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ASPECTS ON HEART FAILURE AND DRUG TREATMENT IN GERIATRIC PATIENTS

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Aspects on heart failure and drug treatment in geriatric patients

Thesis for Doctoral Degree (Ph.D.)

By

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To my family

Popular science summary of the thesis

Background

Many geriatric patients are multimorbid and have many drug prescriptions and geriatricians devote much time to optimize the prescriptions. In study I wanted to investigate the correlations between making many changes in the medication list and factors such as comorbidity, number of drugs, length of care episode, age, gender, and prescription quality.

The most common cause for admission to hospital among the elderly in the developed world is heart failure (HF). Geriatric care in Stockholm, where our studies have been performed, are not a part of the HF care chain, but still the most common diagnosis in geriatric care. In study II and III I aimed to evaluate investigations and treatment for HF patients prior to admission to geriatric care and during the inpatient geriatric care episode and, additionally, the content in the referrals between the caregivers.

In study IV I wanted to examine the effect of a group of Alzheimer drugs, cholinesterase inhibitors (ChEIs), with known effects also on cardiovascular dysfunction, among patients with both Alzheimer's dementia (AD) and HF. We analyzed the effects on mortality and risk of hospitalization for cardiovascular disorder such as HF.

Methods and results

In study I, patients treated in a geriatric clinic for pneumonia during one care episode in 2005 (n=134), 2010 (n=146), and 2015 (n=140) were included. To evaluate quality in prescribing, an "inappropriate drug use index" (IDU), based on indicators "for good drug therapy among the elderly" developed by the Swedish National Board of Health and Welfare was constructed. The results showed that the patients during 2015 had more comorbidities, more drugs, shorter hospital stays, and fewer drug changes than in 2005. High activity in drug changes was correlated to increased quality in prescribing and to longer care episodes.

In study II, data on 134 patients prior to admission to geriatric care due to HF were collected. We found that most of the patients were investigated according to guidelines for HF diagnostics, such as ultrasound of the heart (ECHO) and blood biomarkers for HF (NT-pro-BNP), but the investigations were old (mean 463 and 156 days respectively). Most patients with HF with reduced heart pump

ability (reduced ejection fraction, HFrEF)) were prescribed drugs according to European guidelines for HF but did not reach adequate dosing.

In study III, the same 134 patients as in Study II were studied, but in Study III, data from their hospital stay in a geriatric clinic for treatment and care for their HF was collected. Very few additional investigations were performed. The physicians did not change disease modifying drugs nor dose for treatment of HF, but use and dose of diuretics were significantly increased. Diuretics reduce fluid excess and are recommended as symptom relief but not as a disease modifying drug.

When the patients were transferred to primary care much of the information given to the geriatric clinic on status of HF and treatment was not transferred to primary care.

In study IV we compared two well-matched groups of 455 individuals each, with both HF and AD. One group was treated with drugs from the anti-dementia drug group cholinesterase inhibitors (ChEIs) and the other group was not. In addition to effects on cognition the ChEIs have been found to affect cardiovascular function. Treatment with ChEIs was associated with a lower mortality (21%) and a lower risk of hospitalization for HF (47%).

Discussion and conclusions

Discussion: HF patients in our studies were investigated according to guidelines for HF diagnostics, but these investigations were often more than one year old. During the geriatric care episode very few additional investigations were made. Since the patients were high consumers of inpatient care, with on average 3.8 admissions the previous 12 months, updated investigations could have given a basis for improved treatment decisions for their HF.

The patients with HFrEF were treated with the two most important recommended drugs, but the doses did not reach the recommended level. During the geriatric care episode, very few changes were made concerning the drugs which can modify the disease. The major drug changes were done with symptom-relieving drugs.

Although HF is the most common disease in geriatric patients, geriatric care in Region Stockholm does not have an assignment to perform HF related investigations nor perform follow-up. This lack of assignment can probably

contribute to the low activity in diagnostics of type of HF and a treatment focus on symptoms rather than long-term effects.

Activity in drug prescribing correlated to quality in prescribing in study I, given that prescription changes reflect quality. It also correlated to the length of the care episode. During the ten studied years, activity decreased along with a decrease in the length of care episodes. Shorter care episodes may also have had effect on the lack of activity concerning HF drugs showed in Study II and III.

In study IV we found a correlation between being treated with ChEIs and reduced mortality and reduced risk of hospitalization due to HF in patients with AD and HF. Changes in the autonomic nervous system and presence of inflammation are common traits in AD and HF and likely important explanations to the effects seen in study IV.

Conclusions: An important reason for the insufficient investigation (aiming to define type of HF) and treatment in geriatric HF is the fact that geriatric care In Region Stockholm is not a part of the care chain and has no assignment for investigation and follow-up. Attitudes to aging may also come into play with less attention towards a patient group with high age, complex multimorbidity and frailty. Further, most geriatric HF patients are not attended to by cardiologists. Better collaboration between geriatricians and other specialties such as cardiology is needed as is a clear responsibility for treatment and care for geriatric HF patients.

The results of study I indicated that when geriatricians were given more time to treat patients, the result was a higher quality of drug prescribing. The present short duration of inpatient geriatric care episodes/hospital stay is probably not beneficial for frail geriatric patients with several comorbidities and complex symptomatology and may increase the risk of readmission.

Treatment with ChEIs in patients with AD and HF was associated with a significant decrease in mortality and large reductions in the risk for readmission for HF. A significant association between ChEI and cardiovascular morbidity was shown, making future studies on effects of the ChEIs in patients with HF but without AD intriguing.

Abstract

Background: Patients with chronic heart failure (HF) are very common in geriatric care, but the prevalence of different types of HF and comorbidities, as well as the nature of investigations, treatment, planning and outcome in this patient group are less well known. The overall aim of this thesis was to assess central aspects of geriatric care such as strategies for drug changes and in particular, investigations and treatment strategies for geriatric patients with HF prior to and during geriatric care. Finally, treatment in a subgroup of patients with both HF and Alzheimer´s disease (AD) was studied.

Study I: Data were extracted during one geriatric care episode in 2005, 2010 and 2015 and prescription trends and factors contributing to drug changes were analyzed. Compared to 2005, patients in 2015 had more comorbidities and used more drugs but had shorter hospital stays and significantly fewer prescription changes. We found that high activity in prescribing correlated to higher quality of drug use and to longer care episodes.

Study II: Data on diagnostics and treatment of HF from a cohort of 134 patients prior to admission to geriatric care for worsening of HF were collected. We found that a majority had been investigated with echocardiography (ECHO) and NT-pro-BNP, but most of the investigations were old and not updated, particularly in patients with HF with preserved ejection fraction (HFpEF, 53%). Patients with HF with reduced ejection fraction (HFrEF) were treated according to guidelines, but only to half of target doses.

Study III: The same cohort as in Study II was used. In Study III, retrospective data on diagnostics and treatment of HF during an inpatient hospital stay in a clinic specialized in geriatric medicine was obtained. Few additional investigations on etiology and status of HF were performed. The geriatricians did not change the prescriptions of angiotensin converting enzyme inhibitors or angiotensin II receptor blockers (ACEI/ARB) or beta blocking agents (BB) but increased the treatment with furosemide to a large extent and mineralocorticoid receptor antagonists (MRA) to some extent. The information given from the previous caregiver to geriatric care was at discharge significantly washed-out in the referrals from geriatricians to primary care physicians.

Study IV: In a (propensity score) matched cohort of individuals with HF and AD where 455 were treated with cholinesterase inhibitors (ChEIs) and 455 were not, we wanted to investigate whether use of ChEI, known to affect cardiovascular function, affect the risk of hospitalization for HF and mortality. Indeed, it was

found, that treatment with ChEIs was associated with a significantly lower mortality (21%) and a lower risk of hospitalization for HF (47%).

Conclusion: This thesis shows that many geriatric patients with chronic HF do not have up-dated information on type of HF and consequently do not receive adequate drug treatment nor adequate dosing according to guidelines. There is also a significant loss of information on HF etiology and treatment in referrals between caregivers. One reason may be short care episodes. The results of study I indicated that when geriatricians were given more time to treat patients, the result was a higher quality of drug prescribing.

It is urgent to increase adherence to HF guidelines regarding investigations and treatment for HF in older people. In addition, the collaboration between specialists in cardiology and geriatric medicine and primary care must be increased and encouraged.

Interestingly, we also found that individuals with HF and AD who were treated with ChEIs was associated with improved survival and a decreased risk of hospital care for HF. This may be explained by the anti-inflammatory properties and negative chronotropic effects of the ChEIs and warrants further study.

List of scientific papers

This thesis is based on the following papers, which will be referred to in the text by their roman numerals (I-IV).

I Reimers Wessberg, M., Eriksdotter, M., Seiger, A., Fastbom, J.
Prescription Changes During Geriatric Care Episodes:
A Trend Analysis Conducted in Sweden
Drugs Aging 2018, 35:243–24

II Reimers Wessberg, M., Seiger, A., Fastbom, J., Eriksdotter, M.
Few Geriatric Heart Failure Patients Investigated According to Clinical Guidelines: A Retrospective Review of Patient Records
BMC Geriatrics 2023, Mar 21;23(1):155

III Reimers Wessberg, M., Fastbom, J., Ugarph-Morawski, A., Seiger, A. Eriksdotter, M.
Geriatric Contribution to Heart Failure Care: A Retrospective Review of Patient Records
In manuscript

IV Reimers Wessberg, M., Xu, H., A., Fastbom, J., Seiger, A., Eriksdotter, M.
Cholinesterase Inhibitors and Reduced Risk of Hospitalization and Mortality in Patients with Alzheimer's Dementia and Heart Failure
Submitted to European Journal of Heart Failure

Contents

List of abbreviations

ACEI	Angiotensin converting enzyme inhibitor
ACh	Acetylcholine
AD	Alzheimer's Disease
ADR	Adverse drug reactions
ARB	Angiotensin II receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitors
ANS	Autonomic nervous system
BB	Beta blocking agents
BFCN	Basal forebrain cholinergic neurons
CAP	Cholinergic anti-inflammatory pathway
CCI	Charlson's Comorbidity Index
ChEI	Choline esterase Inhibitors
CVD	Cardiovascular disease
ECHO	Echocardiography
ESC	European Society of Cardiology
EF	Ejection fraction
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
IDU	Inappropriate drug use
LV	Left ventricle
NYHA	New York Heart Association
MRA	Mineralocorticoid receptor antagonists
NT-pro-BNP	N-terminal-pro-brain natriuretic peptide

1 Introduction

I started my education in medicine at the age of 44, after a career as a journalist in politics and in musicology and thereafter as an entrepreneur in music publishing with focus on classical music. In the middle of life, I found myself at a path choice and decided to fulfill my childhood dreams of becoming a physician. Without moral and concrete support from my late husband HG Wessberg it would not have happened.

When I eventually decided to specialize in geriatrics, I was obviously a mature person and could carry responsibilities in the role with confidence. In clinical daily life we worked in a stream of patients with several disorders, and I started to reflect on what we really did on an aggregated level. One task was the daily extensive work with monitoring drug changes – what was the effect of our work? This simple question led eventually to study I in my thesis.

Somewhere along the road Kristina Jarl, head of the physicians at the geriatric clinic, asked me if I should start research and write a thesis. I thought it through and remembered that research was another of my secret wishes. I told Kristina the next day that I would.

Heart failure is the disease that I have been working with. Being the most common cause of admission to geriatric care, it was a natural start: what do we do as geriatricians, how do we do it, what benefit do we achieve for our patients? Such questions could be applied to several diseases but in the center of geriatric care stands heart failure: the aging heart in the aging person dependent on our knowledge, understanding, competence, and willingness to act.

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Geriatrics is a specialty with a mission of investigation and treatment of illness in aging people. The field is extensive and complicated, due to the high rate of diversity between patients and interactivity between accumulating damages, illnesses, treatments, and effects of aging. However, partly due to this complexity, clinical science has been more occupied with illness in younger people, with more limited or well-defined conditions. The results of research may be caring programs with conflicting content for people with several illnesses. Still, the need of health care is larger among old multimorbid patients and therefore the need of knowledge is extensive. Partly due to the knowledge gap about complicated health situations among older people, there has been a relatively

greater focus on short-term symptom relief rather than curing or disease modifying activities.

Aging per se brings several changes in a human body. It entails loss of function, and increased vulnerability to environmental challenges and diseases, as well as different responses to treatment.

Knowledge about the aging body is far from fully explored. Older people are treated with more drugs than younger, even though the knowledge about the effect on the body is lower among the elderly. Many elderlies are multimorbid and hence treated with several drugs, potentially inducing conflicting drug effects.

In this thesis, my focus is on some major aspects of diseases and treatment among older persons where there is a lack of knowledge. Patterns of drug changes during a geriatric care episode are investigated. Since heart failure (HF) is the most common cause for admission to hospital among people over 65 years of age, in developed countries worldwide we chose to study HF in geriatric patients from investigation and treatment, outside and inside the geriatric ward. In addition, we have also studied HF in older patients with Alzheimer disease (AD) and based on previous knowledge on cardiovascular effects by the AD drugs cholinesterase inhibitors (ChEI) investigated their cardiovascular effects in patients with both AD and HF.

In total, this work wants to contribute to the picture of assessments and treatments of geriatric patients, particularly with HF.

2 Literature review

2.1 Aging

Aging may be seen as a progressive loss of functions leading to increased vulnerability to environmental challenges and diseases[1]. Research on aging explores the decline in function during adulthood and aging has grown with close to 300.000 publications during the last decade. Lopez-Otin et al. suggested in 2013[2] nine hallmarks of aging and in 2023[3] twelve: genomic instability, telomere attrition, epigenic alterations, loss of proteostatis, disabled macro autophagy, reregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis.

Aging also brings psychological challenges and increased risks of depression. Zenebe[4] reported in a review that the average expected prevalence of depression in old age was 31.7%. Zhang[5] et al reported that depression was a risk factor for cardiovascular diseases and can affect the prognosis.

Of particular interest when studying two of the major diseases, heart failure (HF) and Alzheimer's disease (AD), among geriatric patients are changes in the autonomic nervous system, including the cholinergic system and development of inflammation.

A longer life span also accumulates age-related changes such as inflammation, and inflammation plays a distinct role in AD[6] but also in HF with preserved ejection fraction (HFpEF), the most common type of HF among geriatric patients. Holmes[6] reported that systemic inflammation is largely considered to be a contributor to the disease progression, however emerging evidence suggest that its role may precede the deposition of amyloid. Holmes also emphasized that discussion on inflammation in AD has been too much focused on central inflammation in contrast to systemic inflammation. Inflammation has also been suggested to play a key role in development of cardiac diseases, especially in HF[7, 8]. Murphy et al[8] reported that the strongest associations of inflammatory markers may exist in the context of HFpEF, the form of HF that increases in prevalence with age.

2.2 Geriatric care

2.2.1 Historic remarks on aging and geriatric care

Care of and interest for elderly and elderly ill people has a long history. Hippocrates has been thought to consider age as a disease[9], whereas Aristotle regarded aging as a natural process associated with increasing illnesses, but not as a disease entity in its own right[9]. The oldest essay on aging is written by Cicero: "On old age" in 44 B.C.[10].

Despite the long history, the need for advanced care has developed along with aging populations only during the last 150 years. George E. Day published his "Practical treatise on the domestic management and most important diseases of advanced life" in 1849[11]. J.M. Charcot published his "Clinical lectures on the Diseases of Old Age" in 1881, discussed by Huard[12]. The term geriatrics was first suggested by I.L. Nascher in "Geriatrics: The Diseases of Old Age and Their Treatment" in 1914[13]. The first chair of geriatric medicine in the UK was established in Glasgow 1965[14].

2.2.2 Contemporary geriatric care

The development of geriatrics during the 20th century has been impressing. Still, the nature of geriatric care depends on the complexity of diseases and diversity of the aging patient. This leads to a situation where symptom relief may be relatively more attended to than in most other specialties, sometimes at the cost of disease modifying activities. The tension between these two cornerstones may further complicate the care for elderly.

Geriatric care differs between countries, in terms of recognition, training, educational and professional standards, academic representation and working context[15]. The recognition of geriatric medicine differs significantly. A survey of geriatric rehabilitation showed large differences with respect to recognition as well as days in a geriatric rehabilitating setting (7-65)[16]. In Greece, for example, it is still (2020) not recognized as a specialty, subspecialty, or a competence[15].

Frailty is a relatively new concept in geriatric care, discussed since the 1980-ies[17] and defined as a condition of decreased physiologic reserve that leads to vulnerability to stressors that increase the risk of negative health-related outcomes, such as premature mortality, hospitalization or development of disabilities in basic daily living[19].

Risk factors for development of frailty are cognitive decline, physical inactivity, poor nutrition, and lack of social support. Frailty has also been discussed as a risk factor for cardiovascular diseases, as well as cardiovascular diseases being a risk factor for frailty[20]. There are several proposals made on how to assess frailty, including the Frailty Index [17] and the Clinical Frailty Scale [21] but no gold standard has yet been established. Frailty can also be described as a transition between successful aging and disability[22].

Comprehensive geriatric assessment (CGA) is a multidisciplinary method developed to identify and evaluate medical, functional, psychological, and social capabilities, to assess frailty and geriatric syndromes[23]. CGA in primary care delivered to older adults at high risk of hospitalization has been found to be cost-effective with lower cost and greater effect at follow-up after 24 months[24].

2.2.3 Pharmacological aspects of geriatric care

Aging per se brings new challenges for drug treatment among the elderly. Older people become more sensitive to drugs due to age-related physiological changes in both pharmacokinetics and pharmacodynamics[25].

The pharmacokinetic changes lead to reduced elimination of drugs and thus the risk for prolonged action and increased levels in the body. Most importantly, kidney function declines[26], which leads to a reduced excretion of water-soluble drugs and drug metabolites. The liver's size and blood flow can also decrease, as well as the capacity of some of its enzymes, which can lead to impaired metabolism of fat-soluble drugs[27]. Further, the amount of body water decreases with age, which leads to an increased proportion of body fat. This means that fat-soluble drugs, for example many psychotropic drugs, get a larger volume of distribution which may lead to prolonged effects[28].

Pharmacodynamic changes affect how the drugs act on cells, organs, and regulatory systems. For example, with increasing age, the brain becomes more sensitive to drugs with central nervous effects. This increases the risk of side effects such as sedation, cognitive impairment and falls, from for example sedatives, hypnotics, opioids and drugs with anticholinergic effects[25]. The ability to regulate blood pressure is also affected, which can lead to an increased sensitivity to drugs with blood pressure-lowering effects, with an increased risk of blood pressure falls. Moreover, the protective mechanisms in the mucosa of

the gastrointestinal tract are impaired[29], leading to an increased risk of ulcers and bleeding from drugs that affect the mucosa, especially anti-inflammatory drugs and acetylsalicylic acid.

Moreover, the number of drugs prescribed to older patients has been constantly growing during the last decades. Reasons for this are new drugs, new indications, and improved care. With new drugs and enhanced care patients survive longer and medication will be prolonged.

Polypharmacy, often defined as five or more drugs[30], is therefore a growing phenomenon. This development can be understood from various aspects. Disease-specific guidelines often lack management of comorbidities and multimorbidity is rising in the population. New drugs and new indications are presented. Improvement of welfare and progress in treating elderly extends the lifespan and increases the number of very old with long medication lists. Deprescribing is less developed.

The number of prescribed drugs among old people has increased with age and with time in recent decades. Polypharmacy in persons aged 77 increased from 18% to 42% during 1992-2002[31]. The percentage of adults with five or more prescriptions doubled from 11.4% to 20.5 between 1995 and 2010[32]. In Sweden in 2013, 20% hade five or more drugs at age 65 and 55% at age 95[33]. In 2018, Midao et al[34] reported rates of polypharmacy between 26.3 and 39.9 in patients 65 years and older in 17 European countries.

Risk factors for polypharmacy include the presence of one or more chronic conditions, poor medical records, automatic prescriptions of ongoing medication, transition errors, prescriptions focused only on disease-specific needs[30], and persons cared for by multiple subspecialist physicians but no primary care physician[35]. Other risk factors associated with polypharmacy are recent hospital discharge, high number of prescribers, comorbidities including circulatory diseases, neurological motor dysfunctioning, old age, cognitive impairment, and disability in daily living[36].

Risks for adverse outcomes, such as drug-drug interactions, drug-disease interactions, and adverse drug reactions, as well as the risk of medication errors, increase with the number of drugs. Still, polypharmacy can be appropriate in patients with complex medical issues.

The potentially harmful interactions for drug use in elderly patients are associated with age-related physiological changes in pharmacokinetic and pharmacodynamic parameters and to the simultaneous use of drugs for different diseases. Hines and Murphy[37] discussed the risks with drugs including angiotensin converting enzyme inhibitors/angiotensin II receptor blockers (ACEIs/ARBs), benzodiazepines, phenytoin, lithium, tamoxifen, and warfarin and concluded that increased awareness and actions to reduce exposure and minimizing the risks when introducing drug combinations in the elderly are needed.

The relationship between polypharmacy and frailty has been discussed by Gutierrez-Valencia et al[38], suggesting that the causal relationship may be bidirectional, and that polypharmacy may be a major contributor to the development of frailty.

Studies on the influence of geriatric care on quality in drug prescription are infrequent and report conflicting effects. A Danish study of effects of a geriatric care episode[39] showed that the anticholinergic and benzodiazepine prescriptions were reduced significantly in the geriatric ward and to a greater degree than in other medical wards. Dauphinot[40] on the other hand reported that the use of anticholinergic and sedative drugs increased during stays in geriatric clinics in France. Larsen[41] showed that geriatric care resulted in relatively few changes in medication prescriptions.

Although it is easy to identify risks in changes in drug treatment among geriatric patients it is still also correct to state that progress in pharmaceutical treatment has contributed to the large improvements seen in medical care during the last decades.

2.3 Heart failure

2.3.1 Definitions, classifications

HF can be described more as a clinical syndrome than a specific disease, which makes definitions and classifications more complex than for diseases with strict pathologic standards for diagnosis.

HF constitutes an inability of the heart to deliver sufficient output. HF is often a result of disturbed myocardial function or valvular or pericardial illness, that lead

to disturbed blood flow and fluid retention, which in turn results in peripheral edemas, dyspnea, and/or fatigue.

The inability to deliver the needed cardiac output can relate to disturbances in both contracting and relaxing functions of the myocardium[42]. Ejection fraction (EF) is defined as the fraction of the blood content in the ventricle that is being ejected at a heartbeat. An EF of 50% or above is defined as normal. When the contracting function is disturbed, the EF will be reduced.

The definition of HF requires two or three criteria[43], see Table 1.

TABLE 1 Criteria for definitions of HF type

Criteria	HFrEF	HFmrEF	HFpEF
1	Symptoms and/or signs	Symptoms and/or signs	Symptoms and/or signs
2	LVEF≤40%	LVEF 41-49%	LVEF ≥50%
3			Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction or raised LV filling pressures, including raised NT-pro-BNP/BNP.

LV: Left ventricle

HF with reduction of ejection fraction (HFrEF) was, by the European Society of Cardiology (ESC) during the period of 2016-2021[44], defined as an EF of less than 40% and is since 2021[43] by ESC defined as an ejection of 40% or less, of the blood volume in the ventricle. When, instead, the relaxing function is disturbed, the EF can be normal or preserved, but still the cardiac output will be too low due to reduced filling of the heart. In these cases, the HF is referred to as HF with preserved EF (HFpEF; EF≥50%). HF with an EF between 41 and 49% is called HF with mildly reduced ejection fraction (HFmrEF). Since HFpEF have a preserved EF an additional criterion of structural and/or functional abnormalities or raised NT-pro-BNP is needed.

Recently there has been a proposal of yet another type of EF, the supra normal with an EF>65% (HFsnEF)[45]. Wehner et al[46] report a high prevalence of cardiovascular complications and a U-shaped mortality curve among patients with HFsnEF.

NT-pro-BNP and BNP are of diagnostic and prognostic value in HF patients[47]. Low values of NT-pro-BNP or BNP is, together with a normal ECG considered excluding HF. NT-pro-BNP and BNP are dependent on age and of comorbidities such as chronic renal failure, type 2 diabetes, and acute coronary syndrome, as well as on manufacturer. Therefore, determination of reference values as well as interpretation of results are challenging.

TABLE 2: Changes in definition of HFrEF and HFmrEF according to ESC

	HFrEF	**HFmrEF**	**HFpEF**
Definitions by ESC 2012-2021	EF <40%	EF 40-49%	EF ≥50%
Definitions by ESC since 2021	EF ≤40%	EF 41-49%	EF ≥50%

In a Consensus statement 2021[48], the heart failure societies in America, Europe and Japan suggested a new universal definition and classification of heart failure, see Table 3.

TABLE 3: Suggestion for new definition and classification of HF according to HF societies in America, Europe, and Japan 2021.

At-risk for heart failure (Stage A)	Pre-Heart failure (Stage B)	Heart failure (Stage C)	Advanced heart failure (Stage D)
Patients at risk för HF but without current or prior symptoms or signs of HF and without structural, biomarker, or genetic markers of heart disease	Patients without current or prior symptoms or signs of HF but evidence of one of the following: structural heart disease, abnormal cardiac function or elevated levels of NT-pro-BNP or elevated cardiac troponin levels in the setting of exposure to cardiotoxins	Patients with current or prior symptoms and/or signs of HF caused by structural and/or functional cardiac abnormality	Severe symptoms and/or signs of HF at rest, recurrent hospitalizations despite GDMT, refractory or intolerant to GDMT requiring advanced therapies such as consideration for transplant, mechanical circulatory support, or palliative care

GDMT=Guideline-directed medical therapy

Further, HF is classified into stages based on the patient's limitations during physical activity, according to New York Heart Association (NYHA)[49], see Table 4.

TABLE 4: Classification according to NYHA

NYHA I	No symptoms
NYHA II	Symptoms like dyspnea and fatigue at more than moderate effort
NYHA III	Symptoms like dyspnea and fatigue at mild to moderate effort
NYHA IV	Symptoms like dyspnea and fatigue at rest

2.3.2 Prevalence

The prevalence of HF varies considerably between countries and studies[50], but about 10% of the population aged 70 and older are considered to suffer from HF[51]. Over 50% of HF are assessed as HFpEF[52]. With aging the number of patients with HFpEF is increasing more than the number of patients with HFrEF. HFpEF has increased in relative prevalence and the patients are older, more often women and more often suffer from hypertension and atrial fibrillation. In older women, more than 80% of new HF have HFpEF[53]. Nearly all patients aged 90 and older with HF have HFpEF[54].

Bui et al estimated the worldwide prevalence of HF to 23 million in 2011[52] and Savarese et al. to 64 million in 2021[55].

2.3.3 Etiology and pathogenesis

HF is characterized by a heterogenous etiology. The heart needs to adequately both relax and contract the ventricles to produce effective heart beats and effective oxygenation of the body. Thus, there are numerous causes and contributing factors when this complex activity is not properly performed.

The causes are found at the molecular, cellular, organ, and functioning levels. To understand HF, it is crucial to view it from several angles: hemodynamic, cardiorenal and neurohumoral aspects as well as abnormal calcium metabolism, hypertension, storage diseases, toxic effects, kidney failure, diabetes, cell apoptosis, and genetics[56].

Structural changes in the myocardium due to myocardial infarction, cardiomyopathies or fibrosis can result in hemodynamic changes leading to impaired contraction or relaxation. A decreased pumping ability in the heart will lead to decreased flow through the kidneys. Such a decreased flow will lead to activation of the renin-angiotensin-aldosterone-system (RAAS) and reduced secretion of erythropoietin. The activation of the RAAS system will lead to increased vasoconstriction and salt and water retention with increased secretion of noradrenalin and reduced diuresis[57] which will enhance the vicious circle. A reduced secretion of erythropoietin will cause a reduction in hemoglobin production, which decreases the ability of the blood to transport oxygen.

Amyloidosis constitutes a form of structural change. Amyloidosis comprises a heterogeneous group of disorders leading to the extracellular deposition of amyloid, a fibrillar material derived from various precursor proteins[58]. When amyloid deposits occur in the heart it causes an infiltrative and restrictive cardiomyopathy[59]. Wildtype transthyretin amyloidosis has been recognized as a cause of HFpEF, accounting for 13% of HFpEF[60].

However complex HFrEF and HFpEF are, they mainly belong to two different comorbidity groups.

HFrEF is correlated to ischemic heart disease including myocardial infarction with scarring, remodeling of the heart muscle and eventually an inability to contract the muscle efficiently, leading to a reduction in the proportion of blood (<40%) being ejected from the heart into the aorta.

HFpEF is distinguished from HFrEF and has more comorbidities, particularly more atrial fibrillation, and chronic kidney disease[61]. The stress on the heart will decrease its ability to relax, leading to a decreased filling of blood into the heart chambers. The heart will then, despite a normal EF (50% or above), not provide the body with sufficient cardiac output. Although there are several mechanisms contributing to HFpEF, central to the pathogenesis seems to be the inflammation-induced endothelial dysfunction and impaired natriuretic peptide signaling, leading to cardiac stiffness[62].

Over time, many factors contribute in different ways to HF, which can be due to damaged myocardium, arrhythmias or abnormal loading conditions[63]. Examples of damaged myocardium are myocardial scarring, endothelial dysfunction, toxic damage from alcohol, heavy metals or radiation, infiltration in for example amyloidosis, metabolic derangements, or genetic abnormalities. Examples of abnormal loading conditions is hypertension, valve defects, myocardium structural defects, pericardial and endomyocardial pathologies. Arrhythmias can be both tachyarrhythmias and bradyarrhythmias.

HFpEF, being the most common type of HF among elderly[64], is of special interest for geriatricians. Hypertension is the single factor with the greatest risk for HF[65]. There are however many structural and functions abnormalities present in HFpEF, including cardiac, pulmonary, vascular, metabolic, kidney and hepatic changes[66]. Three pathways to HFpEF have been outlined by Redfield et al[66]: i) hypertensive heart disease, ii) proinflammatory comorbidities and iii) pathophysiologic heterogeneity.

HFmrEF was introduced in the 2016 ESC heart failure guidelines as a third category and seems to have more similarities with HFrEF than HFpEF, with a high prevalence of ischemic heart disease. HFmrEF is milder than HFrEF and has a lower risk of cardiovascular events[67] .The risk of non-cardiovascular events is however more similar between HFmrEF and HFpEF than between HFmrEF and HFrEF.

Aging per se increases the risks for HF. The aging heart suffers from deteriorated release of calcium from contractile proteins and delayed calcium reuptake by the sarcoplasmic reticulum, leading to a decline in the relaxation ability of the heart. Age is also associated with a decline of autophagy and increase of apoptosis[68] associated with a reduction in cellular division and decline in stem

cell function. This leads to decrease in number of myocytes, hypertrophy in myocytes and increased interstitial fibrosis.

Elderly have also been exposed to cardiovascular risk factors during a longer period and may have developed several comorbidities including hypertension, kidney failure and diabetes, that affect the capacity of the heart. A high level of comorbidity, measured with Charlson's comorbidity index (CCI)[69], is an independent prognostic factor for higher 1-year mortality among elderly patients experiencing a first acute HF hospitalization[70].

Of special interest in a geriatric context, is the development from hypertension to HF, since hypertension may be the main contributor to HFpEF, which is the most common type of HF among old persons. PREFERS hypertension study is a current ongoing study over six years following 250 patients with biomarkers and cardiac imaging variables to explain disease progression from hypertension to hypertensive heart disease and HFpEF[71].

2.3.4 HF Investigation

European Society of Cardiology (ESC) has established a diagnostic algorithm for investigation of HF[43], including assessment of risk factors, symptoms and/or signs, electrocardiogram (ECG), measurement of N-terminal-pro-brain natriuretic peptide/natriuretic peptide (NT-pro-BNP/BNP), echocardiography (ECHO), characterization of type of HF, and determination of etiology, see Figure 1.

When HF is suspected due to risk factors, symptoms and/or signs, and an abnormal ECG or measurement of NT-pro-BNP or BNP has been identified, ECHO should be performed. If ECHO shows abnormal findings, HF is confirmed and type of HF should be defined: HFrEF, HFmrEF or HFpEF. The level of HF is determined by assessment of NYHA, see Table 4.

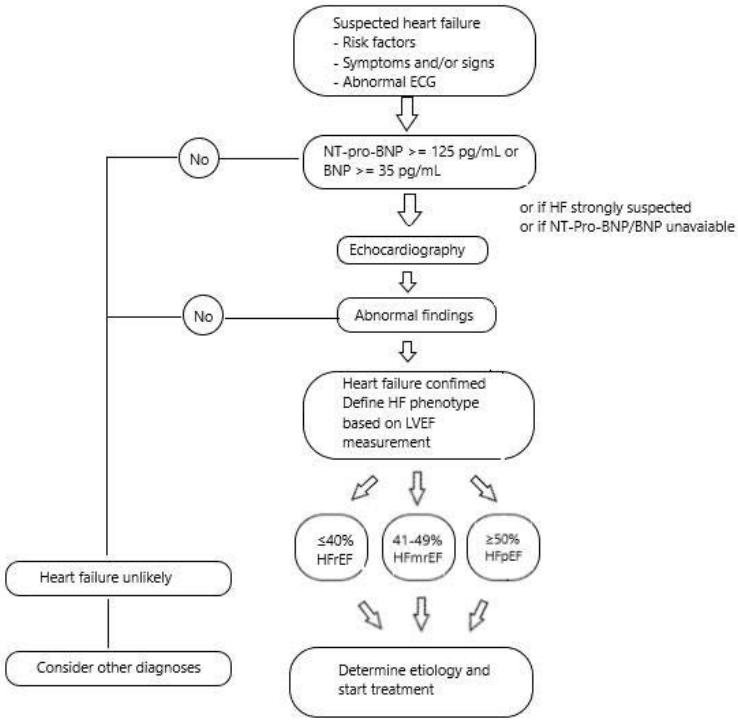

FIGURE 1. Modified flowchart for investigation of HF according to ESC 2021.

2.3.1 Pharmacological HF treatment

Several drugs can be used to treat HF. Recommendations follow the different types of HF defined by the ESC (Table 2) and the classification according to the New York Heart Association (NYHA)[72], comprising class I to class IV, Table 4.

2.3.1.1 Pharmacological treatment of HFrEF

The treatment strategies for HFrEF are built on strong evidence. Recommendations from the ESC has however changed during the period of work with this thesis. According to guidelines from 2012 and 2016 ESC patients with HFrEF are recommended to be treated with an angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) and a beta-blocking agent (BB), with the addition of mineralocorticoid receptor antagonist (MRA) if symptoms are still present[63]. An angiotensin receptor neprilysin inhibitor (ARNI), a naturally occurring vasodilator peptide, can be considered as addition to or replacement of ACEI. Diuretics are recommended for symptom relief.

New recommendations were published 2021[43]. The main change is a new recommendation of treating HFrEF patients with the sodium-glucose-co-transporter 2 (SGLT2) inhibitors dapagliflozin or empagliflozin in addition to the other drugs for HF described above. Among HFrEF the effects of dapagliflozin, regardless of whether patients have diabetes or not, have been shown to reduce the risk of cardiovascular (CV) death and worsening of HF[73]. See Figure 2.

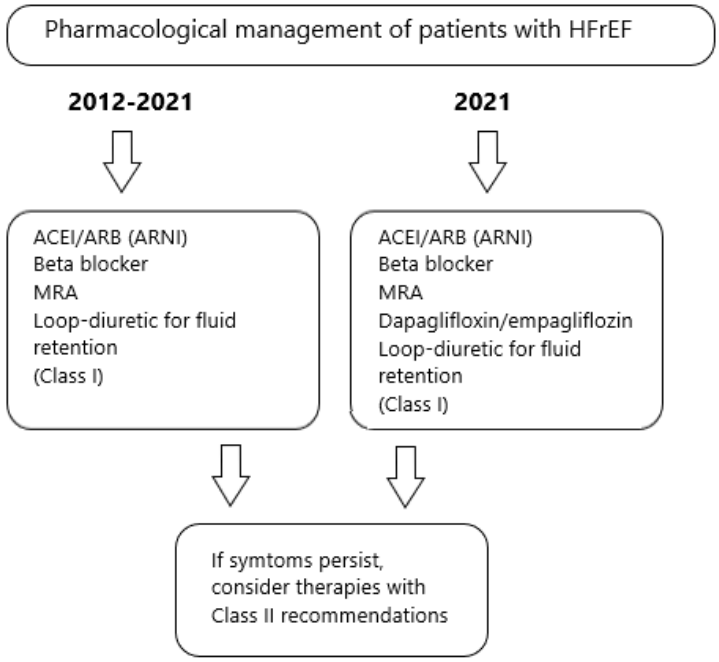

FIGURE 2: Recommendations from ESC.

The pharmacodynamic effect of SGLT2-inhibitors is a reduction in reabsorption of glucose in the kidney together with a decrease of reabsorption of sodium, leading to decrease in volume overload and blood pressure, with beneficial effects on cardiac remodeling and diastolic function.

Further, the American guidelines from 2022 also recommend SGLT2-inhibitors for HFrEF patients, regardless of the presence of type 2 diabetes[74]. Research on finding new therapies for HF include intravenous iron for deficiency treatment, transthyretin stabilizers, soluble guanylate cyclase stimulators, cardiac myosin activators, and new potassium binders[75]. Cell therapy, using autologous bone marrow and cardiac progenitor cells, and gene therapy has also been suggested[56].

HFrEF patients treated by cardiologists seem to have good adherence to treatment recommendations. Maggioni[76] reported that HFrEF patients in cardiologist care are to a high degree treated with BB (92.7%), ACEI/ARB (92.2%) and MRA (67.0%). Crespo-Leiro[77] reported only a very limited undertreatment. As for primary care, Hirt[78] et al reported that guideline adherence was "higher than expected" with 76% ACEI/ARB and 73% BB among primary care practitioners. Stork et al[79] on the other hand, investigated almost 124.000 patients with HF in Germany. 63.3% of new HF diagnoses were made in ambulatory settings and of those only 14.8 were made by cardiologists. 20.9% of these were assessed according to the NYHA classification and of those 45.1% received a guideline-based treatment, i.e., less than 10% of HF patients treated by family practitioners received guideline-based treatment. The conflicting results seem to be due to treatment by cardiologists or not and probably also differences in patients treated by cardiologists or not since ESC reported patients treated by cardiologists, and Stork et al reported patients treated mainly by general practitioners.

Biglane[80] reported that there is lack of knowledge about safety and efficacy regarding guidelines for elderly with HFrEF. Recommendations for treatment are based on investigation mainly on younger persons and too little is known about their applicability for elderly[81].

2.3.1.2 Pharmacological treatment of HFpEF

Treatment strategies for patients with the more heterogenous HFpEF have a weaker scientific support. The general recommendations from ESC are to address the comorbidities and alleviate symptoms.

The difficulties to develop successful therapies for the management of HFpEF may be due to poor understanding of the pathophysiology of HFpEF, inadequate standardization of the diagnosis and the lack of strict definitions and differentiation of subgroups[54]. According to Polsinelli et al[62] It is likely that further improvements in the treatment of these patients will demand a nuanced, subgroup-specific approach instead of one solution for all. A recent suggestion on how to manage different phenotypes of HFpEF has been presented by Polsinelli[62], whereby ACEI/ARB plays a central role for all the phenotypes.

There has been a large interest in also evaluating BB as a treatment for HFpEF, due to the positive effects in HFrEF. BB are well tolerated in an elderly population[82]. A lower heart rate is associated with decreased death also among

HFpEF patients[83],[84],[85],[86],[87], at least among those with sinus rhythm and risk of readmission[84]. Whether lowering the heart rate with BB is also associated with better outcome is uncertain. Studies by Ruiz[85] as well as a meta-analysis[86] showed decreased mortality with the use of BB, also for HFpEF. However, there is still a demand for RCTs to confirm the potential benefit of BB for HFpEF, or possibly subgroups of HFpEF. In reality, however, patients with HFpEF are often treated with BB due to atrial fibrillation, a common comorbidity[88].

The new recommended treatment with SGLT2 in HFrEF have also been studied in HFpEF patients and beneficial effects have been reported. In patients with HFpEF treated with empagliflozin, reductions in cardiovascular death, hospitalizations for HF or emergency or urgent HF visits requiring intravenous treatment[89] have been reported. Dapagliflozin has also been shown to have beneficial effects in reducing the combined risk of worsening of HF or CV death among patients with HFmrEF and HFpEF[90].

SGLT2 inhibitors have therefore been recommended for HFpEF patients with diabetes type 2 at high risk of CV disease or with CV disease, to prevent hospitalizations, according to ESC 2021[43].

The American guidelines for management of HF from 2022[74] mention SGLT2-inhibitors as a recommendation with weaker scientific support for HFmrEF and HFpEF.

In Stockholm, Sweden, recommendations in favor of SGLT2 inhibitors have also been published in *viss.nu*, a website from the Stockholm Region with recommendations on treatments for various conditions, including HF. At *viss.nu* SGLT2 inhibitors are presented as base treatment for HFrEF and as a possibility for patients with HFmrEF and HFpEF, leading to decreased risk of hospitalization.

Beside drugs that increase the pumping ability of the heart, symptom relieving drugs are used. Diuretics are a cornerstone in symptom relief among HF patients. When patients are decompensated, i.e., suffer from fluid retention, the acute treatment is diuretics, with the aim to bring the patient into euvolemia. However, this treatment does not improve the symptom control or other outcome measures over time. Diuretics may even increase the risk of death or other adverse outcomes[91].

To evaluate the adherence to guidelines for HFpEF patients is more difficult, due to less articulated guidelines, weaker scientific support for the guidelines, and

less data about HFpEF patients. Abete[68] however, stated that many HF patients are undertreated with BB and ACEI/ARB and that this may be the case for both HFrEF and HFpEF.

2.3.2 Non-pharmacological HF treatment

Cardiac resynchronization therapy and heart transplantation are examples of modern non-pharmacological HF treatment. However, we will not refer to these treatments in this summary, as they are not relevant in geriatric care.

There have been several trials with different intervention programs for HF patients, showing better adherence to drug treatment and better outcome when monitoring the treatment with non-pharmacological measures[92], such as interprofessional HF teams.

A meta-analysis from 2016[93] included 52 studies from the 1990s and onwards, noted that multicomponent interventions with multidisciplinary teams could significantly reduce hospital admissions, readmissions, mortality and costs, and increase the quality of living among patients with HF. Studies have also shown that interventions supporting maintenance or increase of drug treatment resulted in lower levels of NT-Pro-BNP, increased heart function and fewer planned or acute visits to health care providers. The drug-related interventions have included telephone support and other support for titration of drugs while non-pharmacological interventions include occupational therapy, physical activity etc[94]. A weakness with the presented studies is the large heterogenicity regarding the details in the interventions and that much information about the patient's other conditions is lacking. Another weakness is that no studies included attention to comorbidities, geriatric syndromes, or frailty.

Further, lifestyle modifications also have a place in preventing and treating HF. Avoiding obesity, higher physical activity, modest alcohol intake and not smoking have been reported to markedly lower the risk of HF[95].

2.3.3 Prognosis

HF is a severe disease with high risk of readmission and mortality. Rates of 60-90 days readmission are comparable for HFrEF (36.1%) and HFpEF (35.3)[96]. Fernandez-Gasso[97] found that age and comorbidity were main predictors of any readmission.

Shah[98] showed that the 5-year mortality after admission to hospital among 39.982 individuals was similar in HFrEF (75.3%) and HFpEF (75.6%), while Andersson[99] reported that mortality prognoses for HFpEF vary substantially, partly due to varying diagnostic criteria. Bouvy[100] showed that predictors of mortality were diabetes mellitus, a history of renal dysfunction, NYHA III-IV, lower weight, lower blood pressure, and ankle edema. Bauduceau[101] and Sandesara[102] reported that cardiovascular complications to diabetes type 2 are strongly correlated to mortality.

2.3.4 The geriatric heart failure patient

Patients with HF are very common in geriatric care, but the prevalence of different types of HF and comorbidities, as well as the nature of investigation, treatment, planning and outcome in this patient group, is less well known. Fu[103] called already in 2008 for treatment strategies for patients in the "real world". In the Stockholm Region, great efforts have been made to improve HF care via the project 4D (4 diagnoses: HF, breast cancer, arthritis, and diabetes), where care chains for HF were established between cardiologists and primary care physicians. However, the 4D project did not consider the inpatient care at geriatric clinics, although the geriatric care is well developed in the region and HF is the most common diagnosis in geriatric care.

The interest in HF has traditionally and not surprisingly been most immanent in cardiology. Interest has been focusing more on HFrEF and direct heart related physiology, etiology, treatment, and evaluation, than on other types and issues of HF. HF patients are, however, treated not only by cardiologists but also by geriatricians and general practitioners. Stork et al[79] have shown that only 14.8% of elderly HF patients in ambulatory settings in Germany were diagnosed by a cardiologist. Munoz[104] investigated HF patients in primary care and found that only 8.5% of the patients had their EF noted in the medical records. The lack of documentation on EF was associated with adverse outcomes. Rutten[105] et al reported that HF patients treated in primary health care tended to be elderly, more often female, and more frail and that general practitioners used less additional investigations and prescribed less potentially beneficial medications, compared to cardiologists.

Holmström[106] et al. investigated elderly HF patients and found that among patients aged 85 there were more than twice as many HFpEF as HFrEF. This

group was further characterized by being mostly women, having more comorbidities and less pharmacological treatment.

Traditionally HFpEF has been regarded as a disturbance in the diastolic function, but over time another view has developed of HFpEF as a systemic syndrome involving different organ systems with important contributions of aging and multiple comorbidities, typical for geriatric patients[54].

In geriatric care the HF panorama is dominated by chronic HF. Chronic HF can be the result of all explanatory models discussed above and is often characterized by a fluctuating course with recurring episodes of deterioration with increased central congestion and peripheral edemas. If adherence to treatment instructions is low, the risk of recurring deterioration increases.

2.4 Alzheimer's Disease

2.4.1 Definitions and classifications

Alzheimer's disease (AD) is a neurodegenerative disorder, characterized by a decline in multiple cognitive domains, including impairment in memory, orientation, and language. Neuropsychiatric symptoms are common and increase during the progression of the illness[107].

AD was originally defined as a clinical-pathologic disease, confirmed at autopsy and during life described as possible or probable AD[108]. Later, efforts have been made to identify cerebrospinal fluid biomarkers in living persons, amyloid-β 42, total tau, and phosphorylated tau 181[109] as well as amyloid depositions in brain assessed with positron emission tomography (PET). Recent efforts in finding plasma-based biomarkers are reported[109, 110]. Since the disease processes start many years before the development of symptoms, there is also room for definitions of preclinical AD[111].

AD, being a gradually progressive disease, is classified in several phases: pre-clinical, mild, or early-stage AD, moderate AD, and severe AD[112, 113]. The pre-clinical phase can last for several years and is characterized by mild memory loss and early pathological changes in the brain, but without functional impairment in daily life. In the mild or early stage[114] of AD several symptoms appear, such as trouble in the daily life of the patient with loss of concentration and memory, disorientation in place and time, mood changes, and development

of depression. In the moderate AD stage, the disease spreads to several cortical areas, resulting in an increased memory loss with trouble recognizing family and friends, loss of impulse control, and difficulty in reading, writing, and speaking. Severe or late-stage AD involves the spread of the disease to large cortex areas resulting in a progressive functional and cognitive impairment where the patients cannot recognize their family at all, need help with everything and have difficulties in swallowing, eventually leading to the patient's death.

2.4.2 Prevalence, incidence, mortality

Alzheimer is the most common cause of dementia in the world, accounting for 60-80% [114] or 50-70%[115] of the dementia cases. The total number of AD patients was estimated to 40 million people worldwide in 2016[116] and is prognosed to reach 154 million people by mid-century[115].

Although the prevalence of dementia is expected to continue to increase worldwide, the incidence in developed countries may have decreased, in part possibly due to better vascular health[116]. Elimination of the seven most important risk factors for dementia, would lead to a substantial reduction in dementia incidence, estimated to 30% according to de Bruijn[117].

AD is at diagnosis associated with a doubled risk of death compared to patients without AD[118].

2.4.3 Etiology and pathogenesis

Acetylcholine (ACh) is a neurotransmitter that has been shown to be a potent chemical messenger[119]. ACh is synthesized from choline and acetyl-CoA via the choline acetyltransferase (ChAT) enzyme. ACh is transported into vesicles and released into the synaptic cleft, where it binds to muscarinic and/or nicotinic ACh receptors. In the synapse, ACh is broken down to choline and acetyl-CoA by AChE. ACh is synthesized not only by neurons, but also by cells from skin, kidney, eyes, and liver[120]. Also, T-cells synthesize ACh and have been shown to release ACh, which acts on macrophages via the nicotinic receptor α7 nAChR[121].

Increased levels of ACh are associated with conditions like increased salivation, diarrhea, and blurry vision, while decreased levels are associated with memory loss (AD) and muscle disorder (myasthenia gravis). The balance of ACh is managed by regulating two classes of enzymes: the ACh producing enzyme ChAT and the ACh degrading enzymes AChE and butyrylcholinesterase (BuChE).

The ratio between ACh production and clearance is called the "cholinergic index" and has been found to be changed in AD patients[122].

The cholinergic anti-inflammatory pathway (CAP) consists of ACh, acetylcholine receptors, particularly α7 nAChR, the vagus nerve, spleen and the splenic nerve[123], [124]. ACh is the main mediator of CAP.

The cholinergic pathway has been reported to be severely damaged in AD. Aβ and tau has been reported to be present in cholinergic neurons of the basal forebrain system early in AD[125], which correlates with observations that significant cholinergic dysfunctions appear in aged and demented persons[126].

Basal forebrain cholinergic neurons (BFCN) are found to be degenerated very early in AD, leading to the development of the cholinergic hypothesis of geriatric memory dysfunction[126]. BFCNs are in fact considered one of the earliest signs of cognitive decline in the pre-clinical phase[127] resulting in cholinergic hypofunction[128]. There is a significant association between hippocampal volume decline and different AD stages, indicating a close association between cholinergic dysfunction and hippocampal atrophy[129].

Two main hypotheses proposed for AD are the cholinergic hypothesis (see above) and the amyloid hypothesis. The amyloid hypothesis states that AD is mediated by formation of amyloid-β plaques and neurofibrillary tangles of tau[130] found in the brains of AD patients. In addition, atrophy of the AD brain due to neural and synaptic loss is found.

However, in clinical studies reducing Aβ peptide production and amyloid formation did not markedly slow down cognitive decline[131]. Hence, the amyloid hypotheses may not be sufficient to explain the character and variation in cognitive decline among individuals with AD and further studies are needed[132]. Kurkinen et al[131] recently suggested alternative hypotheses, such as the presenilin hypothesis, synaptic glutamate signaling, the role of astrocytes and the glutamate transporter EAAT2, as possible mediators in causes of the development of AD.

Additionally, several risk factors for development of AD have been identified: aging, genetic factors, head injuries, vascular diseases, infections, and environmental factors.

2.4.4 Treatment

The major approved AD therapies available are the acetylcholinesterase inhibitors (ChEIs) and memantine[133].

ChEIs (donepezil, galantamine, and rivastigmine), by enhancing the cholinergic pathway signaling by inhibiting breakdown of ACh, have been shown to slow down cognitive decline[134] and delay functional disability[135]. Treatment with ChEI has also been associated with reduced mortality in patients with dementia[136-139].

ChEIs increase the acetylcholine levels in the brain, which facilitates the transmission between cholinergic neurons playing a role in memory. The anti-glutaminergic drug memantine regulate glutamate through a noncompetitive antagonistic effect on the N-methyl-D-aspartate (NMDA). Glutamate is a neurotransmitter correlated to learning and memorization[140].

These drugs are used to delay the development of the symptoms of disease and sometimes temporarily improve cognitive functioning and decrease behavioral symptoms. Treatment with ChEIs is associated with recued use of antipsychotics, antidepressants, and anxiolytics[141]. However, these effects are partial and temporary and affect the consequences of AD, but not the cause.

New treatment strategies target amyloid using monoclonal antibodies which bind to Aβ soluble protofibrils with high affinity[142, 143]. Drugs developed using anti-Aβ antibodies include aducanumab[144], lecanemab[142], and donanemab[145].

Although the observed ability of the anti-Aβ antibodies to clear Aβ from the brain tissue, their long-term effects on cognition and side-effects need to be further investigated[146].

Important complements to drugs are non-pharmacological interventions including cognitive training, improved nutrition, and physical activity, which can have effects both as prevention[147] and treatment.

2.5 Heart failure and Alzheimer's Disease

2.5.1 Common traits and risk factors

HF, particularly HFpEF, and AD can be considered geriatric giants and share some common traits. Aging per se is the most important risk factor for both conditions. In fact, a concept of "pure AD" may be less realistic in patients with

late onset of dementia, where it is more likely that a number of age-related changes are present, the most common being vascular changes[148].

Several cardiovascular risk factors have been associated with an increased risk of cognitive decline in nondemented persons[149]. Control of vascular risk factors has also been shown to reduce the incidence of dementia in healthy and cognitively impaired individuals[150]. Further, the presence of intracerebral atherosclerotic vascular disease exacerbated AD[151]. Calik et al[152] reported increased aortic stiffness and reduced diastolic function in patients with AD compared to control subjects.

Changes in the autonomic nervous system[153] (ANS) among patients with AD[154],[155],[156]and with HF[154],[157] have been demonstrated. The parasympathetic activation has been shown to decrease during the development of AD, along with a more dominant role of sympathetic activation, leading to an increase in cardiovascular disorders[154]. Also, deficits in central cholinergic function observed in AD could lead to autonomic dysfunction[155]. These alterations in the ANS actively contributes also to cardiac disease progression[158, 159].

Inflammation plays a distinct role in AD and has also been suggested to play a key role in cardiac diseases, especially in HF. Murphy[8] reported that in HF the strongest associations of inflammatory markers are found in HFpEF.

ACh has been shown to, through the earlier mentioned cholinergic anti-inflammatory pathway[124], have anti-inflammatory properties and the role of cholinergic signaling may be a key regulator of cardiac inflammation[160]. Khuanjing et al[161] have in a review article demonstrated that ACh may improve autonomic and cardiac functions through various mechanisms, including direct action of ACh on anti-arrhythmogenic, anti-apoptotic, anti-oxidative, anti-inflammatory, anti-hypertrophic and anti-fibrotic processes. The cholinergic system regulates several immunological mechanisms that can decrease myocardial inflammation and constitute a cardioprotective effect[162]. A degeneration of the cholinergic neurons will therefore contribute to cardiovascular dysfunction, as well as to cognitive impairment. Interesting, our group and others have shown that ChEIs are associated with reduced risk for myocardial infarction[138] and stroke[163].

Further, Aβ, the amyloid peptide and the hallmark of AD brain pathology, is at the same time an independent cardiovascular risk factor[164, 165]. Normally there exists

an equilibrium between Aβ production and removal both inside and outside the central nervous system[166]. Deregulation of this balance may lead to accumulation of Aβ1-40 in blood, vascular wall, and heart tissues, which has been associated with cardiovascular disorders (CVD). Moreover, Aβ has been found to accumulate in the heart of patients with AD[167] and accumulation of Aβ40 in blood has been associated with cardiac dysfunction and cardiovascular mortality[168].

Another possible connection between HFpEF and AD is amyloidosis. Wildtype transthyretin amyloidosis is increasingly being recognized as a cause of HFpEF, accounting for 13% of HFpEF[60]. Schaich et al[169] raised the hypothesis that amyloidosis of the brain and the heart, might be two sides of the same coin.

Since dementia (including AD) is diagnosed in old age and data from the Swedish registry of cognitive/dementia disorders, SveDem, show that the mean age at diagnosis is 79 and that several comorbidities, not least CVDs, are common [170]. However, little is known about the impact of treatment when subgroups with AD in combination with a specific CVD diagnosis such as HF is studied.

3 Research aims

Patients with HF are very common in geriatric care, but the prevalence of different types of HF and comorbidities, as well as the nature of investigations, treatment, planning and outcome in this patient group are less well known. The overall aim of this thesis was to assess some central aspects of geriatric care, such as, strategies for drug changes and in particular, investigations and treatment strategies for geriatric patients with HF prior to and during geriatric care. Finally, treatment in a subgroup of patients with both HF and AD was studied.

The specific objectives of Studies I–IV were:

Study I: To investigate over time the effect of drug changes on the quality of drug prescribing during inpatient geriatric care episodes, using an index based on "indicators for good drug treatment for elderly" by the Swedish National Board of Health and Welfare.

Study II: To assess adherence to guidelines for investigations and drug treatment among geriatric patients with HF prior to referral to geriatric care, as well as to assess the content in the referrals.

Study III: To assess the extent of the geriatric contribution concerning investigations and treatment of geriatric patients with HF during a geriatric care episode, including factors contributing to medical decisions and further planning, as well as to assess the content in the referrals to further care in primary care.

Study IV: In a subgroup of patients with both HF and AD, investigate whether use of ChEI, known to affect cardiovascular function, affect the risk of hospitalization for HF and mortality.

4 Materials and methods

4.1 Overview

TABLE 5. Overview of materials and methods used in Studies I-IV.

	Study I	Study II	Study III	Study IV
Design	Retrospective	Retrospective	Retrospective	Epidemiological
Data source	Patients' records at Stockholms Sjukhem	Patients' records prior to admission to a geriatric clinic in Stockholm	Patients' records during an inpatient geriatric care episode in Stockholm	SveDem, TPR, NPR, PDR, CDR registries*
Study time	10.9 +- 6.47 days (SD)	1996–2016	9.6 +- 4.75 days (SD)	200810101–20181016
Outcome	Number of drug changes. Correlations of drug changes and quality of prescribing. Factors influencing the number of drug changes.	Performed investigations, Instigated treatment. Adherence to guidelines for investigation and treatment. Information to next care giver	Performed investigations, changed and instigated treatment. Adherence to guidelines for investigation and treatment. Information to next care giver.	Hospitalization due to stroke, HF or AMI together or separately. All-cause mortality
Methods of analyses	Student's t-test, PR-test (chi2), Wilcoxon's rank sum text, linear regression analyses	Student's t-test, PR-test (chi2), logistic regression analyses	Student's t-test, PR-test (chi2), logistic regression analyses	Cox Hazard Ratio based on propensity score matched cohorts

*TPR=Total Population Registry; NPR=National patient Registry; PDR=Prescribed Drug Registry; CDR=Causes of Death Registry.

Four studies are included in this thesis. I-III are retrospective studies with data derived from medical records, analyzing several aspects of investigation and/or treatment. IV is an epidemiological study using linkage of fives registers to obtain information on diagnoses, comorbidities, prescribed medications, rehospitalization, and death.

4.2 Data sources and collection

4.2.1 Data sources and collection study I

Data were extracted from Cosmic (Cambio Healthcare Systems, Stockholm, Sweden) for 2005 and from TakeCare (CompuGroup Medical, Stockholm, Sweden) for 2010 and 2015.

Drugs at admission and discharge were analyzed in a computer program, miniQ using the ATC-system (anatomical, therapeutic, and chemical classification of drugs) standardized by the World Health Organization.

4.2.2 Data sources study II and III

Data were extracted from Take Care (CompuGroup Medical, Stockholm, Sweden) or from Cosmic (Cambio Health care Systems, Stockholm, Sweden), which is the electronic medical register used by the main provider of data on HF of the included patients during the period 1st of July 2015 until 30th of June 2016 from patients treated with the main diagnosis HF.

Furthermore, in study II, retrospective data from Take care or Cosmic records from these patients were collected prior to admission to geriatric care: data was obtained as far back as 19 years.

4.2.3 Data sources study IV

Data were obtained by linking five registers: the Swedish dementia register SveDem, National Patient Registry (NPR), Total Population Registry (TPR), Cause of Death Registry (CDR), and Prescribed Drug Registry (PDR).

4.3 Study population

4.3.1 Study population study I

Patients treated with the main diagnosis pneumonia [ICD J189.9 according to International Statistical Classification of Diseases and related Health Problems, tenth revision, Clinical Modification (ICD-10-CM)][171] admitted to a geriatric clinic during 2005 or, 2010 or 2015 were included. During 2005, 134 patients were included, during 2010, 146 and during 2015, 140 patients. If a person had more than one care episode for the studied year, data from the first care episode was used.

The following data were collected: all regularly used drugs at admission and discharge and all prescription changes during the care episode for drugs that were still ongoing at discharge. Drugs related to the main diagnosis pneumonia were not included. Drugs administered as needed were likewise not included. The following data were analyzed: age, sex, length of care episode, CCI[69], number of drugs at admission, number of drugs at discharge, number of drug changes and an inappropriate drug use (IDU) index based on recommendations on

"indicators for good drug therapy among the elderly" from the Swedish National Board of Health and Welfare[172].

4.3.2 Study population study II

Patients with the main diagnosis of HF (codes I50.0, I 50.1, I 50.9, and I11.0) according to ICD-10-CM[171] admitted to a geriatric clinic due to a main diagnosis of HF were included. Out of 280 eligible patients 135 were selected using a random number table. One of these patients was excluded due to erroneous registration. Thus, data from 134 patients were collected.

The following data were registered from patient charts, from any hospital or primary care center in the Stockholm region prior to referral to inpatient geriatric care for HF worsening: age, sex, referral origin, number of inpatient care episodes during the last 12 months, days since last EF assessment by ECHO, level of EF, number of days since last analysis of NT-Pro-BNP, classification according to NYHA, recent (less than a year) contact with a cardiologist, comorbidity index according to CCI[69] and presence of atrial fibrillation, myocardial infarction, hypertension or diabetes mellitus.

In addition, blood/serum levels of NT-pro-BNP, hemoglobin and creatinine prior to the care episode were registered.

HF-related pharmacological treatment at the time of referral was also collected, i.e., angiotensin converting enzyme inhibitors (ACEI: Enalapril, C09AA02, Ramipril C09AA05), angiotensin II blockers (ARB: Cozaar C09CA01, Candesartan C09CA06, Irbesartan C09CA04), beta blockers (BB: Bisoprolol C07AB07, Metoprolol C07AB02, Atenolol CA7AB03) and mineralocorticoid receptor antagonists (MRA: Spironolactone C03DA01). Data on treatment with diuretics (Furosemide C03CA01, Hydrochlorothiazide C03AA03, Bendroflumethiazide + potassium chloride C03AA01, Amiloride + Hydrochlorothiazide C03EA01) was collected when available (86%) 14 days prior to admission.

Types of HF were defined according to the criteria by ESC[63]: Patients with an EF<40% were defined as HFrEF, patients with 40%≥EF<50% as HFmrEF and patients with EF≥50% as HFpEF.

4.3.3 Study population study III

The patients from Study II were followed-up during the inpatient geriatric care to which they were admitted due to worsening of HF. The following data were

collected: age, sex, referral origin, number of inpatient care episodes during the last 12 months, days since last EF assessment, type of HF (HFrEF, HFmrEF, HFpEF), days since last analysis of NT-Pro-BNP, assessment according to NYHA, recent (less than a year) contact with a cardiologist, comorbidity index according to CCI[69] and the presence of atrial fibrillation, myocardial infarction, hypertension or diabetes mellitus, and if additional investigations with ECHO, NT-pro-BNP or NYHA was performed during the geriatric care episode. In addition, blood/serum levels of NT-pro-BNP, hemoglobin, creatinine, as well as estimated Glomerular Filtration Rate (eGFR) at admission, were registered.HF related pharmacological treatment at the time of admission as well as changes during the care episodes were registered: i.e., angiotensin converting enzyme inhibitors (ACEI: enalapril, C09AA02, ramipril C09AA05), angiotensin II blockers (ARB: cozaar C09CA01, candesartan C09CA06, irbesartan C09CA04), beta blockers (BB: bisoprolol C07AB07, metoprolol C07AB02, atenolol CA7AB03) and mineralocorticoid receptor antagonists (MRA: spironolactone C03DA01). Data on chronic treatment with diuretics (furosemide C03CA01, hydrochlorothiazide C03AA03, bendroflumethiazide + potassium chloride C03AA01, amiloride + hydrochlorothiazide C03EA01) were collected when available (86%) 14 days prior to admission.

Also, data in referral from geriatric care to next caregiver concerning etiology, EF and NT-pro-BNP levels were registered.

4.3.4 Study population study IV

This study was based on the Swedish registry of cognitive/dementia disorders, SveDem, www.svedem.se. SveDem is a web-based registry established in 2007 with the aim to register all incident dementia patients in Sweden with annual follow-ups[173]. The baseline registration in SveDem is initiated at the time of the dementia diagnosis. For this study, SveDem was merged with NPR to obtain diagnoses of comorbidities, made in specialist clinics and hospitals, the PDR to obtain data on prescribed medications, and the TPR and CDR to obtain death dates. We identified 9446 patients registered in SveDem with a dementia diagnosis between January 1, 2008, and October 16, 2018, who had had at least one hospitalization with a diagnosis of HF (ICD-10 codes I099, I110, I130, I132, I255, I420, I425-429, I43, I50) prior to the dementia diagnosis. Exclusion criteria were patients who had non-AD dementia (n=7750), were dead at the diagnosis date (n=1) or within 90 days thereafter (n=79) and patients treated with ChEI before the dementia diagnosis date (n=147).

The following data were collected: age, sex, comorbidities (based on the ICD-10 codes[174]): alcohol abuse, atrial fibrillation, cerebrovascular disease (CVD), chronic kidney disease (CKD), chronic pulmonary disease, depression, diabetes, fractures, hearing loss, hypertension, liver disease, myocardial infarction, obesity, peptic ulcer disease, peripheral vascular disease, rheumatic disease, and stroke; and medications using ATC codes: aldosterone antagonists, ACEIs, ARBs, BBs, calcium channel blockers, diuretics, acetylsalicylic acid, antithrombotics, statins, nonsteroidal anti-inflammatory drugs, antipsychotics, antidepressants, anxiolytics, cholinesterase inhibitors (ChEI), hypnotics and memantine.

4.4 Statistical analyses

4.4.1 Statistical analyses study I

Analyses were done using Stata (College Station, Texas, USA9 version 10. A p-value <0.05 was considered statistically significant.

Student's t-test was used to evaluate differences between studied years regarding age, care-episode length and numbers of drugs at admission and discharge. The PR test calculated percentage of females, Wilcoxon's rank-sum test evaluated the CCI and the IDU index. Linear regression analyses evaluated the correlation between endpoint prescription changes and the following factors: age, sex, care-episode length, comorbidity, number of drugs and the IDU index. All factors were entered into the study's statistical model being potential confounders or effect modifiers.

To evaluate the representativeness of patients with pneumonia for all geriatric patients in the clinic, we compared the study with all patients treated in the clinic during each year regarding age, sex, and care-episode length.

To evaluate the quality of the number of drug changes we created an inappropriate drug use (IDU) index based on the "Indicators for good drug therapy among the elderly" proposed by the Swedish National Board of Health and Welfare[172]. The index was composed by the presence of: i) presence of long-acting benzodiazepines; ii) anticholinergic drugs; iii) drug duplications; iv) concurrent use of three or more psychotropic drugs; v) prevalence of drug combinations that may cause drug-drug interactions of class C (drug-drug interactions that may lead to altered effects or adverse drug reactions (ADR) but may be managed by individual dosage and/or plasma concentration monitoring of the drug) and vi) drug-drug interactions class D (that may lead to serious

clinical consequences in the form of severe ADR, lack of effect or is otherwise difficult to manage with individual dosage). Se Table 6.

TABLE 6: Selected indicators of inappropriate drug use in elderly according to the Swedish National Board of Health and Welfare.

Inappropriate drug use indicators	**Description**	**Index score**
Long-acting benzodiazepines		1
Anti-cholinergic drugs		1
Duplicate drugs		1
Concurrent use of three or more psychotropic drugs		1
Class C drug-drug interactions	May lead to altered effects in adverse drug reactions (ADR) but may be managed with individual dosage and/or plasma concentrations monitoring	1
Class D drug-drug interactions	May lead to serious clinical consequences in the form av severe ADR or lack of effect or is otherwise difficult to manage with individual dosage	1

The index was the sum of the instances of at least one occurrence of each of these indicators. So, a lowered index during a care episode indicated improvement of prescribing quality.

4.4.2 Statistical analyses study II

Descriptive analyses concerning demography and investigations were performed. Tests used were pr-test for calculation of differences in proportions between two groups, Student's t-test for calculation of means between two

groups and logistic regression's test used for calculation of the odd's ratio between recent assessments and referral information. Comparisons were made between patients with Student's t-tests comparing HFrEF to non-HFrEF and HFpEF to non-HFpEF. Analyses were performed using Stata (College Station, Texas, USA) version 10. A p-value <0.05 was considered statistically significant.

4.4.3 Statistical analyses study III

Descriptive analyses concerning demography, investigations and treatments were performed. Tests used were pr-test for calculation of differences in proportions between two groups and Student's t-test for calculation of means between two groups. Analyses were performed using Stata (College Station, Texas, USA) version 17. A p-value <0.05 was considered statistically significant.

4.4.4 Statistical analyses study IV

Categorical variables are presented as percentages and were compared by the χ^2 test while continuous variables were compared by the ANOVA test. The impact of ChEIs on clinical outcomes from the time of study entry to latest follow-up, was assessed using multivariable Cox proportional hazards regression. The proportional hazards assumption was checked with the Schoenfeld residuals test. Propensity score (PS) matching in our primary analysis was used to adjust for confounding by indication. PS was calculated using age, sex, whether the diagnosis was issued at a memory clinic visit, whether the patient was living in own home or in nursing home, comorbidities, and ongoing medications. A propensity score (PS) matched cohort of 455 patients with ChEI therapy within 90 days from diagnosis and 455 patients without ChEI therapy was created. We also estimated crude incidence rates per 1000 person years in both cohorts. Further, we evaluated consistency of effect across ChEI types (versus no use) at therapy start (donepezil, galantamine, or rivastigmine). Study covariates had no missing data except for baseline MMSE which was missing in 2.5% and 3.5% of the PS matched cohort and total cohort, respectively. Missing MMSE was grouped into a "MMSE not recorded" category.

All analyses were performed using R 3.4.3 software (The R Project for Statistical Computing, Vienna, Austria) and Stata version 17.0 (Stata Corp, College Station, TX).

4.5 Ethical approvals

4.5.1 Ethical approval study I

The study was conducted with approval from the Swedish Ethical Review Authority 2012/432-31/2.

4.5.2 Ethical approval study II and III

The studies were conducted with approval from the Swedish Ethical Review Authority, 2016/1435-31.

4.5.3 Ethical approval study IV

The study was conducted with approval from the Swedish Ethical Review Authority, 2017/501-31, 2017/148-32, and 2018/663-32.

5 Results

5.1 Results of study I

5.1.1 Changes in comorbidity, drug prescribing and length of care episodes over time

Comorbidity, measured with CCI, increased during the three studied years, 2005, 2010 and 2015, from 1.9 over 2.2 to 2.4. The number of regularly used drugs at admission increased from 6.4 over 8.3 to 8.8 over time as did the number of drugs at discharge, from 6.3 over 7.9 to 8.8. The number of drug changes increased from 1.9 to 2.1 over the first two studied years and thereafter dropped to 1.1. The length of the care episodes decreased from 12.2 in 2005 over 10.8 in 2010 to 9.9 days in 2015.

5.1.2 Changes in drug prescribing and in IDU-index

A decrease in the IDU-index corresponded to an improvement of prescribing quality during the care episode. According to the IDU-index the quality during a geriatric care episode was unchanged during 2005 (0.5–0.49), increased during 2010 (0.57-0.41, decreased IDU-index) and decreased during 2015 (0.66-0.7, increased IDU-index).

5.1.3 Correlating factors

Regression analyses showed that the length of the care episode was the only factor that consistently correlated to the number of drug changes. We found a correlation between drug changes and length of care episodes with a coefficient of 0.0807, adjusted for known parameters. Thus, according to our model, the prevalence of drug changes decreased by 8% for each day of shortening of the care episode. We also found that activity in drug prescribing was negatively correlated to IDU-index, meaning that a higher activity correlated to improvement in prescribing (lower IDU-index).

Our study showed that the patients had significantly more comorbidities and more drugs, but significantly shorter hospital stays and fewer prescription changes in 2015 compared to ten years earlier.

In summary, the patients had more comorbidities, more drugs, and poorer quality of drug prescribing, had a shorter hospital stay and the geriatricians made fewer changes in their drug prescriptions in 2015 compared to 2005.

5.2 Results of study II

5.2.1 The patient characteristics

Information on HF diagnostics and treatment prior to referral was collected from 134 patients referred with HF as the main diagnosis to an inpatient geriatric clinic. Three quarters of the patients were admitted from emergency clinics, 15% from primary care and 10% directly from home. The average number of inpatient care episodes for HF during the last 12 months prior to the present referral was 3.8, i.e., the patients were high consumers of inpatient care. Their comorbidity index showed an average of 3.7. Atrial fibrillation was the most common cardiovascular comorbidity (69%), followed by hypertension (40%) and myocardial infarction (27%). The prevalence of diabetes mellitus was 29%.

5.2.2 Investigations of the patients

EF was assessed for a majority, 78%, of the patients. Based on ECHO examination, 28% of the HF were categorized as HFrEF, 19% as HFmrEF and 53% as HFpEF. In 60% at least one assessment with NT-pro-BNP was performed.

Many of the investigations were old or very old. Only a minority, 22%, were recently (within 90 days prior to admission to a geriatric clinic) investigated with ECHO and NT-pro-BNP, even though they were admitted due to acutely deteriorated HF. Only 3% had their function level assessed according to NYHA.

5.2.3 Comparisons between patient groups according to EF

Comparing the main groups HFrEF and HFpEF we found, as expected, that HFrEF patients more often had experienced myocardial infarction and HFpEF more often hypertension and atrial fibrillation. There were however no significant differences in total comorbidities according to the CCI.

Further, HFpEF patients had significantly less often a recent investigation with ECHO or NT-pro-BNP compared with the non-HFpEF group. There was also a significant difference in average age of the analyses of NT-pro-BNP, which was 290 days prior to admission for HFpEF, in contrast to 16 days for the other two groups.

5.2.4 Information in referral

We also analyzed the information on HF in the referrals of these patients to the geriatric clinic for care due to worsening of HF. HFrEF patients were significantly more often presented with HF etiology and EF in the referrals compared to the non-HFrEF group.

A separate analysis showed a strong positive correlation (OR 4,9, $p<0.001$) between having a recent investigation of EF and NT-pro-BNP and being presented with etiology in the referral to inpatient geriatric care, adjusted for level of EF, age, sex, and comorbidity.

5.2.5 Pharmacological treatment and adherence to guidelines

HFrEF patients were more often treated with ACEI or ARB (83% vs 64%) and BB (93% vs 77%) compared to the non-HFrEF group. HFrEF patients were treated according to guidelines (ESC 2012[175] and ESC 2016[63]) in 79%, but only to half of target doses. According to ESC 2016 patients with EF≤35% were recommended treatment with MRA, which was the case among 14% of the patients. There were not sufficient data to evaluate adherence to guidelines among HFmrEF and HFpEF.

5.3 Results of study III

5.3.1 Investigations during the geriatric care episode

There were only very few investigations performed during the geriatric care episode for HF worsening. In total 2% of patients were assessed for EF and 20% with NT-pro-BNP. There were no NYHA assessments performed.

5.3.2 Treatment according to guidelines

At admission, 83% of the HFrEF patients were treated with BB and ACEI/ARB, according to guidelines. Seventy percent of HFmrEF and 50% of HFpEF had the same treatment.

5.3.3 Treatment changes

There were no significant changes concerning total prescription of ACEI/ARB or BB. However, there were significant increases in new prescriptions of furosemide and spironolactone. Prior to admission 18.9% were treated with spironolactone. During the geriatric care episode this increased to 27.6%. Patients who received more spironolactone during the care episode had greater weight loss, longer

hospital stays, more assessments of NT-pro-BNP and were at discharge more often referred to a nursing home.

At discharge 21% of HFrEF patients had reached target doses of ACEI/ARB and 19% of BB.

5.3.4 Information to next care giver

The majority (68%) of the patients was discharged to own home with follow-up in primary care. Information on etiology of HF, when known, was rarely transferred from geriatricians to primary care physicians.

5.4 Results of study IV

The results below are given for the propensity score matched cohort of 455 persons with AD and HF and treated with ChEI and 455 persons with AD and HF but not treated with ChEI. The groups were well matched in age, gender, comorbidities and only differed in use of dementia drugs.

5.4.1 Risk of death

In persons with AD and HF, treatment with ChEIs was associated with a 21% decrease in the risk of all-cause death.

5.4.2 Risk of hospitalization

ChEIs were associated with a significantly 35% decreased risk of hospitalization due to composite CVD events of HF, stroke, or myocardial infarction (MI). This finding, however, was driven by a significant association with the reduced risk of hospitalization due to only HF (decreased with 47%) but no due to stroke or MI.

5.4.3 Differences between the ChEIs

Donepezil (20%) and galantamine (36%) but not rivastigmine were associated with a lower risk of all-cause death compared with non-users.

Donepezil was associated with a 52% decreased risk of hospitalization due to HF compared to non-users.

There was no significant association in hospitalization for bradycardia, AV block or implantation of pacemaker, between ChEI users and non-users.

6 Discussion

In this thesis, we have studied patterns of drug choice and drug changes among geriatric patients and particularly geriatric HF patients. We have further studied the investigations and drug treatment among geriatric HF patients and the content communicated between caregivers. Finally, we have studied treatment with ChEI (a drug group known to have effects on cardiovascular function), in a subgroup of HF patients, i.e., those with both HF and AD.

6.1 Findings and interpretations

6.1.1 Investigations prior to and during inpatient care

Medicine has developed from organ or system deficiencies. Major improvements have been made over many years by isolating and studying problems, such as ischemic heart diseases, diabetes, inflammatory bowel diseases or infections. The geriatric patients however often carry multiple disorders[176] and a broader perspective in investigations and treatment could benefit these patients.

In study II we studied the extent and age of investigations of HF among patients prior to them being transferred to geriatric care for continuing treatment of HF worsening. In study III we studied the contribution to HF etiology and care performed during an inpatient hospital stay in a geriatric clinic.

According to Rutten[105] there are substantial differences in investigations in HF when comparing cardiologists and primary care physicians, with ECHO being performed in 97 vs 12% of the cases. Stork et al[79] reported that only 14,8% of HF patients were diagnosed by cardiologists, which leaves a great deal of uncertainty about the basis for diagnosing in real life.

In our studies, most patients were, according to guidelines[63], investigated with ECHO and NT-pro-BNP prior to the geriatric care episode. However, the investigations were often old or very old. The patients in the studied group had experienced many care episodes during the year prior to the study; they could be termed high consumers of inpatient care and possibly updated investigations were needed as basis for a good quality of HF care, at least concerning NT-pro-BNP. Sadly, only 22% had an updated investigations with ECHO and NT-pro-BNP.

During the geriatric care episode few investigations were performed. It is not surprising that ECHO was not carried out, since it was not accessible in the studied clinic, but if needed patients could have been referred for ECHO

assessment. However, NT-pro-BNP analysis is easily accessible and cheap, but still was not performed among more than 20% of the patients.

A reason why NT-pro-BNP assessment was not often performed may be that disease modifying drug changes were not carried out. The patients were given furosemide to decrease fluid excess, an activity that can be evaluated with weight measuring. If the physicians had changed ACEI/ARB or BB they would probably have been interested in the effect on NT-pro-BNP as a measurement of success in treatment, although NT-pro-BNP provides challenges in interpretation among multimorbid patients, but still relative changes would be useful.

Basal investigation of HF also includes evaluation according to NYHA[63]. NYHA is needed to determine the level of HF. NYHA is obviously free of charge and easy to perform but was still not carried out and noted in the medical records other than exceptionally. This was the case both prior to and during the geriatric care episode. A reason why NYHA was not used may be that the result can be hard to interpret among multimorbid patients, whose signs of fatigue may have other causes than HF. Still, in advanced HF NYHA assessment probably is easier to interpret and more important to perform. It is really disturbing that NYHA is not used in geriatric HF patients.

Another aspect of investigations is the assignments. In Stockholm Region, Sweden, where the studies have been performed, the assignments for investigations in HF are aimed at specialists in cardiology and primary care. Geriatric care in Stockholm is not a part of the care chain for HF, according to 4D. 4D is the initiative earlier presented to improve care quality for four diagnoses, including HF, in Stockholm. Although HF is the most common diagnosis in geriatric care in the region, geriatric care is not included in the regional planning for the HF patients. These facts contribute to the explanations to the low activities for investigation and follow-up that has been seen in our studies.

6.1.2 Adherence to clinical treatment guidelines

Adherence to clinical treatment guidelines can be studied from two main perspectives: the adherence by the physician to prescribe drugs according to guidelines and the adherence among patients to follow the prescriptions. In this thesis we have examined the adherence to treatment guidelines by physicians. The question can only be answered if patients are correctly diagnosed with type and level of HF.

Adherence to treatment guidelines in clinical studies seems high[177], but the first general question is whether these patients are typical of HF patients in the "real world". We have shown in our studies here that most geriatric HF patients do not meet cardiologists and are thus probably less likely to be included in clinical studies. It is also well known that old individuals with several comorbidities are usually not included in clinical intervention studies, also for diseases commonly found in the older population.

Clinical guidelines for HFrEF have strong evidence and adherence to them seemed high in study II and III, at least at first sight and regarding ACEI/ARB and BB. There are however two principal problems: the precision in diagnostics and follow-up, and the readiness to increase doses.

Although most patients were investigated with ECHO many of the assessments were old, which decreased their relevance for treatment strategies during the current care episode. One way to follow treatment is to use NT-pro-BNP, which was clearly underused in both study II and III. There was little information on previous diagnostics found in the records in these studies and patients were only rarely characterized as HFrEF or HFpEF. Therefore, physicians may not always have been aware of whether HFrEF guidelines were applicable.

This lack of knowledge could affect the readiness to increase doses. The increase of symptom-relieving furosemide was significant in study III, but this was not the case for ACEI/ARB and BB. An interpretation is that the patients did need and could endure more medication, but still, increasing doses and/or disease-modifying drugs (if lacking) were seldom performed, possibly due to suboptimal awareness on type and level of HF. With a systematic follow-up patients could have received more adequate prescriptions.

HFpEF patients have more diverse causes for their illness and guidelines are therefore also less clear. Guidelines focus on management of comorbidities and adherence was not possible to evaluate. However, a step that would improve the possibilities for betterment would be to state type and level of HF.

6.1.3 Treatment in the real world

Treatment, whether it be drugs, surgery, psychotherapy, social interventions, or any other, should be considered as a logical step after the investigations and analyses have adequately described and proven the underlying reasons for a disease or discomfort in patients. In the real world, this is often not possible,

leaving physicians and nursing staff to relieve symptoms according to experience or as a negotiation solution with the patient. Most geriatric HF patients are not treated by cardiologists[79] and there may also be geriatric HF patients not identified by primary care physicians either. Since most geriatric HF patients in our studies were not diagnosed with respect to the type and level of HF, treatment often had no solid basis.

Concentration on symptom relief may be attractive in a situation where patients have multiple disorders with potentially conflicting strategies according to recommendations. This also reflects a reality, where knowledge on many geriatric medical issues is poorly known and understood. Consequently, there is often a lack of reliable and feasible recommendations on how to perform investigations and interpret the results among multimorbid geriatric patients. Thus, there are several explanations to why geriatric care often aims directly to symptom relief.

An example indicating such a strategy is the emphasize on fluid retention in HF care. Prescribing furosemide is obviously needed in a situation with acute symptoms of HF with central or peripheral fluid retention, but a more disease-modifying approach with a successive transition to adjust the treatment with such drugs is preferable.

The observation in study III that spironolactone was significantly more often instigated, or dose increased, compared to ACEI/ARB or BB, in patients treated for HF in the geriatric clinic, can be seen as a pragmatic solution that allows a decrease in both furosemide and potassium replacement therapy.

The lack of investigation assignments may influence decisions in geriatric care and may at least partly explain the seemed focus on symptom relief rather than disease modifying drug treatment.

The typical symptom-relieving focus among geriatricians may be seen as both a strength and a weakness. It is obviously a strength to see and understand what the patient really needs and wants, independent of care programs. But it may also be a weakness, or risk, if the required analysis is overlooked due to low ambitions. Balancing symptom relief and disease-modifying treatment cannot be managed with simple algorithms, but requires knowledge on symptoms, signs, and several investigating measures.

6.1.4 Presentation of investigations and conclusions

Care providers generally depend on information from previous care giver and are responsible for conveying relevant information to the next care provider. This is even more true in geriatrics in the Stockholm Region, being a link in a chain between acute hospital care and primary care with no independent assignment of follow-up. Although medical records may be available for other care givers, it is of interest what is emphasized in the referrals, presuming that this information reflects priorities along the care chain. Suboptimal care transitions increase risks[178], particularly regarding adherence to medication[179].

This was obvious in study III, where the information in the referrals to and from geriatric care was compared. The observation that much of the content from previous care giver was washed out and not transferred from the geriatric clinic to the next caregiver is intriguing. This may be another reflection of the earlier discussed possible lack of long-termism, partly due to the lack of responsibility for follow-up and a possible consequence of the lack of knowledge of etiology.

The fact that geriatrics in Stockholm do not have assignments for investigation (i.e., get reimbursed) and follow-up for many diseases such as HF, except for memory investigations - can partly explain why information on etiology often is not transferred to the next caregiver. One the other hand, one could also think that this would be an argument to increase the ambition to transfer all available information to primary care.

6.1.5 Extent of drug changes

Clinical pharmacological research has mostly focused on the number and choice of drugs. One exception is Viktil et al[180], who also studied the number of drug changes, as in our study I, and found that there were many drug changes during the hospital stays and many changes again after discharge. Viktil also found that the number of drugs increased during the hospital stay. The IDU-index created by our group, is not validated, or used in other settings. The strength is however that is built on recommendations with scientific support, such as presence of long-acting benzodiazepines, presence of anticholinergic drugs, presence of duplicate drugs, concurrent use of three or more psychotropic drugs, prevalence of drug combinations that can lead to class C drug-drug interactions or drug D drug-drug interactions.[172]

In study I we wanted to study the effect of drug changes, with the hypothesis that many changes would imply improvement of the quality of prescribing compared to fewer changes. This was confirmed by our results, since a higher number of drug changes correlated to improved quality according to the IDU-index. An interpretation is that geriatricians who are given the opportunity to review the drug prescription also do improve it. Such an interpretation is strengthened by the analysis showing that the only factor that consistently correlated to the number of drug changes was the length of care episode, indicating that the physicians needed time to change and evaluate the changes in prescribing. We could also, consequently, observe that the number of drug changes during a geriatric care episode decreased along with the shortening of the care episodes over the studied years.

In study III we analyzed the changes regarding all HF related drugs and found that the changes generally were very small, except for furosemide and to some extent for spironolactone. Since we did not count the drug changes apart from the HF related drugs, we have no knowledge about the total number of drug changes during the care episodes with HF patients. Still, we know that changes in HF-related drug treatment had a clear appearance: symptom-relieving management was predominant. Changes in disease-modifying treatment (ACEI/ARB and BB) might have been more common with longer care episodes, according to the conclusions in study I.

6.1.6 Quality in drug prescribing

Quality in drug prescribing can be evaluated from a negative angle, where inappropriate drugs should be avoided when necessary, or from a positive angle, where treatment that can improve disease prospects or decrease symptom burden, should be instigated if possible.

Onder et al[181] studied 13 quality indicators in an Italian older population (n=12,301.537), addressing polypharmacy, adherence to treatment of chronic diseases, prescribing cascade, undertreatment, drug-drug interactions, and drugs to be avoided and found a high frequency of suboptimal drug prescribing in older adults. Since prescribing to older, multimorbid and frail patients is very complicated it is not surprising that drug treatments can be questioned with varying arguments.

In study I we created an inappropriate drug use index, IDU-index, to evaluate the effects of the changes in drug prescribing during the geriatric care episode with

respect to indicators of inappropriate/hazardous drug use, from the Swedish National Board of Health and Welfare, i.e., from the negative angle. We could observe a correlation between many drug changes and improvement (decrease) of the IDU-index, indicating that an active approach from the physicians in the clinic was positive for the patients.

In study II we evaluated the drug prescription decisions from earlier care givers in HF patients according to guidelines, i.e., from a positive angle. Among HFrEF patients we found that most patients were treated with ACEI/ARB and BB as guidelines recommend. However, only a small minority reached target doses and, in addition, patients (those with EF≤35%) treated with spironolactone were few, indicating a low adherence to guidelines.

In study III we investigated the effect of the geriatric contribution to drug prescribing for HF during a geriatric care episode. We found conflicting results: the activity in changing ACEI/ARB and BB, or rather to increase doses towards target doses, was very low, indicating a passive role in drug changes concerning HF. However, the activity in increasing furosemide treatment was high, and the increase of spironolactone was modest. Increasing furosemide should be characterized as an activity to decrease symptoms of fluid excess, i.e., aiming towards symptom relief and not disease modification. It would have been more beneficial for many patients to increase ACEI/ARB or BB, than to increase furosemide. The increase of spironolactone might be seen as a double-edged ambition. While spironolactone can be instigated as a disease-modifying approach, it may also be the result of a pragmatic decision that allows the physician to decrease both furosemide and potassium replacement therapy, which could be seen as an attractive alternative, reducing the number of pills in the patients' list of drugs.

6.1.7 The lack of follow-up

The logical continuation of care of chronic disorders such as chronic HF is the follow-up. In Stockholm Region, Sweden, geriatrics has only the full responsibility for one whole process – investigation, treatment, and follow-up - for cognitive/dementia disorders. Therefore, geriatric care for all other disorders is always dependent on the next caregiver i.e., primary care for follow-up. Thus, the long-term planning is the responsibility for primary care and the ambition for patient long-term planning initiated in the geriatric clinic may be low. Pedersen

et al[182] showed that 34% of readmissions after geriatric care were avoidable with a follow-up plan.

This reality may also affect the balancing of short-term and long-term ambitions and activities in both investigation, treatment, and planning, resulting in more short-sighted and symptom-oriented strategies among geriatricians in HF care. Further, the fact that too little is known about complicated patients with several diseases and potentially conflicting treatment guidelines, also directs towards symptom relief and, accordingly, short-term care.

When geriatric clinics, as in the cases with memory investigations, do perform specialized investigations in memory in outpatient clinics, they also have the logical mission to decide on treatment, initiate and follow-up the chosen drugs. This is an example where geriatrics does deliver on long-term planning for a patient group.

6.1.8 Length of care episodes

During the last thirty years the number of hospital beds have clearly decreased, in Sweden and elsewhere. Minz et al[183] reported a reduction with 27% in Germany. Reasons for the reduction and related consequences are of course multiple. One clear effect of relevance for geriatric patients is that the length of the inpatient care episodes has been shortened[183]. In study I we saw that the average length of care episodes at the geriatric clinic at Stockholms Sjukhem decreased from 12 to 10 days during the period 2005 to 2015. Today, 2023, the average length is 7 days.

There are several reasons for this development. Some major explanations concern improvement of treatment in many areas, including both new and improved drug treatment, improved methods in surgical proceedings, and improved rehabilitation. In general, a decrease in the length of care episodes, is beneficial in many respects: patients need shorter stays and risks correlated to hospital stays, such as infections, can be reduced.

For at least some geriatric patients there are fewer motifs for shorter hospital stays. Old people with chronic conditions live longer but still need hospital care for different ailments. When in need for hospital care, the aging patients with concomitant comorbidities, and frailty contribute to need for longer hospital stays than younger. In study I we could observe that comorbidity burden among the pneumonia patients, measured with the CCI, raised from 1.9 in 2005, over 2.2

in 2010 to 2.4 in 2015. The same year, in study II and III, we saw that the HF patients had a CCI-index of 3.7. Although an average 80-year-old person may be more vital today than some decades ago, the patients in the clinic may still have higher comorbidity and frailty, and physiology and mobility may not have improved significantly. Further, as discussed above, a shorter care episode may correlate to lower ambitions and fewer trials with improved medication, since there may be too little time for evaluation.

Some consequences of shorter hospital stays are seen in Study I, where the number of drug changes decreased during the years, as well as the lengths of the care episodes, while the quality of drug use declined, according to the IDU quality index.

In fact, in study I we could observe that many drug changes correlated to better prescription, and we also showed, that the number of drug changes correlated to the length of the care episode. Therefore, shortening of care episodes may have decreased at least one aspect of quality in geriatric care during the last decades.

In study III, we also observed that the pragmatic changes from furosemide and potassium compensation to spironolactone was more prevalent in the group of patients that were transferred to nursing homes and therefore had longer care episodes. This may also be considered as an indication that a longer care episode may be beneficial for geriatric patients.

The ongoing trend of shortening of the length of care episodes could further reduce the possibility for geriatricians to perform their role in quality prescribing during inpatient care. The risk of such a strategy, if compensatory measures are not developed, may be recurrent hospitalizations, reduced quality of life as well as reduced life span for elderly in need of medical care.

6.1.9 Risks of hospitalizations and rehospitalization

Hospitalization is a response to a need of medical treatment and therefore the risk of hospitalization is higher among older persons, particularly if they are multimorbid and frail. Geriatric syndromes and polypharmacy have been reported to increase 30-day readmission risk[179].

Risk for hospitalization is particularly high among HF patients, due to the nature of the disease. The typical time loop of HF includes recurrent deteriorations with fluid excess that may require inpatient care. This could be the main contributor

to the fact that HF is the most common cause for inpatient care in patients 65 years and older in the developed world[184].

Hospitalization per se is a risk for patients, particularly the elderly. Hospitalization is correlated to a situation where patients are confined to a bed, due to monitoring equipment but also to a limitation in the possibilities to leave the bed, resulting in sarcopenia, infections, or loss of independence, which may additionally prolong the hospital stay[185].

Hospitalizations are also costly for society and decrease the quality of life for patients and should only be carried out when alternative measures are insufficient. Therefore, it should be a goal in HF care to decrease the number of hospitalizations in the patient group.

There may however be a correlation between short hospital stays and rehospitalization. If the hospital stay was too short to perform relevant caring measures such as adjustments and evaluation of drug prescribing, the risks of rehospitalization rise.

In study III we saw that disease-modifying drug changes were not performed, and this may increase the risk of rehospitalization.

In study IV a new potential opportunity, that treatment with ChEIs, may decrease the risks of death, hospitalization, and rehospitalization in AD-patients with HF, is presented. If the results with large reductions of hospitalization due to HF would be confirmed also among HF patients without AD, intriguing new perspectives could be opened.

6.1.10 Cholinergic pathways

Age-related changes in the autonomic nervous system (ANS) have been reported among patients with AD[156] and with HF[157]. The parasympathetic activation has been shown to decrease during development of AD along with a more dominant role of sympathetic activation, leading to an increase in the incidence of cardiovascular disorders such as hypertension and HF[154]. Also, deficits in central cholinergic function observed in AD could lead to autonomic dysfunction[155]. These alterations in the ANS actively also contributes to cardiac disease progression[158, 159].

Moreover, the cholinergic pathways constitute a protection against inflammation seen in both AD and HF.

ACh has through the cholinergic anti-inflammatory pathway[124] been shown to have anti-inflammatory properties and the role of cholinergic signaling may be a key regulator of cardiac inflammation[160].

Moreover, using SveDem-data, it has previously been shown that treatment with ChEI is associated with reduced all-cause mortality[138], [137]. Similar findings have also been found in a Taiwanese AD cohort treated with ChEI[154] and in a meta-analysis by Isik[139]. Interestingly, significant associations with ChEI and reductions of risk of CVD such as MI[138] and stroke[163] have been shown.

Therefore, there is logical to presume that ChEIs, which increase the level of ACh, would have beneficial effects also on mortality and rehospitalization due to HF, as seen in study IV. The fact that rivastigmine did not have the same effect as the other ChEIs require consideration. Rivastigmine has a different molecular structure and bind, in contrast to the other ChEIs, to both ACh and BuCh. BuCh has a central nervous system selectivity rather than a peripheral[186], which could explain the lack of effect on heart in the study. Another explanation could be that rivastigmine is used in patients with other characteristics such as higher levels of frailty or psychiatric symptoms that increase the demand for medication via patches. One could also speculate, that this can be related to inadequate dosing, a statement, however that needs further study.

6.2 Methodological considerations

6.2.1 Internal validity

Internal validity analyses how well a study measures what is intended to be measured and checks the absence of systematic or random errors. Systematic errors do not change with sample size as do random errors. A study is considered valid only when three alternative explanations have been eliminated: bias, confounding and random errors[187].

Bias is a systematic error in design or conduct of the study that leads to an incorrect association between exposure and outcome.

Confounding factors can be defined as the mixing of effects between exposure, an outcome, and a third variable. Confounding factors are factors that can cause or prevent the outcome of interest but are not intermediate variables of the

factors under investigation. The confounder distorts the true association between exposure and outcome.

Random errors concern the probability that the result is due to "chance", an uncontrollable force that seems to have no connection to the cause.

6.2.2 Selection bias

In study I we wanted to study effects of drug decisions in a "typical geriatric patient" during a care episode. We wanted a find a proxy for this typical geriatric patient and wanted to see effects in a "crude" medication list. Therefore, we aimed to study a group where the condition that initiated the care episode did not in itself have long-term effects on prescribing. Our choice was to study all patients treated during three years with the main diagnosis pneumonia and therefore retracted antibiotics from the analysis of drug use.

The idea of a "typical geriatric patient" is obviously an abstraction since geriatric patients differ in very many respects. Still, pneumonia is a condition that affects many geriatric patients. Since we were studying all patients with pneumonia as main diagnosis for three different years, we believe that we had a relevant selection of "typical geriatric patients".

As we also wanted to explore the timeline, we selected three years during a ten-year period. We thought that ten years would be enough to detect changes in comorbidities, drug treatment, and length of care episodes as well as some other parameters.

In study II and III we wanted to examine a group of HF patients referred to and treated at an inpatient geriatric clinic. HF is common, both as main diagnosis and as secondary diagnosis. We thought that patients who received HF as main diagnosis would be the most appropriate group, assuming that HF was their main problem. During the studied year we found 280 patients treated with HF as main diagnosis. According to a power analysis based on statistics from the Swedish National Board of Health and Welfare we needed 110 patients and finally we selected 134.

In study IV we included all AD patients registered in SveDem during 2008 to 2018 who also had a diagnosis of HF (data from NPR) prior to the AD diagnosis We chose to include only patients with AD and not patients with mixed AD or any other dementia diagnosis, assuming that such an exclusion would make analyses of outcomes more cohesive. The results may, however, be influenced

by factors not registered in SveDem. The coverage of SveDem is about 40% which means that all AD patients are not included. On the other hand, the representativeness, the proportion of AD in relation to other dementia disorders is similar to that reported in other countries. Moreover, the diagnosis of HF was collected from the NPR registry, which has data on hospitalization but not diagnoses from primary care. Further, the proceeding of propensity score matching may distort the comparability between the users and non-users of ChEIs.

6.2.2.1 Confounding errors

In study I we examined the number of drug changes and the correlation between the number of drug changes and the effect on medication lists. To control for confounding, we also included several other parameters in the analyses, parameters that we believed could influence the probability of making many drug changes, as well as the quality of drug prescribing: age, sex, number of drugs at admission, comorbidity, and length of hospital stay. There may be other confounders that we did not consider that influenced the results.

In study II we investigated – among other things – the correlation between having new investigations and being presented with certain information in the referral to next care giver. There may, however, be one or several factors influencing both the readiness for investigations and the presentation in referral, perhaps some personal characteristics of the patients that we have not been able to adjust for.

In study III we examined – among other things – the simultaneous increase in spironolactone and being transferred to a nursing home. Since we found no differences in the studied variables between patients transferred to nursing homes and others, we obviously could not understand or determine the reason why some patients were admitted to nursing homes. A possibility is that they had a higher degree of frailty, which was not measured in our material, and that frailty is a confounder to the suggested correlation between increased prescription of spironolactone and transferal to nursing homes.

In study IV there is of course also the possibility of residual and unknown confounders such as for example physicians' attitudes to prescribing ChEIs. Also, we had no information on type or level of HF.

6.2.2.2 Random errors

Random errors constitute the probability that the observed results are due to "chance". The extent of random errors correlates with sample size.

In study I we examined all individuals treated with pneumonia as main diagnosis for three years. The group did not constitute a sample, since all eligible persons were investigated. Still, other parameters can be registered or interpreted with random errors.

In study II and III the sample size could have influenced our results. A larger sample size would decrease the random errors.

In study IV we studied all individuals registered with AD and HF in SveDem. Thus, it was a sizeable study population, which decreased the risk of random errors.

6.2.3 External validity

External validity is about whether the results can be generalized to another population[187].

In study I we wanted to examine a "typical geriatric patient". If drug changes differ systematically between pneumonia patients and other groups of patients, we have not found the "typical geriatric patient" and thus the results cannot be generalized. Perhaps the likelihood of making changes is different when chronic diseases are not in focus, when treating an acute infection.

Studies I-III were performed in geriatric clinics in Stockholm. Geriatric care in Stockholm is more extensive with more hospital beds than in other regions of Sweden. This means that geriatric patients in Stockholm have a higher likelihood of being treated in geriatric clinics. Therefore, results may not be possible to generalize outside the region. As we have discussed earlier, geriatric care differs substantially between countries, which decreases the generalizability internationally. Also, differences in organization of health care system differ in many respects, which could influence the external validity.

In study IV we examined patients from the whole of Sweden and all eligible patients for ten years were included. The generalizability may decrease when compared to treatment in other health care systems, where hospitalization may be more or less frequent. There is data from AD cohorts from other cohorts showing associations with ChEI treatment and reduced mortality strengthening

our findings although our cohort in study IV analyzed data from a subgroup of AD patients.

7 Conclusions

Some important conclusions which can be drawn from the studies in this thesis are:

- Most geriatric HF patients prior to admission to geriatric care had old or very old investigations of ECHO and NT-pro-BNP and almost no assessments of NYHA. Care of HF patients in a geriatric clinic did not contribute to improved diagnostics of HF.

- Type and level of HF or etiology of HF was mostly not presented in the medical records.

- HFrEF patients were mostly treated according to clinical guidelines, but rarely with target doses. HFrEF with low EF were mostly not treated with MRA, as guidelines recommend.

- Adherence to guidelines for HFpEF was not possible to assess.

- Disease-modifying drugs were not altered during geriatric care but furosemide and MRA were. Focus was on symptom relief. NT-pro-BNP was rarely used to evaluate or manage drug treatment.

- Information on etiology and EF, when known in the referrals from hospital care, was washed out and not transferred further to primary care.

- High activity in drug changes overall was correlated to an increase in quality of prescribing and to longer care episodes.

- Geriatric care in Region Stockholm is not commissioned/reimbursed to diagnose nor follow-up patients with HF, which may influence the readiness to titrate doses or to forward relevant information in referrals to next caregiver.

- Length of care episodes has decreased during the last decades, which may not be beneficial for treatment of geriatric patients where time for evaluation of drug changes is needed. Inpatient care is costly for society

and contributes to lower quality of life for patients. Increased length of care episodes could possibly decrease the number of readmissions.

- Treatment with ChEIs in patients with AD and HF was associated with a decreased mortality and major reductions in hospital admissions due to HF. Possible reasons for this are the anti-inflammatory and negative chronotropic effects of ChEIs on HF. Readmissions due to HF may be preventable by treating HF patients with AD with ChEIs.

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8 Points of perspective

The fact that geriatric care in Stockholm is not commissioned/reimbursed by the region to diagnose or follow-up the most common disease among elderly people, HF, raises questions and thoughts. Cardiology and primary care on the other hand should diagnose and follow-up these patients. This thesis shows that development of care for geriatric HF patients needs new approaches.

It does not seem realistic to expect that cardiology nor primary care should have full responsibility for geriatric HF patients and even not desirable. Also, care of geriatric patients takes knowledge on aging, frailty, and other typical geriatric conditions. Therefore, it seems more fruitful to strengthen the care chain through better cooperation between cardiology, geriatrics, and primary care. There is a need for division of labor between the specialties and distinct responsibilities for different stages of HF. To, in addition to cardiology and primary care, also commission the responsibility for investigations/diagnostics and follow-up of old patients with chronic HF to geriatricians would be beneficial for the patients. Such a reform could increase the precision in diagnosing HF by type and level, which would increase possibilities of tailoring relevant treatment for this heterogeneous patient group.

A possible addition is to redefine the geriatric care episode and prolong the responsibility by geriatrics to include a follow-up period in the patients' homes. Such a reform would decrease the negative side effects of short hospital stays and increase the long-term perspectives in geriatric care. This would also benefit geriatric patients with other conditions as it would increase the possibilities to instigate and evaluate drugs and drug changes and reduce the focus on shortening inpatient care episodes.

Moreover, it is of great importance to further explore the possibilities of treatment with ChEIs in HF patients. The proposed mechanisms of effects on inflammation and chronotropy might have bearing also on HF patients without AD.

Finally, it is of interest to explore possible connections between amyloid storage in the brain and heart.

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