cost-benefit analysis showed that despite higher pharmacy

costs, patients treated with sacubitril-valsartan had lower monthly medical and total healthcare costs.

Safety monitoring of novel therapies in clinical practice

When novel therapies are introduced, either with the systematic introduction approach or with conventional methods, it is important that drug safety is monitored in routine care. Our approach means that eligible patients get earlier access to the novel treatment compared to routine care. Earlier access gives the patient an opportunity to gain treatment benefits, yet in the same time earlier access also increases the risk of unexpected or rare side effects. Therefore, the EMA post-authorisation pharmacovigilance system involve important safety assessments after a new medicine is approved on the market. In the case of sacubitril-valsartan, it is under additional monitoring because there are limited clinical experience with the new substance sacubitril.

CER is another tool to provide vital information on new substances, such as sacubitril. We have a small study population in this thesis, however, the systematic approach complements the framework of the Swedish CER study previously described [149], since we can chart and follow-up on a real-world heart failure population. For example, Paper III showed a high proportion of symptomatic hypotension (26%), but no serious adverse events during the first year of treatment. Notably, three patients developed an itching rash leading to discontinuation of sacubitril-valsartan, which was not reported in PARADIGM-HF, probably due to the exclusion of patients with adverse events during the run-in phase.

Clinical implications for the Systematic introduction approach

We tested the systematic introduction approach in clinical practice as a case study. The approach showed to be a useful and effective method for implementation of sacubitril-valsartan to patients with chronic heart failure. We have developed the model to be flexible enough to apply within any therapy or healthcare facility. When novel therapies receive regulatory approval, our systematic approach can be customized according to, *e.g.*, enrollment criteria from clinical studies, guideline-recommended national or local implementation criteria. Based on available electronic systems, the selection process can be modified to fit the specific therapy. For instance, we are soon about to use the model for implementation of dapagliflozin in our heart failure population.

The model can also be applicable for older drugs that are underutilized, as long as the evidence is still valid. Possible areas would be to introduce, *e.g.*, MRA treatment in patients with HFrEF and moderate renal impairment [182, 194, 195], or prophylactic treatments in patients with osteoporosis [196-198].

By using computerized medical records/databases/registries in a systematic way, it is possible to identify eligible patients within a specified region with limited resources and time. In the case study, we were able to do a broad introduction of sacubitril-valsartan to eligible patients within Umeå healthcare region. The approach guaranties that strict criteria are used in the selection process - assuring that the right patients are assessed - which contributes to the cost-effectiveness and a higher quality of care.

The swift and effective introduction of sacubitril-valsartan was reflected in the national drug statistics from 2016 [199], which was the first year after the drug approval. Figure 20 shows that even with our strict interpretation of the PARADIGM-HF study criteria, our county (Västerbotten) had the fastest introduction of sacubitril-valsartan in the country.

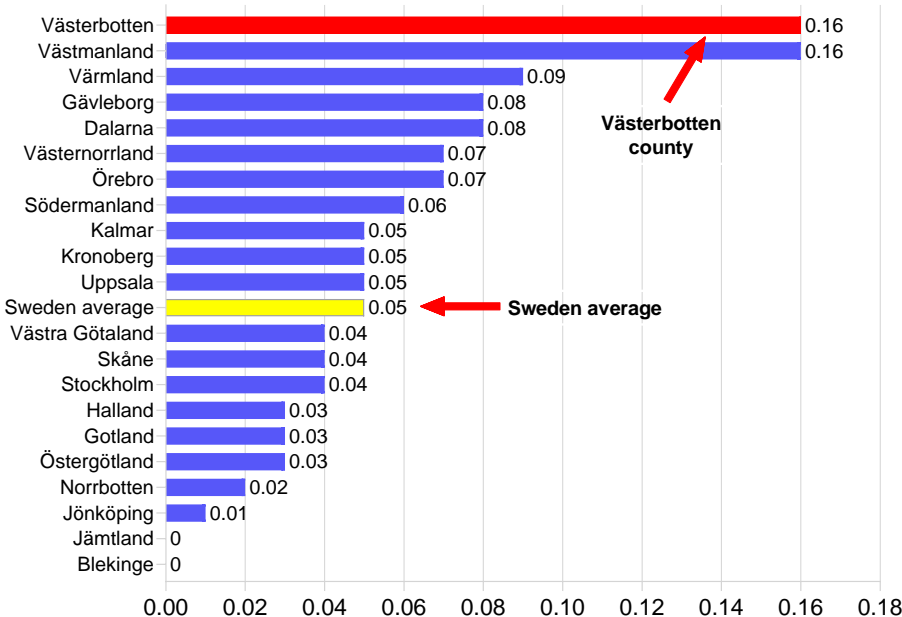


Figure 20. Patients on sacubitril-valsartan per 1000 inhabitants in year 2016 [199].

If healthcare would start using the systematic introduction approach during implementation of novel - or underutilized older - treatments, many patients with chronic disease would get an earlier eligibility assessment. The model is based on strict criteria ensuring that the patient selection is objective and minimizes discrimination due to age, sex, gender, comorbidities etc. A more effective implementation process would result in patients getting access to therapy faster and the healthcare would have a better chance to prevent disease progression and future harmful events.

Instead of waiting for massive education campaigns to be evolved, and rely on the interest and knowledge of the individual clinician meeting the patients, our suggestion is that a dedicated implementation group manage the patient selection with our systematic approach. This group would preferably consist of specialists, nurses, pharmacists, physiotherapists or other appropriate healthcare professionals that are interested in the specific therapy.

Finally, the initial workload is probably more intense with the systematic introduction approach than the conventional implementation process in clinical practice. We have not performed any cost-benefit analyses with the approach, yet it is based on already available data and is therefore easy accessible. If a thoroughly work is made during planning and criteria selection it is possible to choose the most appropriate data sources for the patient selection, and hence, minimizing the workload with the new approach as much as possible. Additionally, the regular annual visits that patients with chronic diseases are summoned to in routine care, are primarily focused on treatment and symptom control and rarely result in an active measure. Our case study showed that using the approach resulted in treatment initiation in the majority of cases, which indicates that the extra work effort was focused on the right patients. Moreover, if the result with the initiated therapy is healthier patients, we believe that the initial short-term budgetary impact will be balanced with cost savings in the long run.

Conclusions

We found that only a quarter of a real-world heart failure population would be eligible for the novel drug sacubitril-valsartan, if treatment guidelines would be as strict as the landmark trial criteria. The majority of patients, and disproportionately many females, were excluded due to intolerance of renin-angiotensin system inhibitors in target doses. Biological sex differences - such as higher age, lower body weight and lower renal function - were the most prominent factors why less women than men achieved target doses of heart failure medications. When the strict landmark trial criteria are applied, they have an inherent bias versus the old and the frail, which in turn disproportionately affects women.

Our simplified initiation management with a direct switch to maximum-dose sacubitril-valsartan, in patients who already tolerated target doses of renin-angiotensin system inhibitors, was safe and generally well tolerated with no serious adverse events or safety issues during the first year.

We developed a new systematic introduction approach for implementation of novel treatments to patients with chronic disease. By applying our approach in routine care, we showed that it was a swift and effective method to introduce a novel drug with limited resources and time. The patients were overall satisfied with the new approach and their confidence in healthcare was maintained.

This is a promising example of how to reduce the gap between clinical trials and clinical practice in patients with chronic disease.

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References

1. Fu M, Vedin O, Svennblad B, Lampa E, Johansson D, Dahlström U, et al. Implementation of sacubitril/valsartan in Sweden: clinical characteristics, titration patterns, and determinants. *ESC heart failure*. 2020. Online ahead of print.
2. Sumarsono A, Vaduganathan M, Ajufo E, Navar AM, Fonarow GC, Das SR, et al. Contemporary Patterns of Medicare and Medicaid Utilization and Associated Spending on Sacubitril/Valsartan and Ivabradine in Heart Failure. *JAMA cardiology*. 2020; 5(3): 336-9.
3. Sangaralingham LR, Sangaralingham SJ, Shah ND, Yao X, Dunlay SM. Adoption of Sacubitril/Valsartan for the Management of Patients With Heart Failure. *Circulation Heart failure*. 2018; 11(2): e004302.
4. DeVore AD, Hill CL, Thomas L, Sharma PP, Albert NM, Butler J, et al. Patient, Provider, and Practice Characteristics Associated With Sacubitril/Valsartan Use in the United States. *Circulation Heart failure*. 2018; 11(9): e005400.
5. Luo N, Fonarow GC, Lippmann SJ, Mi X, Heidenreich PA, Yancy CW, et al. Early Adoption of Sacubitril/Valsartan for Patients With Heart Failure With Reduced Ejection Fraction: Insights From Get With the Guidelines-Heart Failure (GWTG-HF). *JACC Heart failure*. 2017; 5(4): 305-9.
6. Hatala R, Lunati M, Calvi V, Favale S, Goncalvesová E, Haim M, et al. Clinical implementation of cardiac resynchronization therapy-regional disparities across selected ESC member countries. *Ann Noninvasive Electrocardiol*. 2015; 20(1): 43-52.
7. Merkely B, Roka A, Kutyla V, Boersma L, Leenhardt A, Lubinski A, et al. Tracing the European course of cardiac resynchronization therapy from 2006 to 2008. *Europace*. 2010; 12(5): 692-701.
8. Lavoie KL, Rash JA, Campbell TS. Changing Provider Behavior in the Context of Chronic Disease Management: Focus on Clinical Inertia. *Annual review of pharmacology and toxicology*. 2017; 57: 263-83.
9. Kanis JA, Cooper C, Rizzoli R, Reginster JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2019; 30(1): 3-44.
10. Komajda M. The EuroHeart Failure Survey programme—a survey on the quality of care among patients with heart failure in Europe Part 2: treatment. *European heart journal*. 2003; 24(5): 464-74.

11. Savarese G, Carrero JJ, Pitt B, Anker SD, Rosano GMC, Dahlström U, et al. Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: an analysis of 11 215 patients from the Swedish Heart Failure Registry. *European journal of heart failure*. 2018; 20(9): 1326-34.
12. Savarese G, Sartipy U, Friberg L, Dahlström U, Lund LH. Reasons for and consequences of oral anticoagulant underuse in atrial fibrillation with heart failure. *Heart*. 2018; 104(13): 1093-100.
13. Thorvaldsen T, Benson L, Dahlstrom U, Edner M, Lund LH. Use of evidence-based therapy and survival in heart failure in Sweden 2003-2012. *European journal of heart failure*. 2016; 18(5): 503-11.
14. Scott PE, Unger EF, Jenkins MR, Southworth MR, McDowell TY, Geller RJ, et al. Participation of Women in Clinical Trials Supporting FDA Approval of Cardiovascular Drugs. *Journal of the American College of Cardiology*. 2018; 71(18): 1960-9.
15. Tahhan AS, Vaduganathan M, Greene SJ, Fonarow GC, Fiuzat M, Jessup M, et al. Enrollment of Older Patients, Women, and Racial and Ethnic Minorities in Contemporary Heart Failure Clinical Trials: A Systematic Review. *JAMA cardiology*. 2018; 3(10): 1011-9.
16. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation*. 2020; 141(9): e139-e596.
17. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. *Nature reviews Cardiology*. 2011; 8(1): 30-41.
18. Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S, et al. Heart failure: preventing disease and death worldwide. *ESC heart failure*. 2014; 1(1): 4-25.
19. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet (London, England)*. 2012; 380(9859): 2163-96.
20. Lindmark K, Boman K, Olofsson M, Tornblom M, Levine A, Castelo-Branco A, et al. Epidemiology of heart failure and trends in diagnostic work-up: a retrospective, population-based cohort study in Sweden. *Clinical epidemiology*. 2019; 11: 231-44.
21. Zarrinkoub R, Wettermark B, Wandell P, Mejhert M, Szulkin R, Ljunggren G, et al. The epidemiology of heart failure, based on data for 2.1 million

- inhabitants in Sweden. *European journal of heart failure*. 2013; 15(9): 995-1002.
22. Taylor CJ, Ordonez-Mena JM, Roalfe AK, Lay-Flurrie S, Jones NR, Marshall T, et al. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population based cohort study. *BMJ (Clinical research ed)*. 2019; 364: l223.
 23. Mamas MA, Sperrin M, Watson MC, Coutts A, Wilde K, Burton C, et al. Do patients have worse outcomes in heart failure than in cancer? A primary care-based cohort study with 10-year follow-up in Scotland. *European journal of heart failure*. 2017; 19(9): 1095-104.
 24. Agvall B, Borgquist L, Foldevi M, Dahlstrom U. Cost of heart failure in Swedish primary healthcare. *Scandinavian journal of primary health care*. 2005; 23(4): 227-32.
 25. Tanai E, Frantz S. Pathophysiology of Heart Failure. *Comprehensive Physiology*. 2015; 6(1): 187-214.
 26. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *European heart journal*. 2016; 37(27): 2129-200.
 27. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart*. 2007; 93(9): 1137-46.
 28. Mann DL, Zipes DP, Libby P, Bonow RO, Braunwald E, editors. Braunwald's heart disease : a textbook of cardiovascular medicine. 10th ed. Philadelphia, PA: Elsevier; 2015.
 29. Cleland J. The EuroHeart Failure survey programme—a survey on the quality of care among patients with heart failure in Europe Part 1: patient characteristics and diagnosis. *European heart journal*. 2003; 24(5): 442-63.
 30. Schaufelberger M, Ekestubbe S, Hultgren S, Persson H, Reimstad A, Schaufelberger M, et al. Validity of heart failure diagnoses made in 2000-2012 in western Sweden. *ESC heart failure*. 2020; 7(1): 36-45.
 31. Kossmann CE, editor. Diseases of the heart and blood vessels: nomenclature and criteria for diagnosis. 6th ed. Boston: Little, Brown; 1964. p. 114.

32. Persson S. Kardiologi: hjärtsjukdomar hos vuxna [Eng. Cardiology - heart disease in adults]. 5th ed. Lund: Studentlitteratur; 2003.
33. Camm AJ, Lüscher TF, Maurer G, Serruys PW, editors. The ESC textbook of cardiovascular medicine. 3rd ed. Oxford, United Kingdom: Oxford University Press; 2019.
34. Otterstad JE, Froeland G, St John Sutton M, Holme I. Accuracy and reproducibility of biplane two-dimensional echocardiographic measurements of left ventricular dimensions and function. *European heart journal*. 1997; 18(3): 507-13.
35. Wikström G. Hjärtsvikt : fysiologi, diagnostik, behandling och omvårdnad [Eng. Heart failure: physiology, diagnosis, treatment and care]. 1st ed. Lund: Studentlitteratur; 2014.
36. Camm AJ, Lüscher TF, Serruys PW, editors. The ESC textbook of cardiovascular medicine. 2nd ed. Malden, Mass: Blackwell Publ.; 2009.
37. D'Elia E, Iacovoni A, Vaduganathan M, Lorini FL, Perlini S, Senni M. Nephrylsin inhibition in heart failure: mechanisms and substrates beyond modulating natriuretic peptides. *European journal of heart failure*. 2017; 19(6): 710-7.
38. Wong PC, Guo J, Zhang A. The renal and cardiovascular effects of natriuretic peptides. *Advances in physiology education*. 2017; 41(2): 179-85.
39. Diez J. Chronic heart failure as a state of reduced effectiveness of the natriuretic peptide system: implications for therapy. *European journal of heart failure*. 2017; 19(2): 167-76.
40. Singh JSS, Burrell LM, Cherif M, Squire IB, Clark AL, Lang CC. Sacubitril/valsartan: beyond natriuretic peptides. *Heart*. 2017; 103(20): 1569-77. Figure 2, The mechanism of action and the pathways of metabolism of ANP, BNP and CNP; p. 1572.
41. Nakagawa Y, Nishikimi T, Kuwahara K. Atrial and brain natriuretic peptides: Hormones secreted from the heart. *Peptides*. 2019; 111: 18-25.
42. Singh JSS, Burrell LM, Cherif M, Squire IB, Clark AL, Lang CC. Sacubitril/valsartan: beyond natriuretic peptides. *Heart*. 2017; 103(20): 1569-77.
43. Maack T. The broad homeostatic role of natriuretic peptides. *Arq Bras Endocrinol Metabol*. 2006; 50(2): 198-207.

44. Beale AL, Meyer P, Marwick TH, Lam CSP, Kaye DM. Sex Differences in Cardiovascular Pathophysiology: Why Women Are Overrepresented in Heart Failure With Preserved Ejection Fraction. *Circulation*. 2018; 138(2): 198-205.
45. Regitz-Zagrosek V. Therapeutic implications of the gender-specific aspects of cardiovascular disease. *Nat Rev Drug Discov*. 2006; 5(5): 425-38.
46. Lam CSP, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, et al. Sex differences in heart failure. *European heart journal*. 2019; 40(47): 3859-68c.
47. Shin JJ, Hamad E, Murthy S, Pina IL. Heart failure in women. *Clinical cardiology*. 2012; 35(3): 172-7.
48. Shore S, Grau-Sepulveda MV, Bhatt DL, Heidenreich PA, Eapen ZJ, Hernandez AF, et al. Characteristics, Treatments, and Outcomes of Hospitalized Heart Failure Patients Stratified by Etiologies of Cardiomyopathy. *JACC Heart failure*. 2015; 3(11): 906-16.
49. Levinsson A, Dube MP, Tardif JC, de Denus S. Sex, drugs, and heart failure: a sex-sensitive review of the evidence base behind current heart failure clinical guidelines. *ESC heart failure*. 2018; 5(5): 745-54.
50. Nakano A, Egstrup K, Svendsen ML, Schjodt I, Jakobsen L, Mehnert F, et al. Age- and sex-related differences in use of guideline-recommended care and mortality among patients with incident heart failure in Denmark. *Age and ageing*. 2016; 45(5): 635-42.
51. Opasich C, De Feo S, Ambrosio GA, Bellis P, Di Lenarda A, Di Tano G, et al. The 'real' woman with heart failure. Impact of sex on current in-hospital management of heart failure by cardiologists and internists. *European journal of heart failure*. 2004; 6(6): 769-79.
52. Lenzen MJ, Rosengren A, Scholte op Reimer WJ, Follath F, Boersma E, Simoons ML, et al. Management of patients with heart failure in clinical practice: differences between men and women. *Heart*. 2008; 94(3): e10.
53. Gracia Gutierrez A, Poblador-Plou B, Prados-Torres A, Ruiz Laiglesia FJ, Gimeno-Miguel A. Sex Differences in Comorbidity, Therapy, and Health Services' Use of Heart Failure in Spain: Evidence from Real-World Data. *International journal of environmental research and public health*. 2020; 17(6): 2136.
54. O'Meara E, Clayton T, McEntegart MB, McMurray JJ, Pina IL, Granger CB, et al. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: results of the Candesartan in Heart

- failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *Circulation*. 2007; 115(24): 3111-20.
55. Martínez-Sellés M, Doughty RN, Poppe K, Whalley GA, Earle N, Tribouilloy C, et al. Gender and survival in patients with heart failure: interactions with diabetes and aetiology. Results from the MAGGIC individual patient meta-analysis. *European journal of heart failure*. 2012; 14(5): 473-9.
 56. Stolfo D, Uijl A, Vedin O, Strömberg A, Faxén UL, Rosano GMC, et al. Sex-Based Differences in Heart Failure Across the Ejection Fraction Spectrum: Phenotyping, and Prognostic and Therapeutic Implications. *JACC Heart failure*. 2019; 7(6): 505-15.
 57. Dewan P, Rorth R, Jhund PS, Shen L, Raparelli V, Petrie MC, et al. Differential Impact of Heart Failure With Reduced Ejection Fraction on Men and Women. *Journal of the American College of Cardiology*. 2019; 73(1): 29-40.
 58. Tamargo J, Rosano G, Walther T, Duarte J, Niessner A, Kaski JC, et al. Gender differences in the effects of cardiovascular drugs. *European heart journal Cardiovascular pharmacotherapy*. 2017; 3(3): 163-82.
 59. Rosano GM, Lewis B, Agewall S, Wassmann S, Vitale C, Schmidt H, et al. Gender differences in the effect of cardiovascular drugs: a position document of the Working Group on Pharmacology and Drug Therapy of the ESC. *European heart journal*. 2015; 36(40): 2677-80.
 60. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. *Annals of internal medicine*. 1992; 117(3): 234-42.
 61. Santema BT, Ouwerkerk W, Tromp J, Sama IE, Ravera A, Regitz-Zagrosek V, et al. Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study. *Lancet (London, England)*. 2019; 394(10205): 1254-63.
 62. Franconi F, Brunelleschi S, Steardo L, Cuomo V. Gender differences in drug responses. *Pharmacological research*. 2007; 55(2): 81-95.
 63. Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. *Clinical pharmacokinetics*. 2009; 48(3): 143-57.
 64. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, et al. Trends in heart failure incidence and survival in a community-based population. *Jama*. 2004; 292(3): 344-50.

65. Taylor CJ, Ordóñez-Mena JM, Jones NR, Roalfe AK, Lay-Flurrie S, Marshall T, et al. National Trends in Heart Failure Mortality in Men and Women, United Kingdom, 2000-2017. *European journal of heart failure*. 2020. Online ahead of print.
66. Shafazand M, Schaufelberger M, Lappas G, Swedberg K, Rosengren A. Survival trends in men and women with heart failure of ischaemic and non-ischaemic origin: data for the period 1987-2003 from the Swedish Hospital Discharge Registry. *European heart journal*. 2009; 30(6): 671-8.
67. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation*. 1993; 88(1): 107-15.
68. Baumhakil M, Muller U, Bohm M. Influence of gender of physicians and patients on guideline-recommended treatment of chronic heart failure in a cross-sectional study. *European journal of heart failure*. 2009; 11(3): 299-303.
69. Zachariah D, Taylor J, Rowell N, Spooner C, Kalra PR. Drug therapy for heart failure in older patients-what do they want? *Journal of geriatric cardiology : JGC*. 2015; 12(2): 165-73.
70. Skrzypek A, Mostowik M, Szeliga M, Wilczynska-Golonka M, Debicka-Dabrowska D, Nessler J. Chronic heart failure in the elderly: still a current medical problem. *Folia medica Cracoviensia*. 2018; 58(4): 47-56.
71. Lazzarini V, Mentz RJ, Fiuzat M, Metra M, O'Connor CM. Heart failure in elderly patients: distinctive features and unresolved issues. *European journal of heart failure*. 2013; 15(7): 717-23.
72. Turnheim K. Drug therapy in the elderly. *Experimental gerontology*. 2004; 39(11-12): 1731-8.
73. Mogensen UM, Ersboll M, Andersen M, Andersson C, Hassager C, Torp-Pedersen C, et al. Clinical characteristics and major comorbidities in heart failure patients more than 85 years of age compared with younger age groups. *European journal of heart failure*. 2011; 13(11): 1216-23.
74. Mahjoub H, Rusinaru D, Souliere V, Durier C, Peltier M, Tribouilloy C. Long-term survival in patients older than 80 years hospitalised for heart failure. A 5-year prospective study. *European journal of heart failure*. 2008; 10(1): 78-84.
75. Mangoni AA. Cardiovascular drug therapy in elderly patients: specific age-related pharmacokinetic, pharmacodynamic and therapeutic considerations. *Drugs & aging*. 2005; 22(11): 913-41.

76. Bader F, Atallah B, Brennan LF, Rimawi RH, Khalil ME. Heart failure in the elderly: ten peculiar management considerations. *Heart failure reviews*. 2017; 22(2): 219-28.
77. Vasan RS, Xanthakis V, Lyass A, Andersson C, Tsao C, Cheng S, et al. Epidemiology of Left Ventricular Systolic Dysfunction and Heart Failure in the Framingham Study: An Echocardiographic Study Over 3 Decades. *JACC Cardiovascular imaging*. 2018; 11(1): 1-11.
78. Ho JE, Gona P, Pencina MJ, Tu JV, Austin PC, Vasan RS, et al. Discriminating clinical features of heart failure with preserved vs. reduced ejection fraction in the community. *European heart journal*. 2012; 33(14): 1734-41.
79. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Age- and gender-related differences in quality of care and outcomes of patients hospitalized with heart failure (from OPTIMIZE-HF). *The American journal of cardiology*. 2009; 104(1): 107-15.
80. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *European journal of heart failure*. 2017; 19(12): 1574-85.
81. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet (London, England)*. 1997; 349(9054): 747-52.
82. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *The New England journal of medicine*. 2008; 359(23): 2456-67.
83. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *European heart journal*. 2005; 26(3): 215-25.
84. Dungen HD, Apostolovic S, Inkrot S, Tahirovic E, Topper A, Mehrhof F, et al. Titration to target dose of bisoprolol vs. carvedilol in elderly patients with heart failure: the CIBIS-ELD trial. *European journal of heart failure*. 2011; 13(6): 670-80.
85. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *European heart journal*. 2006; 27(19): 2338-45.

86. Konrat C, Boutron I, Trinquart L, Auleley GR, Ricordeau P, Ravaud P. Underrepresentation of elderly people in randomised controlled trials. The example of trials of 4 widely prescribed drugs. *PLoS one*. 2012; 7(3): e33559.
87. Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials*. 2015; 16: 495.
88. Cherubini A, Oristrell J, Pla X, Ruggiero C, Ferretti R, Diestre G, et al. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Archives of internal medicine*. 2011; 171(6): 550-6.
89. Masoudi FA, Havranek EP, Wolfe P, Gross CP, Rathore SS, Steiner JF, et al. Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. *American heart journal*. 2003; 146(2): 250-7.
90. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *The New England journal of medicine*. 2014; 371(11): 993-1004.
91. U.S. Food and Drug Administration (FDA). Evaluation of Sex-Specific Data in Medical Device Clinical Studies - Guidance for Industry and Food and Drug Administration Staff [Internet]: FDA; 2014 [updated 2014 Aug 22; cited 2020 Jul 3]. Available from: <https://www.fda.gov/media/82005/download>.
92. Foulkes MA. After inclusion, information and inference: reporting on clinical trials results after 15 years of monitoring inclusion of women. *J Womens Health (Larchmt)*. 2011; 20(6): 829-36.
93. Geller SE, Koch A, Pellettieri B, Carnes M. Inclusion, analysis, and reporting of sex and race/ethnicity in clinical trials: have we made progress? *J Womens Health (Larchmt)*. 2011; 20(3): 315-20.
94. U.S. Food and Drug Administration (FDA). FDA Research, Policy, and Workshops on Women in Clinical Trials [Internet]: FDA; 2019 [updated 2019 Jun 6; cited 2020 Jul 8]. Available from: <https://www.fda.gov/science-research/womens-health-research/fda-research-policy-and-workshops-women-clinical-trials>.
95. European Medicines Agency (EMA). Medicines for older people [Internet]: EMA; 2020 [cited 2020 Sep 2]. Available from: <https://www.ema.europa.eu/en/human-regulatory/research-development/medicines-older-people>.

96. Andries G, Yandrapalli S, Aronow WS. Benefit-risk review of different drug classes used in chronic heart failure. *Expert opinion on drug safety*. 2018; 1-13.
97. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017; 136(6): e137-e61.
98. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *The New England journal of medicine*. 1991; 325(5): 293-302.
99. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet (London, England)*. 2003; 362(9386): 772-6.
100. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet (London, England)*. 1999; 353(9146): 9-13.
101. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet (London, England)*. 1999; 353(9169): 2001-7.
102. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation*. 2002; 106(17): 2194-9.
103. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *The New England journal of medicine*. 1999; 341(10): 709-17.
104. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *The New England journal of medicine*. 2011; 364(1): 11-21.
105. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *The New England journal of medicine*. 2003; 348(14): 1309-21.

106. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *The New England journal of medicine*. 1987; 316(23): 1429-35.
107. European Medicines Agency (EMA). Renitec - Summary of Product Characteristics [Internet]: EMA; 2003 [updated 2003 Dec 2; cited 2020 Sep 2]. Available from: <https://www.ema.europa.eu/en/medicines/human/referrals/renitec#all-documents-section>.
108. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *The New England journal of medicine*. 2001; 345(23): 1667-75.
109. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial--the Losartan Heart Failure Survival Study ELITE II. *Lancet (London, England)*. 2000; 355(9215): 1582-7.
110. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet (London, England)*. 2009; 374(9704): 1840-8.
111. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet (London, England)*. 2003; 362(9386): 767-71.
112. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *The New England journal of medicine*. 2003; 349(20): 1893-906.
113. Gheorghiade M, Colucci WS, Swedberg K. Beta-blockers in chronic heart failure. *Circulation*. 2003; 107(12): 1570-5.
114. Hall SA, Cigarroa CG, Marcoux L, Risser RC, Grayburn PA, Eichhorn EJ. Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta-adrenergic blockade. *Journal of the American College of Cardiology*. 1995; 25(5): 1154-61.
115. Jhund PS, McMurray JJ. The neprilysin pathway in heart failure: a review and guide on the use of sacubitril/valsartan. *Heart*. 2016; 102(17): 1342-7.

116. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, et al. Effect of nesiritide in patients with acute decompensated heart failure. *The New England journal of medicine*. 2011; 365(1): 32-43.
117. Lillyblad MP. Dual Angiotensin Receptor and Neprilysin Inhibition with Sacubitril/Valsartan in Chronic Systolic Heart Failure: Understanding the New PARADIGM. *The Annals of pharmacotherapy*. 2015; 49(11): 1237-51.
118. Bevan EG, Connell JM, Doyle J, Carmichael HA, Davies DL, Lorimer AR, et al. Candoxatril, a neutral endopeptidase inhibitor: efficacy and tolerability in essential hypertension. *Journal of hypertension*. 1992; 10(7): 607-13.
119. Rouleau JL, Pfeffer MA, Stewart DJ, Isaac D, Sestier F, Kerut EK, et al. Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomised trial. *Lancet (London, England)*. 2000; 356(9230): 615-20.
120. Packer M, Califf RM, Konstam MA, Krum H, McMurray JJ, Rouleau JL, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation*. 2002; 106(8): 920-6.
121. Kostis JB, Packer M, Black HR, Schmieder R, Henry D, Levy E. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *American journal of hypertension*. 2004; 17(2): 103-11.
122. Singh JS, Lang CC. Angiotensin receptor-neprilysin inhibitors: clinical potential in heart failure and beyond. *Vasc Health Risk Manag*. 2015; 11: 283-95.
123. Singh JS, Lang CC. Angiotensin receptor-neprilysin inhibitors: clinical potential in heart failure and beyond. *Vasc Health Risk Manag*. 2015; 11: 283-95. Figure 1, Overview of the mechanisms and effects of nesiritide, candoxatril, omapatrilat, and LCZ 696; p. 287.
124. McCormack PL. Sacubitril/Valsartan: A Review in Chronic Heart Failure with Reduced Ejection Fraction. *Drugs*. 2016; 76(3): 387-96.
125. Gu J, Noe A, Chandra P, Al-Fayoumi S, Ligueros-Saylan M, Sarangapani R, et al. Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi). *J Clin Pharmacol*. 2010; 50(4): 401-14.

126. Dargad RR, Prajapati MR, Dargad RR, Parekh JD. Sacubitril/valsartan: A novel angiotensin receptor-neprilysin inhibitor. *Indian Heart J.* 2018; 70 Suppl 1: S102-s10.
127. Singh JSS, Burrell LM, Cherif M, Squire IB, Clark AL, Lang CC. Sacubitril/valsartan: beyond natriuretic peptides. *Heart.* 2017; 103(20): 1569-77. Figure 3, Schematic representation of mechanism of sacubitril/valsartan on the natriuretic peptide and RAAS; p. 1573.
128. European Medicines Agency (EMA). Entresto: EPAR - Product Information [Internet]: EMA; 2020 [updated 2020 Jul 22; cited 2020 Sept 2]. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/entresto#product-information-section>.
129. U.S. Food and Drug Administration (FDA). Entresto: Highlights of prescribing information [Internet]: FDA; 2017 [updated 2017 Nov 1; cited 2020 Aug 26]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207620s008lbl.pdf.
130. Gan L, Langenickel T, Petruck J, Kode K, Rajman I, Chandra P, et al. Effects of age and sex on the pharmacokinetics of LCZ696, an angiotensin receptor neprilysin inhibitor. *J Clin Pharmacol.* 2016; 56(1): 78-86.
131. Jhund PS, Fu M, Bayram E, Chen CH, Negrusz-Kawecka M, Rosenthal A, et al. Efficacy and safety of LCZ696 (sacubitril-valsartan) according to age: insights from PARADIGM-HF. *European heart journal.* 2015; 36(38): 2576-84.
132. Ruilope LM, Dukat A, Bohm M, Lacourciere Y, Gong J, Lefkowitz MP. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. *Lancet (London, England).* 2010; 375(9722): 1255-66.
133. Williams B, Cockcroft JR, Kario K, Zappe DH, Brunel PC, Wang Q, et al. Effects of Sacubitril/Valsartan Versus Olmesartan on Central Hemodynamics in the Elderly With Systolic Hypertension: The PARAMETER Study. *Hypertension.* 2017; 69(3): 411-20.
134. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *The Lancet.* 2012; 380(9851): 1387-95.
135. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *The New England journal of medicine.* 2019; 381(17): 1609-20.

136. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al. Angiotensin-Nepriylsin Inhibition in Acute Decompensated Heart Failure. *The New England journal of medicine*. 2019; 380(6): 539-48.
137. Wachter R, Senni M, Belohlavek J, Straburzynska-Migaj E, Witte KK, Kobalava Z, et al. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. *European journal of heart failure*. 2019; 21(8): 998-1007.
138. ClinicalTrials.gov. Prospective ARNI vs ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI (PARADISE-MI) [Internet]: NIH U.S. National Library of Medicine; 2016 [updated 2020 Aug 5; cited 2020 Sep 2]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02924727>.
139. European Medicines Agency (EMA). Pharmacovigilance: Overview [Internet]: EMA; 2020 [cited 2020 Sept 2]. Available from: <https://www.ema.europa.eu/en/human-regulatory/overview/pharmacovigilance-overview>.
140. European Medicines Agency (EMA). Pharmacovigilance: Post-authorisation [Internet]: EMA; 2020 [cited 2020 Sept 2]. Available from: <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance-post-authorisation>.
141. Swedish Medical Products Agency. Reporting side effects [Sv: Rapportera biverkningar] [Internet]: Swedish Medical Products Agency; 2020 [updated 2019 Oct 28; cited 2020 Jun 30]. Available from: <https://www.lakemedelsverket.se/sv/rapportera-biverkningar/lakemedel>.
142. European Medicines Agency (EMA). Pharmacovigilance: Medicines under additional monitoring [Internet]: EMA; 2020 [cited 2020 Sept 2]. Available from: <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/medicines-under-additional-monitoring>.
143. European Medicines Agency (EMA). Pharmacovigilance: Post-authorisation safety studies [Internet]: EMA; 2020 [cited 2020 Sept 2]. Available from: <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/post-authorisation-safety-studies-pass-o>.
144. Schaumberg DA, McDonald L, Shah S, Stokes M, Nordstrom BL, Ramagopalan SV. Evaluation of comparative effectiveness research: a practical tool. *J Comp Eff Res*. 2018; 7(5): 503-15.

145. Williams CM, Skinner EH, James AM, Cook JL, McPhail SM, Haines TP. Comparative effectiveness research for the clinician researcher: a framework for making a methodological design choice. *Trials*. 2016; 17(1): 406.
146. Schneeweiss S. Developments in post-marketing comparative effectiveness research. *Clinical pharmacology and therapeutics*. 2007; 82(2): 143-56.
147. Gray EA, Thorpe JH. Comparative effectiveness research and big data: balancing potential with legal and ethical considerations. *J Comp Eff Res*. 2015; 4(1): 61-74.
148. Meyer AM, Wheeler SB, Weinberger M, Chen RC, Carpenter WR. An overview of methods for comparative effectiveness research. *Semin Radiat Oncol*. 2014; 24(1): 5-13.
149. Cars T, Lindhagen L, Sundström J. A framework for monitoring of new drugs in Sweden. *Ups J Med Sci*. 2019; 124(1): 46-50.
150. Godman B, Wettermark B, Hoffmann M, Andersson K, Haycox A, Gustafsson LL. Multifaceted national and regional drug reforms and initiatives in ambulatory care in Sweden: global relevance. *Expert Rev Pharmacoecon Outcomes Res*. 2009; 9(1): 65-83.
151. Wettermark B, Persson ME, Wilking N, Kalin M, Korkmaz S, Hjemdahl P, et al. Forecasting drug utilization and expenditure in a metropolitan health region. *BMC Health Serv Res*. 2010; 10: 128.
152. Region Stockholm. Janusinfo.se: Managed introduction – this is how it works [Internet] Stockholm: Region Stockholm; 2020 [updated 2018 Apr 17; cited 2020 Apr 23]. Available from: <https://www.janusinfo.se/nationelltinforandeavlakemedel/managedintroductionthisishowitworks.4.6b32b8ec162bd97od6bb885.html>.
153. Eriksson I, Wettermark B, Persson M, Edstrom M, Godman B, Lindhe A, et al. The Early Awareness and Alert System in Sweden: History and Current Status. *Front Pharmacol*. 2017; 8: 674.
154. Eriksson I, von Euler M, Malmstrom RE, Godman B, Wettermark B. Did we see it Coming? An Evaluation of the Swedish Early Awareness and Alert System. *Appl Health Econ Health Policy*. 2019; 17(1): 93-101.
155. Lubloy A. Factors affecting the uptake of new medicines: a systematic literature review. *BMC Health Serv Res*. 2014; 14 469.
156. Brody H, Light DW. The inverse benefit law: how drug marketing undermines patient safety and public health. *Am J Public Health*. 2011; 101(3): 399-404.

157. Fonarow GC, Hernandez AF, Solomon SD, Yancy CW. Potential Mortality Reduction With Optimal Implementation of Angiotensin Receptor Nephilysin Inhibitor Therapy in Heart Failure. *JAMA cardiology*. 2016; 1(6): 714-7.
158. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse education today*. 2004; 24(2): 105-12.
159. Weidmann ZM, Breidthardt T, Twerenbold R, Zusli C, Nowak A, von Eckardstein A, et al. Prediction of mortality using quantification of renal function in acute heart failure. *International journal of cardiology*. 2015; 201: 650-7.
160. Jonsson A, Viklund I, Jonsson A, Valham F, Bergdahl E, Lindmark K, et al. Comparison of creatinine-based methods for estimating glomerular filtration rate in patients with heart failure. *ESC heart failure*. 2020; 7(3): 1150-60.
161. Elo S, Kyngas H. The qualitative content analysis process. *Journal of advanced nursing*. 2008; 62(1): 107-15.
162. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qual Health Res*. 2005; 15(9): 1277-88.
163. Pellicori P, Urbinati A, Shah P, MacNamara A, Kazmi S, Dierckx R, et al. What proportion of patients with chronic heart failure are eligible for sacubitril-valsartan? *European journal of heart failure*. 2017; 19(6): 768-78.
164. Nordberg Backelin C, Fu M, Ljungman C. Early experience of Sacubitril-Valsartan in heart failure with reduced ejection fraction in real-world clinical setting. *ESC heart failure*. 2020; 7(3): 1049-55.
165. Perez AL, Kittipibul V, Tang WHW, Starling RC. Patients Not Meeting PARADIGM-HF Enrollment Criteria Are Eligible for Sacubitril/Valsartan on the Basis of FDA Approval: The Need to Close the Gap. *J Am Coll Cardiol HF*. 2017; 5(6): 460-3.
166. Simpson J, Benson L, Jhund PS, Dahlström U, McMurray JJV, Lund LH. "Real World" Eligibility for Sacubitril/Valsartan in Unselected Heart Failure Patients: Data from the Swedish Heart Failure Registry. *Cardiovascular drugs and therapy*. 2019; 33(3): 315-22.
167. Chen X, Schaufelberger M, Fu M. The eligible population of the PARADIGM-HF trial in a real-world outpatient clinic and its cardiovascular risk between 2005 and 2016. *J Cardiovasc Med (Hagerstown)*. 2020; 21(1): 6-12.

168. Kapelios CJ, Lainscak M, Savarese G, Laroche C, Seferovic P, Ruschitzka F, et al. Sacubitril/valsartan eligibility and outcomes in the ESC-EORP-HFA Heart Failure Long-Term Registry: bridging between European Medicines Agency/Food and Drug Administration label, the PARADIGM-HF trial, ESC guidelines, and real world. *European journal of heart failure*. 2019; 21(11): 1383-97.
169. Oh J, Lee CJ, Park JJ, Lee SE, Kim M-S, Cho H-J, et al. Real-World Eligibility for Sacubitril/Valsartan in Heart Failure with Reduced Ejection Fraction Patients in Korea: Data from the Korean Acute Heart Failure (KorAHF) Registry. *Int J Heart Fail*. 2019; 1(1): 57-68.
170. Savarese G, Hage C, Benson L, Schrage B, Thorvaldsen T, Lundberg A, et al. Eligibility for sacubitril/valsartan in heart failure across the ejection fraction spectrum: real world data from the Swedish Heart Failure Registry. *J Intern Med*. 2020. Online ahead of print.
171. Lam PH, Dooley DJ, Fonarow GC, Butler J, Bhatt DL, Filippatos GS, et al. Similar clinical benefits from below-target and target dose enalapril in patients with heart failure in the SOLVD Treatment trial. *European journal of heart failure*. 2018; 20(2): 359-69.
172. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation*. 1999; 100(23): 2312-8.
173. Investigators TN. Clinical outcome with enalapril in symptomatic chronic heart failure; a dose comparison. *European heart journal*. 1998; 19(3): 481-9.
174. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. *Annals of internal medicine*. 2009; 150(11): 784-94.
175. Dungen HD, Musial-Bright L, Inkrot S, Apostolovic S, Edelmann F, Lainscak M, et al. Heart rate following short-term beta-blocker titration predicts all-cause mortality in elderly chronic heart failure patients: insights from the CIBIS-ELD trial. *European journal of heart failure*. 2014; 16(8): 907-14.
176. Fiuzat M, Wojdyla D, Kitzman D, Fleg J, Keteyian SJ, Kraus WE, et al. Relationship of beta-blocker dose with outcomes in ambulatory heart failure patients with systolic dysfunction: results from the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial. *Journal of the American College of Cardiology*. 2012; 60(3): 208-15.

177. Metra M, Torp-Pedersen C, Swedberg K, Cleland JG, Di Lenarda A, Komajda M, et al. Influence of heart rate, blood pressure, and beta-blocker dose on outcome and the differences in outcome between carvedilol and metoprolol tartrate in patients with chronic heart failure: results from the COMET trial. *European heart journal*. 2005; 26(21): 2259-68.
178. Vardeny O, Claggett B, Packer M, Zile MR, Rouleau J, Swedberg K, et al. Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial. *European journal of heart failure*. 2016; 18(10): 1228-34.
179. Rossello X, Ferreira JP, Pocock SJ, McMurray JJV, Solomon SD, Lam CSP, et al. Sex differences in mineralocorticoid receptor antagonist trials: a pooled analysis of three large clinical trials. *European journal of heart failure*. 2020; 22(5): 834-44.
180. Luzier AB, Killian A, Wilton JH, Wilson MF, Forrest A, Kazierad DJ. Gender-related effects on metoprolol pharmacokinetics and pharmacodynamics in healthy volunteers. *Clinical pharmacology and therapeutics*. 1999; 66(6): 594-601.
181. Levitan EB, Van Dyke MK, Loop MS, O'Beirne R, Safford MM. Barriers to Beta-Blocker Use and Up-Titration Among Patients with Heart Failure with Reduced Ejection Fraction. *Cardiovascular drugs and therapy*. 2017; 31(5-6): 559-64.
182. Dev S, Hoffman TK, Kavalieratos D, Heidenreich P, Wu WC, Schwenke DC, et al. Barriers to Adoption of Mineralocorticoid Receptor Antagonists in Patients With Heart Failure: A Mixed-Methods Study. *Journal of the American Heart Association*. 2016; 5(3): e002493.
183. Antol DD, Casebeer AW, DeClue RW, Stenkowski S, Russo PAJAiT. An Early View of Real-World Patient Response to Sacubitril/Valsartan: A Retrospective Study of Patients with Heart Failure with Reduced Ejection Fraction. 2018; 35(6): 785-95.
184. Hsiao FC, Wang CL, Chang PC, Lu YY, Huang CY, Chu PH. Angiotensin Receptor Neprilysin Inhibitor for Patients With Heart Failure and Reduced Ejection Fraction: Real-World Experience From Taiwan. *J Cardiovasc Pharmacol Ther*. 2020; 25(2): 152-7.
185. Martens P, Verluyten L, Van de Broek H, Somers F, Dauw J, Dupont M, et al. Determinants of maximal dose titration of sacubitril/valsartan in clinical practice. *Acta cardiologica*. 2019; 1-10.
186. Pharithi RB, Ferre-Vallverdu M, Maisel AS, O'Connell E, Walshe M, Sweeney C, et al. Sacubitril-Valsartan in a routine community population:

- attention to volume status critical to achieving target dose. *ESC heart failure*. 2020; 7(1): 158-66.
187. Kennedy C, Smith A, Doran S, Barry M. Sacubitril/Valsartan (Entresto®) utilisation and prescribing patterns in the context of a Reimbursement Application System. *Br J Clin Pharmacol*. 2020. Online ahead of print.
 188. Martens P, Belien H, Dupont M, Mullens W. Insights into implementation of sacubitril/valsartan into clinical practice. *ESC heart failure*. 2018; 5(3): 275-83.
 189. Wachter R, Fonseca AF, Balas B, Kap E, Engelhard J, Schlienger R, et al. Real-world treatment patterns of sacubitril/valsartan: a longitudinal cohort study in Germany. *European journal of heart failure*. 2019; 21(5): 588-97.
 190. Dieterle T, Schaefer S, Meyer I, Ackermann G, Ahmed K, Hullin R. Introduction of sacubitril/valsartan in primary care follow-up of heart failure: a prospective observational study (THESEUS). *ESC heart failure*. 2020; 7(4): 1626-34.
 191. Lau CW, Martens P, Lamberts S, Dupont M, Mullens W. Effects of sacubitril/valsartan on functional status and exercise capacity in real-world patients. *Acta cardiologica*. 2019; 74(5): 405-12.
 192. Chang HY, Feng AN, Fong MC, Hsueh CW, Lai WT, Huang KC, et al. Sacubitril/valsartan in heart failure with reduced ejection fraction patients: Real world experience on advanced chronic kidney disease, hypotension, and dose escalation. *J Cardiol*. 2019; 74(4): 372-80.
 193. Albert NM, Swindle JP, Buysman EK, Chang C. Lower Hospitalization and Healthcare Costs With Sacubitril/Valsartan Versus Angiotensin-Converting Enzyme Inhibitor or Angiotensin-Receptor Blocker in a Retrospective Analysis of Patients With Heart Failure. *Journal of the American Heart Association*. 2019; 8(9): e011089.
 194. Jonsson A, Norberg H, Bergdahl E, Lindmark K. Obstacles to mineralocorticoid receptor antagonists in a community-based heart failure population. *Cardiovascular therapeutics*. 2018; e12459.
 195. Savarese G, Carrero JJ, Pitt B, Anker SD, Rosano GMC, Dahlstrom U, et al. Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: an analysis of 11 215 patients from the Swedish Heart Failure Registry. *European journal of heart failure*. 2018; 20(9): 1326-34.

196. Vandenbroucke A, Luyten FP, Flamaing J, Gielen E. Pharmacological treatment of osteoporosis in the oldest old. *Clin Interv Aging*. 2017; 12 1065-77.
197. Curtis JR, Safford MM. Management of osteoporosis among the elderly with other chronic medical conditions. *Drugs & aging*. 2012; 29(7): 549-64.
198. Dell R, Greene D. Is osteoporosis disease management cost effective? *Curr Osteoporos Rep*. 2010; 8(1): 49-55.
199. National Board of Health and Welfare. Drug statistics [internet]. Stockholm: National Board of Health and Welfare; 2016 [2020 Aug 3]. Available from: <https://www.socialstyrelsen.se/statistik-och-data/statistik/statistikamnen/lakemedel/>.

