From DEPARTMENT OF MEDICINE, SOLNA
Karolinska Institutet, Stockholm, Sweden

SEX- AND GENDER ASPECTS IN DRUG UTILIZATION

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Stockholm 2021

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB

ISBN 978-91-7831-977-0

Sex- and gender aspects in drug utilization

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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POPULAR SCIENCE SUMMARY OF THE THESIS

Differences in drug use between men and women are most often due to a combination of biological (sex) and sociocultural (gender) factors. However, it is not easy to get a comprehensive overview because results from studies differ, not only between different therapy areas but also over time and between different populations. The overall aim of this thesis was to study sex- and gender differences in drug use, in general and in some therapy areas, using data from different registers. Also, with the help of qualitative methods, I wanted to try to identify physicians' perceptions of sex and gender aspects when deciding on drug treatment.

In study I, the largest sex differences in drug use in Sweden 2010 were analyzed. Many differences were considered to be wholly or partly explained by the fact that men and women have different disease incidence and biology, while other differences were more difficult to explain medically and may indicate unequal treatment.

In study II, we examined sex differences in reported bleeding complications caused by three blood-thinning medicines: clopidogrel, low-dose aspirin and warfarin. There was no sex difference in reported bleedings for clopidogrel and warfarin. However, reported bleedings for low-dose aspirin was more common in men than in women, which may be due to the fact that men received a higher dose than women.

In study III, focus group discussions were conducted with physicians at five health centers to investigate their perceptions of sex and gender related to drug prescribing. Stereotypical perceptions about men and women occurred, but when deciding on treatment, the physicians said they considered individual factors and followed regional recommendation lists. Although the physicians expressed a lack of knowledge about sex differences in drug treatment, they gave several examples of how the patient's sex was taken into account.

In study IV, we examined the use of blood-thinning medicines in patients with atrial fibrillation in Stockholm in 2011 and 2015, i.e. before and after the introduction of the new oral anticoagulants (NOACs). Both the incidence of atrial fibrillation and the proportions using oral anticoagulants increased in both men and women. In 2011, there were fewer women than men who had any oral anticoagulant, but in 2015 the sex difference had disappeared, except in the elderly and in patients with complicated comorbidity.

In study V, we investigated which epilepsy medicines were used when initiating treatment in patients in Stockholm with epilepsy after stroke, and how long the patients remained on treatment, an indirect measure of tolerability. Levetiracetam was the most common epilepsy medicines in both men and women, and the medicine patients were treated with the longest.

This thesis shows that the prevalence of sex differences in drug use varies between therapy areas and over time, which emphasizes the importance of studying drug use and analyzing sex differences regularly.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Skillnader i läkemedelsanvändning mellan kvinnor och män beror oftast på en kombination av biologiska (kön) och sociokulturella (genus) faktorer. Det är dock inte lätt att få en heltäckande översikt eftersom resultat från studier skiljer sig åt, inte bara mellan olika terapiområden utan också över tid och mellan olika studerade populationer.

Det övergripande syftet med den här avhandlingen var att studera köns- och genusskillnader i läkemedelsanvändningen, i allmänhet och inom några terapiområden, med hjälp av data från olika register. Dessutom ville jag med hjälp av kvalitativa metoder försöka identifiera läkares uppfattningar om köns- och genusaspekter vid beslut om läkemedelsbehandling.

I studie I analyserades de största könsskillnaderna i läkemedelsanvändning i Sverige år 2010. Många könsskillnader bedömdes helt eller delvis kunna förklaras av att kvinnor och män har olika sjukdomsförekomst och biologi, medan andra skillnader var svårare att förklara medicinskt och kan tyda på ojämlik behandling.

I studie II undersöktes könsskillnader i rapporterade blödningsbiverkningar orsakade av tre blodförtunnande läkemedel: klopidogrel, lågdos acetylsalicylsyra och warfarin. Ingen könsskillnad fanns i rapporterade blödningar för klopidogrel och warfarin. Däremot var rapporterade blödningar för lågdos acetylsalicylsyra vanligare hos män än hos kvinnor, vilket kan bero på att män i större utsträckning fick högre dos än kvinnor.

I studie III genomfördes fokusgruppsdiskussioner med läkare på fem vårdcentraler för att undersöka deras uppfattningar om kön och genus relaterat till läkemedelsförskrivning. Stereotypa uppfattningar om kvinnor och män förekom, men vid beslut om behandling sade sig läkarna beakta individuella faktorer och följa regionala rekommendationslistor. Trots att läkarna uttryckte att de hade bristande kunskap om könsskillnader i läkemedelsbehandling gavs flera exempel på hur patientens kön beaktades.

I studie IV granskades användningen av blodförtunnande läkemedel hos patienter med förmaksflimmer i Region Stockholm år 2011 och 2015, dvs. före och efter introduktionen av de nya orala antikoagulantia (NOAK). Både förekomsten av förmaksflimmer och andelen som använde orala antikoagulantia ökade hos både kvinnor och män. År 2011 var det färre kvinnor än män som hade något oralt antikoagulantia, men 2015 hade könsskillnaden försvunnit, förutom hos äldre och hos patienter med komplicerad samsjuklighet.

I studie V undersöktes vilka epilepsiläkemedel som användes vid nyinsättning till patienter i Stockholm med epilepsi efter stroke, samt hur lång tid patienterna stod kvar på behandling, ett indirekt mått på tolerabilitet. Levetiracetam var det vanligaste epilepsiläkemedlet hos både kvinnor och män. Det var även det läkemedel som patienterna behandlades med längst.

Denna avhandling visar att förekomst av könsskillnader i läkemedelsanvändning varierar mellan terapiområden och över tid vilket understryker vikten av att följa läkemedelsanvändning och analysera könsskillnader regelbundet.

ABSTRACT

Drug prescribing is one of the most important processes in healthcare and drugs are also commonly used in the population. Drug use differs between men and women and descriptive reports of sex differences in drug use have been published with examples from different therapeutic areas. However, it's not easy to gain a comprehensive overview as results differs, not only between therapeutic areas but also over time and between different populations.

Differences between men and women are mostly caused by a combination of biological (sex) and socio-cultural (gender) factors. For example, there are differences between men and women in disease prevalence and comorbidity, pharmacokinetics and pharmacodynamics, and hormone levels as well as in perceptions of disease, help-seeking behavior, interaction with healthcare professionals and utilization of healthcare that may affect drug utilization.

Study I was an observational cross-sectional study using data from the Swedish Prescribed Drug Register (SPDR) analyzing differences between men and women in drug utilization, overall and within different pharmacological groups in Sweden 2010. Substantial sex differences in prevalence and incidence of dispensed drugs were found, for example in antibiotics and in cardiovascular drugs. Most differences were rational and reflected differences between men and women in the incidence or prevalence of disease or biological differences. Other differences were more difficult to explain on medical grounds and may indicate unequal treatment.

Study II was an observational cross-sectional study using data from the SPDR and The Swedish Drug Information System (SWEDIS) analyzing differences between men and women in bleeding event reports for clopidogrel, low-dose acetylsalicylic acid (Aspirin) and warfarin. Total number of bleeding event report for each substance was adjusted for dispensed drugs of that substance during the same time-period. For low-dose aspirin, there were significant sex differences with more bleeding event reports in men, regardless of whether the figures were adjusted for dispensed prescriptions or exposed individuals. For clopidogrel, bleeding event reports seemed to be more common in women when adjusting for exposed individuals, however the sex difference was not significant. For warfarin, bleeding event reports were more common in women when adjusting for dispensed prescriptions for the time-period 1999-2010, but otherwise no sex differences were found.

Study III was a qualitative study using focus groups discussions to explore general practitioners' (GPs') awareness of sex and gender differences and assess their perceptions of whether men and women are treated differently in primary care with a particular focus on medical treatment. Stereotyped perceptions of men and women existed among the physicians, but individual factors seemed to be taken into account more often than the patient's sex when deciding on treatment. The physicians described that they followed the recommendations from the respective Drug and Therapeutics Committee (DTC), and that they relied on the DTCs' to have considered sex and gender when making recommendations. The physicians expressed that they had no or very little knowledge of sex differences in drug treatment.

However, they gave several examples of how they considered the patient's sex in drug treatment indicating the opposite.

Study IV was a repeated observational cross-sectional study of individuals in the region of Stockholm with a diagnosis of nonvalvular atrial fibrillation in 2011 and 2015, respectively. Dispensed thromboprophylactic treatment, i.e. warfarin, non-vitamin K antagonist oral anticoagulants (NOACs), and low-dose aspirin, was described by sex and age group, and by sex and CHA_2DS_2-VASc score. The prevalence of atrial fibrillation increased in both men and women between 2011 and 2015, as did the proportion of patients using oral anticoagulants (OACs). Patients with comorbidities potentially complicating OAC use, such as prior severe bleed, anemia, dementia, alcoholism, and frequent falls, used more OAC in 2015 compared to 2011. OAC treatment was less common in women in 2011, however in 2015 the sex difference had disappeared, except in elderly and in patients with complicated comorbidity.

Study V was an observational study following a cohort of patients with epilepsy after stroke treated with antiepileptic drugs (AEDs) using data from a regional healthcare database on diagnoses and dispensed prescription drugs in Stockholm. Choice of AED when initiating treatment in men and women was described. Levetiracetam was most common in both men and women. Multinomial logistic regression identified several factors associated with choice of AED, including for instance patient sex, age, and renal impairment. Furthermore, persistence to therapy was studied for the most used AEDs and levetiracetam had the highest persistence in both men and women. Factors associated with AED discontinuation within 90-days were choice of AED, use of OAC and percutaneous endoscopic gastrostomy tube delivery of the drug (PEG).

LIST OF SCIENTIFIC PAPERS

I. **Loikas D**, Wettermark B, von Euler M, Bergman U, Schenck-Gustafsson K. Differences in drug utilisation between men and women: a cross-sectional analysis of all dispensed drugs in Sweden. *BMJ Open*. 2013;3(5).

II. Rydberg DM, Holm L, Mejyr S, **Loikas D**, Schenck-Gustafsson K, von Euler M, Wettermark B, Malmström RE. Sex differences in spontaneous reports on adverse bleeding events of antithrombotic treatment. *Eur J Clin Pharmacol*. 2014;70(1):117-26.

III. **Loikas D**, Karlsson L, von Euler M, Hallgren K, Schenck-Gustafsson K, Bastholm Rahmner P. Does patient's sex influence treatment in primary care? Experiences and expressed knowledge among physicians--a qualitative study. *BMC Fam Pract*. 2015;16:137.

IV. **Loikas D**, Forslund T, Wettermark B, Schenck-Gustafsson K, Hjemdahl P, von Euler M. Sex and gender differences in thromboprophylactic treatment of patients with atrial fibrillation after the Introduction of non-vitamin K oral anticoagulants. *Am J Cardiol*. 2017;120(8):1302-8.

V. **Loikas D**, Linnér L, Sundström A, Wettermark B, von Euler M. Post-stroke epilepsy and antiepileptic drug use in men and women. *Submitted*

CONTENTS

LIST OF ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ADE	Adverse drug event
ADR	Adverse drug reaction
AED	Antiepileptic drug
ATC	Anatomical Therapeutic Classification
CI	Confidence interval
CYP	Cytochrome P450
DDD	Defined daily dose
DRP	Drug related problem
DTC	Drug and Therapeutics Committee
EMA	European Medicines Agency
FDA	Food and Drug Administration
FGD	Focus group discussion
GFR	Glomerular filtration rate
GP	General practitioner
ICD	International Classification of Diseases
ICSR	Individual case safety report
ILAE	International League Against Epilepsy
INR	International normalized ratio
MedDRA	Medical Dictionary for Regulatory Activities
MPA	Medical Products Agency
NME	New molecular entity
NOAC	Non-vitamin K antagonist oral anticoagulant
NSAID	Nonsteroidal anti-inflammatory drugs
OAC	Oral anticoagulant
OTC	Over-the-counter
PEG	Percutaneous Endoscopic Gastrostomy tube
PPR	Participation to proportion ratio
PSE	Post-stroke epilepsy
RCT	Randomized controlled trial

RE-LY	Randomized evaluation of long-term anticoagulant therapy
RR	Risk ratio
SAGER	Sex and Gender Equity in Research
SALAR	Swedish Association of Local Authorities and Regions
SPC	Summary of product characteristics
SPDR	Swedish Prescribed Drug Register
SWEDIS	Swedish Drug Information System
TTR	Time in therapeutic range
VAL	Region Stockholm administrative health data register
WHO	World Health Organization

1 PREFACE

Until the last quarter of the 20th century, patient's sex was not a recognized variable in health research. Neither was patient's sex a factor that was believed to affect health and illness. In 2001, the American Institute of Medicine made recommendations about sex being an important basic variable that should be taken into consideration when designing, analyzing, and reporting results from studies in all fields and at all levels of biomedical research [1].

Men and women are different in many ways, for example regarding life expectancy, morbidity and biology [1]. In the past, females have been underrepresented in clinical studies which has resulted in inequality between the sexes in the understanding, diagnosing and treatment of diseases [2]. Disparities in physiological functions affect the pharmacokinetics of drugs, meaning that men and women can respond differently to drug treatment [3].

Descriptive reports of differences in drug utilization between men and women have been published with examples from various therapeutic areas [4-11]. Historically, there were only a few studies attempting to explain the rationale behind such differences. The most common explanation was that the differences may be explained by a combination of biological and sociocultural factors, thus an interaction of sex and gender.

In Sweden, thoughts about sex and gender differences in healthcare were raised in the early 1990s. An investigation from 1996 made by the Ministry of Health and Social Affairs (Socialdepartementet) [12] identified many shortcomings in the ability to adapt healthcare to the needs of women and men. This because there was too little knowledge about the specific needs in men and women, respectively. Women risked being treated according to the male norm, however there were also some areas where men were offered treatment designed for women. The investigation gave several suggestions on how disparities could be reduced and how the knowledge on sex- and gender-related factors could be increased. When the National Board of Health and Welfare (Socialstyrelsen) some years later issued a follow-up report on gender equality in healthcare [13] only minor improvements were seen. The report stated, among other things, that many medicines were prescribed to a greater extent to women than to men.

During the years 2008-2012, the Swedish Association of Local Authorities and Regions (SALAR) received money from the Swedish government to support the implementation of gender mainstreaming in municipalities, county councils and regions. The initiative was called Program for Sustainable Gender Equality (Program för hållbar jämställdhet).

Karin Schenck-Gustafsson, founder of the Center for Gender Medicine at Karolinska Institutet, in Stockholm, Sweden and particularly engaged in research on differences between men and women within the cardiovascular field, applied for and received money within the program in collaboration with Björn Wettermark. Their activity goals included, among other things, a survey of differences in drug utilization between men and women in Sweden. For this, a pharmacist was needed, and I began an exciting journey into the world of research.

2 BACKGROUND

This background provides an overview of sex and gender; as concepts, their importance in healthcare and how they can be considered in medical research. Furthermore, it gives a brief introduction to pharmacoepidemiology and drug utilization as well as in factors affecting drug use, adherence and persistence, adverse drug effects and pharmacovigilance. Also, atrial fibrillation and anticoagulant use, and antiepileptic drug use and post-stroke epilepsy in men and women is covered.

2.1 THE CONCEPTS OF SEX AND GENDER

There are no universally accepted definitions of the terms “sex” and “gender”, nor is there any easy separation of them. Sex and gender are often used interchangeably, despite being two different concepts. However, they are not independent variables. They interact and reinforce each other [14]. As defined by the Institute of Medicine in Washington, sex is biology and gender is everything else including psychosocial and cultural factors [1].

Sex refers to a set of biological characteristics in humans and animals. It is mainly associated with the physical and physiological characteristics including chromosomes, gene expressions, gonadal hormones and anatomy and function of the reproductive system. Sex is usually categorized as male or female [15].

Gender refers to the socially constructed roles, expressions, behaviors and identities of girls/women, boys/men and gender diverse individuals. It affects individuals’ perceptions of themselves and others, how they act and interact with others, and the distribution of resources and power in society. Gender identity is not a binary term as a person can have traits of both masculinity and femininity being expressed to different degrees. Gender attributes are fluid and change as cultural norms and values change over time. There is a great diversity in how gender is expressed, perceived and understood, depending on time, place and context [15, 16].

There is a lack of conceptual clarity in the use of the terms sex and gender [17]. The term gender is most often used in medical research articles, although many studies only include data on patient sex. For example, when describing a study population, it is common practice to present how many participants were male/men or female/women. Some authors refer to this variable as sex, while others refer to it as gender. Efforts are made to apply the term sex for biological factors and gender for psychosocial and cultural factors [18], but more work is needed to standardize the way in which sex and gender are reported as well as to clarify how these characteristics influence healthcare, both independently and together [19]. In addition, In Spanish and some other languages these are not two separate words [20].

In this thesis and in the included studies, sex refers to biological factors and gender refers to sociocultural factors.

2.2 SEX AND GENDER IN MEDICINE

Both sex and gender influence an individual's health. Observed differences between men and women seldom involve sex and not gender, and gender does seldom operate outside of the context of sex. The importance of sex and gender varies depending on other factors such as age, race, ethnicity, social class and sexuality [14]. From an intersectionality perspective, an individual's health is always affected by an interplay between multiple factors including sex and gender [21]. Intersectionality is a theoretical framework for understanding how an individual's various social identities such as gender, race/ethnicity, socioeconomic status, sexuality, religion, (dis)ability, and physical appearance overlap and create different forms of discrimination and privilege.

Sex differences in the prevalence and clinical manifestation of diseases, as well as response to treatment originates from the genetic and hormonal differences between males and females. Biological sex also influences behaviors, where males exhibit more aggressive behaviors and females tend to be more caring. Gender-related behaviors, for example lifestyle, nutritional habits and perceived stress, may influence epigenetic mechanisms, which are important for the development of diseases. Gender constructs influence individuals' perceptions of disease, help-seeking behavior, and utilization of healthcare. Gender constructs may also influence treatment and decision making from providers, biased by gender [22].

Historically, erroneous assumptions have been made that male and female cells and animals were biologically identical [23]. Also, females have been underrepresented in clinical studies which has resulted in inequality between the sexes in the understanding, diagnosing and treatment of diseases [2]. Medical research has been centered on male physiology and therefore women have been the driving force for the development of gender equality policies. The focus has been on what women can gain from greater gender equality and the research concentrated on issues important to women's health. Subsequently, men's health came into focus. Mainly because men continued to lag after women in life expectancy and healthcare utilization. To provide effective care for men, there is a need of understanding how the masculine stereotypes affect men's health, for example in preventing men from seeking healthcare [24, 25].

Gender medicine focuses on the influence of sex and gender on health and disease. In gender medicine, the needs of both men and women must be considered. This may mean that greater attention must be given to women in areas where data on women are lacking, and greater attention to men in areas where data on men are lacking [26, 27]. Examples of diseases where more data on men is needed are depression and osteoporosis, while more data on women is needed in the cardiovascular area [26].

2.2.1 Men and women in clinical studies

In the drug development process, clinical trials are conducted to collect data regarding the efficacy and safety of new drugs. Historically, there were several reasons why health researchers preferred to study men, including a general belief that men and women did not

differ significantly in treatment response in most situations, and concerns about confounding effects of the female sex hormones [1]. Also, cost aspects mattered where sample size could be reduced when preserving sex homogeneity, resulting in lower costs. Further, there was intention to protect women and fetuses as well as fear of responsibility from perinatal exposure if pregnancy should occur [2].

After the thalidomide scandal in the early 1960s, there was great fear of drug-induced birth defects. Guidelines from the United States Food and Drug Administration (FDA) recommended to exclude fertile women from the earliest clinical trials. Later, these guidelines were repealed, acknowledging that fetal exposure could be avoided through appropriate protocol design and the use of contraceptives. Despite this, the old guidelines were often cited as a main reason why females continued to be underrepresented in clinical studies [2].

Pre-clinical studies include animal studies investigating a drug's safety in doses equivalent to approximated human doses, pharmacokinetics and pharmacodynamics. Phase I trials, the first studies in which the drug is tested in humans, are usually performed in a small number of healthy and/or diseased volunteers. The drug's effects, metabolism and tolerability are investigated, the appropriate dose is determined and side effects at higher doses are studied. In phase II trials, which are conducted in a small number of individuals with the disease of interest, safety, pharmacokinetics, and pharmacodynamics are explored and the optimal dosing strategies are determined. Phase III trials are conducted in a larger group of patients to define how useful the drug is for treating the disease in question, and to estimate the occurrence of common side effects [28].

If both sexes are not adequately represented in early phases of clinical trials, there is a risk that sex-specific risks or benefits of a drug will not be discovered until much later in the drug development process or even remain undiscovered. For proper application of clinical study results, study participants should represent the populations for which drug treatments are intended.

FDA have investigated the participation of women in clinical trials over the years. In a study that reviewed data from phase I clinical trials submitted in 2006-2007 for 30 new molecular entities (NMEs) for non-sex specific indications in adults [29], a third of the 352 reviewed studies included only male participants. In the other two-thirds, the proportion of women was between 4-100 percent. Two studies included only women. For 29 of the 30 drugs, women were included in at least one phase I study. The conclusion of the investigation was that the number of female participants in clinical phase I studies had increased since 2001, however women were still underrepresented.

In another study by FDA [30], examining women's participation in late-phase clinical trials for 50 new drugs approved in 2007-2009, 53 percent of all enrolled participants were men, 43 percent were women and 4 percent had unspecified sex. Sixty-four percent of the new drug applications had participation to proportion ratios (PPRs) of ≥ 0.80, indicating that the

proportion of women in these clinical trials was similar to or higher than the estimated proportion of women in the disease population.

A study examining data from 206 clinical trials supporting the approval of 86 new drugs in 2011-2013 [31], concluded that men and women were equally represented in clinical trials. In total, calculated for all indications, 50.3 percent of the clinical trial participants were men, and 49.7 percent were women. However, PPRs were not analyzed within the various indications. Instead, the researchers raised the problem that elderly patients and patients from racial and ethnic minorities are underrepresented in clinical trials. The mean proportion of elderly (≥65 years of age) was 29 percent and 79 percent of the participants were white.

Some years later, FDA examined new drug marketing applications for 102 new drugs approved in 2013-2015 for non-sex specific indications in adults [32]. Sex was reported for near all trial participants (>99.9%) enrolled in all phases (phases I, II and III), and women accounted for 40 percent of these. The proportion of women were lower in phase I studies than in later phases. Fifty of a total of 60 indications had a PPR ≥0.80.

When FDA evaluated demographic data of phase III clinical trials of NMEs approved in 2015-2016 for non-sex specific indications in adults [33], 41 percent of all enrolled participants globally were women. The proportion of women varied by therapeutic area from 0 percent in trials within medical imaging and diagnostics to 76 percent in trials for ophthalmology. In cardiovascular disease trials, 34 percent of all enrolled participants globally were women, of which the majority (79%) were white.

A large-scale analysis of data from over 43 000 research studies and more than 13 000 clinical trials analyzed women's participation in clinical studies from 1993 to 2018 [34]. Overall, 49 percent of the participants were women, but for many diseases the proportion of women in the studies did not match the proportion of women with the disease in the population. Substantial underrepresentation of women was seen in HIV/AIDS, cardiovascular diseases, chronic kidney diseases, digestive diseases and hepatitis. Female overrepresentation, which equals male underrepresentation, was only seen in musculoskeletal disorders.

In a study examining women's participation in trials of cardiovascular medications [35], data was collected from clinical trials supporting the approval of 36 new drugs from 2005 to 2015. In total, 34 percent of the participants were women. The proportion of women varied by trial (22-81 %) and cardiovascular area. Women were underrepresented in trials of drugs for heart failure, coronary artery disease, and acute coronary syndrome, and overrepresented in trials of drugs for pulmonary arterial hypertension. Within the areas of hypertension and atrial fibrillation, the proportion of women enrolled in trials roughly matched the proportion of women in the disease population. Minimal sex differences in drug efficacy and safety were observed.

Over the years, proportions of women in clinical trials have increased. However, the same improvement has not been seen regarding in vitro studies where the sex of cell lines too often

are ignored, and preclinical research is still being done mainly using male animal models and male-derived cells. Thus, many conclusions from the earliest studies are made based on incomplete and sex-biased data and may conceal important sex differences [36, 37].

Furthermore, it is not enough that both men and women are included in the clinical studies. The results need to be reported and analyzed by sex. Sex or gender analysis can be crucial to the interpretation, validation, reproducibility and generalizability of research findings [38]. Pooling the results from females and males, which are often done in studies, can mask sex differences and give inexact results.

2.2.2 Sex-disaggregated statistics and analysis

When FDA reviewed 300 new drug applications filed between 1995 and 2000 [39], it was found that 54 percent of them contained a sex analysis. For eleven drugs, a difference in pharmacokinetics of more than 40 percent was shown between males and females. Still, there were no sex-specific dosing recommendations. In later studies by FDA, sex analyses of both safety and efficacy were found in 74 percent of all new drug applications for new drugs approved in 2007-2009 [30], and in 93 percent of all applications for new drugs approved in 2013- 2015 [32].

Tannenbaum et al. [38] mean that to obtain proper sex and gender analysis, joint efforts are needed from the three main actors in academic research; funding agencies, peer-reviewed journals and universities. Government-led funding agencies are leading this progress by requesting information in the application on how sex and gender analysis is relevant in suggested research, or why it is not. Simultaneously, an increasing number of peer-reviewed journals have editorial policies requiring sex- or gender-specific analysis. Although, no standard has been broadly adopted.

In 2016, the European Association of Science launched the Sex and Gender Equity in Research (SAGER) guidelines [40], intended to be implemented across journals and supported by researchers and funders. The guidelines encourage systematic reporting of sex and gender in research across disciplines, describing how to report this information in study design, methods and data analyses, results and interpretation of research findings. The SAGER guidelines were primarily designed to guide researchers and authors in preparing their manuscript, but also for editors as a tool to use when evaluating manuscripts and to raise awareness of this issue among authors and reviewers. A general principle is that the terms sex and gender should be used carefully in order to avoid confusion. The SAGER guidelines suggest that the term sex should be used to classify females and males based on biological distinction. They also point out that by using common definitions, the ability to conduct meta-analyses of published data will be improved.

Schiebinger et al. [41] promote editorial policies for sex and gender analysis and have proposed guidelines on how to report sex and gender in medical journals, highlighting the importance of the following items:

1. Using the terms sex and gender correct and precise.
2. Reporting the sex, gender, or both of the study participants.
3. Consider analyzing data by sex, gender or both, or provide the raw data. Report and discuss the method chosen for sex/gender analysis.
4. Analyze the influence of sex, gender or both on the results where appropriate, or indicate why such analyses were not made.
5. Post hoc analyses of sex or gender may be underpowered and should by interpreted cautiously.

2.2.2.1 Intersectionality

The implementation of intersectional analysis within health research has been mainly through qualitative research and its applicability to quantitative methods is debated. However, there are possibilities and available statistical tools to enable analysis regarding intersectionality such as interaction terms for the operationalization of intersections (e.g. woman*immigrant), various multi-group models for analyzing interactions between categories, and multi-level models for analyzing cross-level interaction [42].

2.2.3 Biological differences between men and women

Biological differences between the sexes are most obvious when applied to the reproductive system. However, there are sex differences at many levels of biological organization, including biochemical, physiological and behavioral [1]. Examples of sex-specific physiological differences are generally smaller organ size, higher percentage of body fat and lower glomerular filtration rate (GFR) in women compared to men. These and other factors may affect the pharmacokinetics and pharmacodynamics of drugs and can make men and women respond differently to drug treatment [3, 43].

2.2.3.1 Sex differences in pharmacokinetics and pharmacodynamics

In general, pharmacokinetic sex differences are more numerous and consistent than pharmacodynamic sex differences, but more and more pharmacodynamic differences between men and women are being identified at a molecular level [44]. Underlying causes of biological sex differences include differences in physiology and hormonal control [45].

The four most important factors for pharmacokinetic variability are bioavailability, distribution, metabolism and elimination, and there is evidence for sex differences in each one [46-48].

On average, men are larger than women and weigh more, but the dosage of most drugs is not adjusted according to body weight. Sex differences in body size result in larger volume of

distribution and higher clearance of most drugs in men than in women. Higher proportion of body fat in women may increase the volume of distribution for fat-soluble substances [47].

Renal excretion is the most common route of drug elimination, and GFR, a standard measure of renal function, is lower in women compared to men. There are also sex differences in the two other major renal processes; tubular secretion, and tubular reabsorption being slower in women [47, 48]. Furthermore, there are sex differences in metabolic enzymes, many concerning the cytochrome P450 (CYP) system. The important drug-metabolizing enzyme CYP3A4 have a higher expression in female livers than in males [44].

Sex differences have been shown in the gastrointestinal system, for example higher gastric pH and lower gastric and bowel transit time in women than in men, which may affect drug bioavailability. Some of these differences depend on the levels of estrogen and progesterone and may thus vary through the menstrual cycle and through pregnancy [44].

In a study of 86 drugs with available sex-specific pharmacokinetic data [49], 76 drugs had higher pharmacokinetic values, i.e. higher blood concentrations and/or longer elimination times, in women than in men. This was strongly linked to the higher incidence of adverse drug reactions (ADRs) in women. The study indicated that many sex differences in ADRs remained after corrections for body weight.

Sex-differences in pharmacodynamics have not been studied as extensively as in pharmacokinetics, however sex differences in the efficacy and safety have been shown for a number of drugs including cardiovascular drugs [45, 50]. For example, women require less warfarin per week than men to maintain a therapeutic international normalized ratio (INR), the reduction in blood pressure and heart rate is greater in women than in men treated with metoprolol, and dry cough is more common in women than in men during treatment with angiotensin-converting enzyme (ACE) inhibitors [50].

There are not only differences between men and women; there are also differences between individuals of the same sex over the life span. In women, the effect of sex hormones varies during the life cycle – before menstruation, in childbearing age, during pregnancy and lactation, during menopause and after menopause – which may be associated with changes in the pharmacokinetics and pharmacodynamics of drugs [51]. However, these variations are poorly studied [2] and not enough considered in studies [1].

2.2.3.2 Sex-specific recommendations

Despite all knowledge about differences between men and women in epidemiology, manifestation, and pathophysiology of diseases there are few sex and gender-specific recommendations in healthcare. If this is a problem or not can be debated. Often, sex and gender are not taken into account in guidelines regarding prevention, management and treatment of many common diseases. There are exceptions, such as the guidelines for the management of atrial fibrillation [52-54], where female sex is highlighted as a risk factor for stroke. However, the importance guidelines place on the difference have varied over time.

Sex-specific dosing recommendations are also rare. However, in 2013 FDA changed the dosing recommendations for zolpidem, a drug used to treat insomnia, due to a slower overall metabolic clearance rate in women and hence an increased risk of experiencing next-morning impairment. Women are recommended a lower initial dose than men [45, 55]. The European Medicines Agency (EMA) made another interpretation and cautioned all patients to be aware of the risk of next-morning impairment [56].

Precision medicine is an approach that uses information about a person's genes, environment and lifestyle to select the treatment that could work best for the individual patient. The recent advances in genetics and the growing availability of health data provides increased opportunities in this area [57]. The term precision medicine has replaced the term personalized medicine, which was defined synonymously. However, personalized medicine was somewhat misleading and could be confused with physician's effort to adapt treatments and preventions to each unique individual [58]. Although biological sex is a basic aspect of human physiology, it is not sufficiently considered when developing personalized medical strategies [18], and recognizing sex and gender as important modifiers of health and disease is an important step towards precision medicine [22].

2.3 PHARMACOEPIDEMIOLOGY AND DRUG UTILIZATION

Pharmacoepidemiology is the study of the utilization and effects of drugs in large populations, in real-world conditions. It can be described as a bridge between clinical pharmacology and epidemiology, applying epidemiological methods on pharmacological issues [59].

In drug utilization studies there are several different perspectives that can be covered. The World Health Organization (WHO) definition of drug utilization research from 1977 is "studies on the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the medical, social, and economic consequences" [60]. A more extensive definition was proposed in the textbook "Pharmacoepidemiology and Therapeutic Risk Management" in 2008 [61]:

> "Drug Utilization Research is an eclectic collection of descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes."

There are two key difference between the two definitions – the more recent emphasize on interventions to improve quality use of medicines and the inclusion of qualitative methods for a deeper understanding. Drug utilization research wants to facilitate a safe and effective use of medicines. Some different focus areas are risks and benefits of drug therapy, inappropriate drug use, and costs of medicines and treatment for patients and society. A wide range of different study designs can be used to conduct drug utilization studies, including both quantitative and qualitative methods [62].

Observational studies are conducted in real-life situations where the researchers observe and do not influence any factors, unlike experimental studies where the conditions are under the direct control of the researchers. Observational studies can be descriptive or analytic. Descriptive studies describe patterns or trends in drug utilization in a population without having any comparison group. Analytical studies are designed to test hypotheses and to investigate the association between exposure and outcome using comparison groups [63].

2.3.1 Sex differences in drug use

In the cardiovascular field, relatively much research has been done regarding sex- and gender differences as compared to other fields. Several scientific studies have shown potential inequities between men and women in drug treatment for cardiovascular disease. In a systematic review and meta-analysis on sex differences in the prescription of cardiovascular drugs in primary care [64], men were more likely to be prescribed aspirin, statins and ACE inhibitors, and women were more likely to be prescribed diuretics. Furthermore, studies have shown undertreatment of women in myocardial infarction [65] and in coronary artery disease [8], underuse of statins for secondary prevention in women [66-69], and undertreatment of women with anticoagulants in atrial fibrillation [70].

Studies in hypertension have shown that men with hypertension were less likely to be treated than women with hypertension [71, 72]. Some studies showed that women were more often prescribed diuretics whereas men were prescribed beta-blockers, calcium antagonists and ACE inhibitors/ARBs more often [9, 72-74]. Another study showed that women used more diuretics, ARBs and beta-blockers, while men used more ACE inhibitors and calcium channel blockers [75].

2.3.2 Factors influencing drug use

Drug use may be influenced by several factors including biology, disease panorama, help-seeking behavior, how patients present their symptoms and how physicians take anamnesis, guidelines, patient adherence and persistence, and occurrence of adverse drug events [76]. In all these areas, there are studies presenting sex- and gender differences.

2.3.2.1 Help-seeking behavior in men and women

Healthcare contact is a prerequisite for obtaining a prescription, and the more visits, the greater probability of a prescription. In general, women seek healthcare more often than men and studies have demonstrated differences between men and women in help-seeking behavior [77-80]. Also, men have been stereotyped as less likely than women to seek healthcare and the masculine norm has been identified as a barrier for seeking healthcare [24].

The largest differences between men and women have been seen in primary care. For example, preventive care utilization, such as blood pressure check, cholesterol check, dental check and flu shots, have been found to be higher in women than in men [78]. A Swedish study on sex differences in healthcare consumption suggested that since women use

reproduction-associated care to a much greater extent than men, it might be easier for women to also seek healthcare for other reasons [81].

A Danish cohort study in individuals aged 60 years or over hospitalized for stroke, myocardial infarction, chronic obstructive pulmonary disease, or gastrointestinal cancers [80], concluded that women's higher use of primary healthcare is likely to be explained by a lower help-seeking threshold in women combined with women's better survival with disabling conditions. The probability of use and the levels of healthcare utilization in primary care increased after hospitalization in both men and women, but the increase was more pronounced among men.

Studies comparing help-seeking behavior in men and women have often been insufficient in explaining factors or processes involved in men's help-seeking behavior. However, a growing number of studies emphasize a trend of delayed help-seeking in men who experience illness, and "traditional masculine behavior" has been highlighted as one explanation [24]. A review of factors associated with men's delays in medical and psychological help-seeking, showed that the most salient barriers to help-seeking were reluctance to express emotions/concerns about health, fear and anxiety, and poor communication with healthcare professionals [82]. A review examining the role of masculinity norms in men's help-seeking behavior for mental health problems, found that traditional beliefs about masculinity can prevent men from seeking help, and the main barriers for seeking help was self-reliance, self-control, and difficulty in expressing emotions [25]. Several studies have emphasized that the barriers preventing men from seeking healthcare must be addressed in order to improve men's health and reduce future morbidity as well as to reduce costs for specialist care [77, 81].

2.3.2.2 The physician-patient interaction

The physician-patient interview is fundamental to all healthcare, especially in primary care, determining the processes and outcomes of consultations. It also affects patients' understanding about their conditions, and the extent to which patients participate in treatment decisions. The interaction between the physician and the patient is influenced by the gender of both parties, and affects the physician-patient communication, the care process and its outcome [83-85].

A systematic review on the impact of gender dyads on physician-patient communication [84] showed that gender dyads influenced the agendas elicited from patients, communication style, non-verbal communication, talk content, and the length of consultations. Consultation length was the phenomenon most studied and most frequently shown to be affected by gender dyads. Consultations with a female physician and a female patient were longer, contained the most talk and were the most patient-centered.

A systematic review and meta-analysis on the effect of physicians' gender on communication and consultation length [85] showed that female physicians spent on average over 2 minutes longer with patients per consultation than male physicians. Female physicians appeared to

devote more time to rapport-building behaviors, such as encouragement, reassurance, lowered dominance, and demonstrating caring and empathy.

A review on gender issues in healthcare communication [83] described some significant differences in practice between male and female physicians. Female physicians devoted more time to preventive services and psychosocial counseling, while male physicians devoted more time to anamnesis and physical examinations. Regarding gender-specific patient characteristics, female patients made more medical visits than men, and their visits were characterized by more preventive services, less physical examination and less discussions about alcohol, tobacco and other substance abuse (controlled for health status and sociodemographic variables).

Lack of communication between patient and physician has been shown to be a common cause of primary nonadherence [86].

2.3.3 Adherence and persistence

Adherence to medication is described as the process through which patients take their medication as prescribed, and it consists of several parts [87]. The process starts when (if) the patient takes the first dose of a prescribed drug. However, problems with primary nonadherence are considerable [88]. It occurs when a patient do not purchase the first prescription of a new medicine within an acceptable time period after prescribing [89]. Secondary adherence is the process following whether or not patients continue to purchase their prescriptions as prescribed during a defined observation period [90]. Persistence relates to the time from initiation until discontinuation. In the recent adherence literature, the terms initiation, implementation and persistence are used for the different aspects of adherence [91].

Rates of primary nonadherence varies across therapeutic areas, drug classes and individual drugs [92]. A systematic review [86] concluded that primary nonadherence, like all types of nonadherence, is multifaceted with many different contributing factors that are closely associated with each other. Patient factors were reported the most, for instance age and sex. Younger patients were found to be more nonadherent than older patients in most studies, and women were consistently found to be more nonadherent as compared to men. Other studies have shown that men were more nonadherent [93]. Also, there are studies concluding that patient sex was not associated with primary nonadherence [94, 95].

Studies of secondary nonadherence, implementation, have also shown conflicting results on whether patient sex is an influencing factor or not. In a study examining patient characteristics associated with medication adherence across eight diseases, sex differences were found in hypertension, diabetes and hyperlipidemia where women had higher nonadherence than men [96]. Other studies have shown higher nonadherence in women in statin therapy [97-99], and higher nonadherence in men in oral anticoagulation therapy [100]. On the contrary, no significant difference between men and women were found in adherence to antihypertensive drug treatment [101].

A Swedish study analyzing gender differences in self-reported nonadherence to prescribed medication [102] found no overall differences between men and women in reporting nonadherence. However, men and women had different adherence behaviors and reported different reasons for nonadherence. Men were more likely to report forgetting to take medication, changing the dosage, and recovering as reasons for nonadherence, whereas women were more likely to report adverse drug reactions as reason for nonadherence. More women than men reported that they purchased the prescribed drug but did not take it.

A study examining adherence to antidepressants [103] showed a significant interaction between age and sex in a regression analysis model with adherence as the dependent variable. Adherence was higher in men than in women among younger individuals (20-40 years), and higher in women than in men in older (50-70 years).

Furthermore, there are conflicting results regarding sex differences in studies on persistence. A higher persistence in women than in men have been shown in antihypertensive treatment [104], whereas female sex has been associated with lower persistence to statin therapy [105] and oral anticoagulants [106], and the persistence to asthma medication has been shown to be lower in girls than in boys [107].

2.3.4 Adverse drug effects

Drugs can have both positive beneficial effects and negative harmful effects. These are either related or unrelated to the drug and its principal pharmacological action. Negative effects of drugs are common and cause substantial morbidity and mortality, nevertheless, often not recognized or handled appropriately [108].

2.3.4.1 Terms and definitions

Several different terms are used to describe the negative effects of drugs. An adverse event means harm in a patient administered a drug, but the harm is not necessarily caused by the drug. An adverse drug reaction (ADR) means harm directly caused by a drug at normal doses. An adverse drug event (ADE) means harm caused by the use of a drug in a broader context including ADRs, overdoses, dose reductions and discontinuation of drug treatment. To be able to determine if it is an ADR or an ADE, you must have information about doses. In registry studies, when dose information often is lacking, it is most appropriate to use the term ADE. However, there is a conceptual confusion, and the terms ADE and ADR are used in scientific articles occasionally outside the definitions. The term side effect refers to any effect of a drug other than the intended therapeutic effect, whether positive, neutral or negative, and should be avoided in this context [108]. In addition, the term drug related problem (DRP) is found in the literature. It is a broader term summarizing problems related to the use of approved drugs [109].

There is a great diversity of ADRs. They can target any organ system or involve several systems simultaneously. They can appear at first administration or several years after treatment initiation. Thus, there is a big challenge as regards their initial recognition, and

thereafter, even when an ADR is well described, it can be difficult to identify in an individual patient [110].

2.3.4.2 Studying drug safety

During drug development the pharmaceutical companies must study and assess efficacy and safety of drug products. Before a drug is licensed for marketing it must go through a regulatory review by a drug regulatory authority. According to the basic requirements for approval the applicant company must demonstrate a positive benefit-risk profile, meaning that the weighted assessment of the benefits outweigh the weighted assessment of the risks. For severe diseases, the benefits may outweigh the risks despite serious adverse effects, while in principle no serious adverse effects are accepted for a drug to be used for a less severe condition. In connection with the approval, a risk management plan is established describing how the company should follow up on the identified and potential risks [111].

When a new drug is approved, the available information on efficacy and safety is limited to the results from clinical trials, which include a selected sample of relatively few patients monitored under controlled conditions and for a limited length of time. Several subgroups have been or are underrepresented in clinical trials, including females [2, 29, 30, 32-35], elderly [31], and individuals from racial and ethnic minorities [31]. Also children are few [112], as well as pregnant women who are generally excluded from drug development clinical trials. After authorization, the drug may be used in many patients of different ages and with different conditions, for long time periods and simultaneously with other drugs, and ADRs not previously observed may emerge. Therefor it is of great importance that the safety of medicines is monitored throughout their use in healthcare practice [113].

Pharmacovigilance is the pharmacological science and activities related to the detection, assessment, knowledge and prevention of adverse effects and other drug-related problems. All regions of the world have their own pharmacovigilance system, based on WHO guidelines. These systems are generally based on a spontaneous reporting system to which healthcare professionals and pharmaceutical companies report events that are suspected to be adverse effects of marketed drugs. The primary aim is rapid detection of either new ADRs or a significant change in the frequency of known ADRs [113].

In Sweden, suspected ADRs are reported from healthcare professionals, pharmaceutical companies, patients and consumers to the Swedish Medical Products Agency (MPA). The reports are reviewed and registered. They are coded according to an internationally used medical terminology, the Medical Dictionary for Regulatory Activities (MedDRA). The MPA also assesses whether more information needs to be requested [114]. Completed reports are sent deidentified to EudraVigilance, the European pharmacovigilance system managed by the EMA [113].

VigiBase is the WHO global database for ADRs, which has aggregated individual case safety reports (ICSRs) from member countries of the WHO Programme for International Drug Monitoring since 1968. Collecting data from several countries increases the possibility of

detecting rare ADRs, which may not have been detected in the data from a single country [115].

The more serious ADR, the greater the likelihood of reporting. Also, novel ADRs and ADRs related to a new drug are more likely to be reported. This is a bias, however it is consistent with the main purpose of spontaneous ADR reporting [116]. Furthermore, reporting ADRs may differ between healthcare professional and patients. A systematic review on ADRs in Norway [117] showed that reports from healthcare professionals most commonly concerned anticoagulants, while reports from patients most commonly concerned psychotropic medicines. In another Norwegian review on all ADR reports from 2010-2013 [118], the drug group most mentioned in patient reports was drugs acting on the nervous system, especially psychotropic drugs and analgesics, while vaccines was the most common drug group in reports from healthcare professionals.

2.3.4.3 Sex and gender differences in the occurrence and reporting of adverse drug reactions

The incidence of ADRs is significantly higher in women [44, 49]. However, the biological causes of this sex difference are unclear, and several possible reasons have been discussed. In the past, sex differences in ADRs have often been attributed to differences in body weight and the fact that women receive higher doses in relation to body weight. However, studies accounting for this have still found significant sex differences suggesting that the action of not dosing according to body weight does not explain the outcome. Other discussed reasons are the fact that women use more drugs than men, and that women have a greater tendency to report ADRs. Since women have more contacts with healthcare than men, they also have increased opportunities to report. Furthermore, increased sensitivity to the drugs' effects in women has been suggested [119, 120].

Recent studies on sex differences in ADRs [44, 49] suggests that hormonal effects likely have great significance, and sex differences in pharmacokinetics and pharmacodynamics contributes to sex differences in ADRs. The administration of the same dose to men and women results in higher blood concentrations and/or longer elimination times in women for many drugs, and these sex differences in pharmacokinetics strongly predicts ADRs in women [49].

To remove or reduce many sex differences in ADRs, researchers recommend that women should receive lower initial doses of drugs with higher blood drug concentrations and/or longer drug eliminating times in women, and the dose should be increased only if the desired therapeutic effect is not achieved. Also, drugs are recommended to be administered adjusted for bodyweight (mg/kg) wherever feasible in both men and women. However, in general many sex differences in ADRs persist after adjusting for body weight [49]. Furthermore, healthcare professionals need to consider differences between men and women in safety profiles of the medicines when initiating or making changes to an ongoing pharmacological treatment.

Sex differences have been shown in ADR reporting, with a higher proportion of reports in women [118, 121-123]. It has been discussed that the occurrence of ADRs is mainly influenced by sex, while the reporting of ADRs is more influenced by gender. Some suggested explanations are that women visit healthcare more often than men, women complain more than men, and physicians underestimate adverse effects in women. Also, the physicians themselves are men or women and their gender perspective may influence their identifying and reporting of ADRs [124].

In a study of more than 15 million ADR reports in VigiBase [123], 60 percent were reports concerning women and 40 percent were reports concerning men. The reports came from 131 different countries and most countries had a similar proportion of ADR reports concerning women. The reports in VigiBase are submitted both from healthcare professionals, and, in some countries, from patients. Also, the manufacturing pharmaceutical company can report. ADR reports were more common in women in all age groups, except in children 0-11 years where they were more common in boys than in girls. The sex difference was most pronounced in the age group 18-44 years, where 66 percent of all reports concerned women. In this age group, which corresponds roughly to woman's reproductive years, use of contraceptives is common which could contribute to the excess of ADR reports in women. However, the removal of all ADR reports including hormonal contraceptives (in fact all drugs acting on the genitourinary system and sex hormones, Anatomical Therapeutic Classification (ATC) group G) in this age group only affected the proportions marginally.

In a Norwegian review on all ADR reports from 2010-2013 [118], 58 percent of the reports from healthcare providers and 63 percent of the reports from patients concerned female patients. A study investigating the influence of age, sex and seriousness on the reporting of ADRs in Sweden [121], indicated that healthcare professionals more frequently reported ADRs for the elderly and for women. Serious reports were more commonly reported for men and non-serious reports were more commonly reported for women. Also in the large VigiBase study [123], serious reports were more common in men. The reasons for this are not clear, but one reason might be that women visit healthcare more and thus ADRs might be detected faster and not leading to any serious events.

In a Korean study exploring sex differences in adverse events associated with cardiovascular drugs, the overall reporting rate was higher in women, while the reporting rate of serious adverse event was higher in men [125].

2.3.5 Atrial fibrillation and anticoagulant use in men and women

2.3.5.1 Atrial fibrillation

Atrial fibrillation is the most common arrhythmia and one of the most common cardiovascular diseases among both men and women. The prevalence has been estimated to about 2 percent in several European countries [126], and to 2.9 percent in Sweden [127]. In Stockholm, the prevalence of diagnosed non-valvular atrial fibrillation has been estimated to 2.1 percent [70].

The prevalence increases with increasing age and is higher among men than among women. Some important risk factors for atrial fibrillation, in addition to age, are hypertension, diabetes mellitus, obesity, smoking, and dyslipidemia. Also, cardiac diseases including heart failure, coronary heart disease, and valvular heart disease constitute major risk factors [128, 129]. The prevalence of these risk factors varies between the sexes, and there are also some women-specific risk factors for atrial fibrillation including pregnancy, preeclampsia, and number of children [128].

Common symptoms of atrial fibrillation are palpitations, dyspnea, and chest pain. Atypical symptoms, such as weakness and fatigue, have been shown to be more frequent in women. Women seem to be more likely to seek healthcare for symptoms, while asymptomatic atrial fibrillation, on the other hand, is more common in men [129]. Atrial fibrillation is associated with increased risk of stroke and death in both men and women. However, the risk is greater in women [128, 130-133].

2.3.5.2 Stroke and bleeding risks assessment

Treatment for atrial fibrillation includes rate or rhythm control, and stroke prevention. Decisions around stroke prevention treatment need to balance the risk of stroke against the risk of major bleeding, and also other factors must be considered including presence of mechanical heart valve, renal function and liver function, patient preferences and patient compliance [134]. A risk scoring system, such as $CHADS_2$ or CHA_2DS_2-VASc, should be used to assess stroke risk [135] and the individual risk of bleeding can be assessed by the scoring system HAS-BLED [136].

CHA_2DS_2-VASc includes more stroke risk factors than $CHADS_2$ (Table 1) and has proven to be better at identifying individuals with low risk and at least as good as $CHADS_2$ in identifying patients who develop stroke and thromboembolism [135]. At present, the CHA_2DS_2-VASc score is the preferred risk scoring system in most major international guidelines [137, 138]. Patients identified as low-risk; CHA_2DS_2-VASc 0 (males), or 1 (females), do not need stroke prevention treatment. In patients with CHA_2DS_2-VASc 1 (males), or 2 (females), oral anticoagulants (OACs) should be considered, and in patients with CHA_2DS_2-VASc $\geq$2 (males), or $\geq$3 (females), OACs are recommended. The latest Australian guidelines recommend use of the sex-less CHA_2DS_2-VA score [139].

Table 1. Stroke risk stratification with the $CHADS_2$ score, CHA_2DS_2-VASc score, and CHA_2DS_2-VA score. Modified from [139, 140].

Letter	Risk factor	$CHADS_2$ score	CHA_2DS_2-VASc score	CHA_2DS_2-VA score
C	Congestive heart failure	1	1	1
H	Hypertension	1	1	1
A	Age ≥75 year	1	2	2
D	Diabetes mellitus	1	1	1
S	Stroke (previous stroke, TIA, thromboembolism)	2	2	2
V	Vascular disease		1	1
A	Age 65-74 years		1	1
Sc	Sex category (female)		1	
	Maximum score	6	9	8

Due to the higher risk of stroke in women compared to men, the CHA_2DS_2-VASc score assigns 1 point for female sex as a stroke risk factor [140]. A systematic review and large meta-analysis conducted by Wagstaff et al. 2013-2014 [131], found a 31 percent higher risk for stroke in women with atrial fibrillation than in men with atrial fibrillation, regardless of oral anticoagulation therapy, and the risk appeared greatest for women 75 years and older. Another systematic review and large meta-analysis, conducted by Marzona et al. 2017-2018 [133], found a 24 percent higher risk for stroke in women, and there was a significant relationship in women between increasing age and increasing risk of stroke, which was most evident in women 65 years and older. Older women have higher blood pressure and higher prevalence of heart failure with preserved ejection fraction than men, two independent risk factors for stroke, and the higher mortality in women with atrial fibrillation is mainly on account of heart failure and stroke [132].

Some recent studies suggest that female sex is rather an age dependent stroke risk modifier [131, 141]. Women with atrial fibrillation and no additional stroke risk factors has been shown to have a stroke risk similar to the stroke risk in men without any stroke risk factors [131, 141, 142]. The excess stroke risk for women was particularly evident among women with two or more non-sex-related stroke risk factors [131, 141].

The HAS-BLED score is commonly used to assess risk of major bleeding in anticoagulated patients with atrial fibrillation (Table 2). It ranges from 0 to 9, with a score of 0 indicating low risk, 1-2 indicating moderate risk, and ≥3 indicating high risk of bleeding. Bleeding risk and stroke risk are closely related, and there is an overlap of some risk factors between HAS-BLED and the stroke risk scores complicating the risk-benefit assessment [136, 143].

Table 2. Bleeding risk stratification with the HAS-BLED score. Modified from [136].

Letter	Risk factor	HAS-BLED score
H	Hypertension	1
A	Abnormal renal or liver function (1 point each)	1-2
S	Stroke	1
B	Bleeding history or predisposition	1
L	Labile INRs	1
E	Elderly (>65 years)	1
D	Drugs or alcohol concomitantly (1 point each)	1-2
Maximum score		9

INR = international normalized ratio

2.3.5.3 Warfarin and non-vitamin K antagonist oral anticoagulants (NOACs)

For a long time, warfarin was the first-line treatment for preventing stroke in patients with atrial fibrillation [135]. However, initiation and management of warfarin therapy is often difficult since warfarin has a narrow therapeutic window and is susceptible to many drug-drug interactions and drug-food interactions. Frequent monitoring and individual dose adjustments are required to maintain the target INR, which is crucial for the safety and efficacy of warfarin therapy [144]. During the last decade, NOACs have been introduced as a safer alternative to vitamin K antagonists like warfarin. NOACs represent two new classes of anticoagulant drugs; oral direct thrombin inhibitors, such as dabigatran, and oral factor Xa inhibitors, such as rivaroxaban, apixaban and edoxaban.

NOACs have similar efficacy to warfarin for stroke prevention, and lower risks of major bleeding and intracranial hemorrhagic event [145]. However, NOACs are associated with an increased risk of gastrointestinal bleedings [145], and dabigatran may increase the risk of intracranial bleeding in elderly patients and patients with renal impairment [134]. Data on long-term safety are limited, but most of the existing data indicates that NOACs are safer compared to warfarin [134, 146]. In a Swedish study comparing prevalent treatment with warfarin or NOAC [147], the rates of ischemic stroke were comparable and the rate of severe bleeding was lower with NOAC. The efficacy and safety of NOACs have been shown to be consistent in both sexes [145, 148], however women were underrepresented in the randomized controlled trials (RCTs) [145].

Warfarin has individualized dosing and many patients require alternating doses. The risk of bleeding is highest during the first three months of warfarin treatment because the INR is still labile, and to prevent bleeding episodes the INR should be frequently monitored during this period. Another risk factor for bleeding is the intensity of anticoagulation. A high INR increases the risk of bleeding, whereas a low INR means that blood clots will not be prevented and increases the risk of thrombosis. Also, several patient characteristics can increase the bleeding risk, including older age, female sex, diabetes, hypertension, previous stroke/TIA, renal failure, non-compliance, lack of knowledge about atrial fibrillation and stroke risk, and use of certain drugs [134].

OACs, and especially warfarin, are highly interactive with other drugs. NOACs have fewer clinically significant drug-drug interactions [149]. Concomitant use of anticoagulants and for example antidepressants, antibiotics, proton pump inhibitors, influenza vaccine or alcohol can increase the risk of bleeding [134]. It is well established that combination with nonsteroidal anti-inflammatory drugs (NSAIDs) increases the bleeding risk, particularly upper gastrointestinal bleeding, and the combination of warfarin and single or dual antiplatelet therapy cause a significantly increased risk of major bleeding. Concomitant use should be routinely assessed. New evidence about drug interactions is added all the time, especially for the NOACs which are relatively new [146]. In addition, various dietary supplements, herbs and food may also interact with warfarin [150].

The prognosis of patients with bleeding following OAC use depends on age, comorbidity, and level of INR. Deaths are not uncommon in patients with intracranial bleedings. In minor bleedings from for instance mucous membranes and hematuria, recovery is common with few complications. However, severe bleeding can cause extensive gastrointestinal or intracranial hemorrhage [134].

2.3.5.4 Underuse of OACs and sex differences in use

A review from 2010 [151] demonstrated underuse of OACs, and mostly in high-risk atrial fibrillation patients. A review from 2015 [152] described a remaining suboptimal use of OACs in patients with atrial fibrillation despite the availability of NOACs, and underuse was apparent especially in patients with a high risk of stroke. Lower probability of initiating treatment with OACs has also been seen in elderly (age ≥ 85 years), patients with co-existing dementia, and in women [153]. Underuse of OACs is especially high in Asian countries [154-156], which also have a particularly high use of aspirin in atrial fibrillation treatment as it is considered a safer alternative to warfarin [155-157].

2.3.6 Antiepileptic drug use in men and women

Antiepileptic drugs (AEDs), also commonly known as anticonvulsants or as antiseizure drugs, are a diverse group of substances used in the treatment of epileptic seizures. AEDs are also widely used in other conditions, for example neuropathic pain conditions and fibromyalgia [158], and psychiatric conditions such as bipolar disorder, social phobia, post-traumatic stress disorder, panic disorder, and opiate withdrawal [159]. AEDs are also used as migraine prophylaxis [160].

Several new AEDs have been introduced in recent decades, and at the same time several of the older substances continue to be used [161]. The different drugs are referred to as either first-, second- or third-generation AEDs (Table 3). Many of the newer AEDs have demonstrated equal efficacy to older AEDs and at least equal or better tolerability having a more favorable pharmacokinetic profile and low risk of drug-drug interactions [162].

Table 3. Antiepileptic drugs approved in Sweden 2020. The substances are sorted by first approval year with the name of the original preparation in brackets.

First generation AEDs	phenobarbital (Fenemal), phenytoin (Epanutin), ethosuximide (Suxinutin), carbamazepine (Tegretol), valproic acid (Absenor), clonazepam (Iktorivil)
Second-generation AEDs	vigabatrin (Sabrilex), felbamate (Taloxa), gabapentin (Neurontin), lamotrigine Lamictal), topiramate (Topimax), oxcarbazepine (Trileptal), levetiracetam (Keppra), pregabalin (Lyrica), zonisamide (Zonegran), stiripentol (Diacomit), rufinamide (Inovelon)
Third-generation AEDs	lacosamide (Vimpat), eslicarbazepine (Zebinix), perampanel (Fycompa), brivaracetam (Briviact), cannabidiol (Epidyolex)

Epilepsy treatment starts with AED monotherapy and choice of AED is mainly based on type of seizures, epilepsy syndrome and etiology. Comorbidity, age, sex and other medications are also of great importance and treatment should be tailored to the individual's life situation [163].

Epilepsy during pregnancy raises special concerns. Seizures are associated with risks both to the fetus and to the pregnant woman, and for most women it is best to continue treatment during pregnancy. At the same time, antiepileptic medications may have adverse fetal effects that must be considered when using AEDs in pregnant women as well as in women of childbearing potential [164]. Valproic acid is a known human teratogen and should not be used in pregnant women, in women of childbearing potential or in girls unless other treatment options are ineffective or not tolerated [165]. Valproic acid is associated with the highest risk of major congenital malformation, and phenobarbital and topiramate are associated with intermediate risks to specific organs. The effects of valproic acid are dose-dependent, and the same probably applies to other AEDs [164]. Furthermore, during pregnancy the pharmacokinetics of AEDs may change significantly. Clinically relevant declines in serum concentrations are seen with lamotrigine, levetiracetam and oxcarbazepine in particular, but also with phenobarbital, phenytoin, topiramate, and zonisamide [164].

AED treatment, and especially use of carbamazepine, phenytoin, phenobarbital, and valproic acid, can affect the levels of different sex hormones in both men and women. This may lead to endocrine side effects such as fertility difficulties, sexual dysfunction, menstrual disturbance, or osteoporosis. Also, appearance changes, such as weight gain, hair loss, and acne may occur [166].

Psychiatric comorbidities, particularly depression, are common in epilepsy [159, 167], and since some AEDs, for example lamotrigine [159, 168], also have effects in psychiatric conditions, treatment decisions can be made that benefit multiple conditions. Likewise, some AEDs, such as levetiracetam and topiramate, should be avoided in depressed patients since they can induce mood disorders [168]. Furthermore, when other psychotropic drugs are used concomitantly with AEDs, consideration of drug interactions is important and complex [159].

The majority of AEDs have great interaction potential. Most clinically important interactions result from induction or inhibition of drug metabolism. Carbamazepine, phenobarbital, and phenytoin are strong inducers of several CYP enzymes (CYP1A2, CYP2C9, CYP2C19 and

CYP3A4), glucuronyl transferases enzymes and epoxide hydrolase. Through these mechanisms they can reduce the efficacy of concurrently administered AEDs (i.e. valproic acid, lamotrigine, and tiagabine) as well as other medications such as OACs, calcium antagonists and steroids. Also, other drugs can influence the efficacy of AEDs through induced or inhibited metabolism. For example, the serum concentration of lamotrigine is decreased by estrogen-containing contraceptives [169].

2.3.6.1 Post-stroke epilepsy

The definitions and classifications of seizures and epilepsy have changed over the years. The definition of an epileptic seizure (which has been updated in 2005 and maintained in 2014) is "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" [170]. Earlier, epilepsy was defined as the presence of at least two unprovoked seizures. Though, in some clinical circumstances, as after a remote brain injury such as a central nervous system infection, stroke or trauma, patients can present with a single unprovoked seizure. Now one unprovoked seizure and a high risk for recurrence of further seizures are sufficient to meet the criteria for diagnosis of epilepsy [170].

After a stroke, two types of seizures can be distinguished: early seizures and late seizures. According to the International League Against Epilepsy (ILAE), seizures occurring within 7 days after stroke are classified as early seizures and those occurring beyond 7 days as late seizures [171]. However, different definitions are used [172]. The occurrence of a late seizure is required for the diagnosis of post-stroke epilepsy (PSE) [173].

Cerebrovascular disease and stroke are important risk factors for the development of epilepsy. The risk of epilepsy increases substantially (up to 20-fold) in the first year after a stroke [174]. The pathogenesis of PSE is not completely understood, but ischemic stroke is definitely one of the most common reasons for epilepsy in adults [175]. In cases where a cause of epilepsy can be determined, stroke accounts for up to half of all cases [174]. Since management of stroke patients has improved over the years and more patients survive, the prevalence of stroke-related seizures is increasing. The long-term cumulative risk of PSE after a stroke have been reported to vary between 2 and 15 percent [176].

The existence of post-stroke epilepsy is substantial, and several new studies point out the need of determining risk factors as well as optimal treatment strategies [177, 178]. Overall, the general principles of management of epilepsy are applied to the management of PSE [173]. Most individuals with PSE respond to AEDs, although up to a quarter could have drug-resistant epilepsy [179]. Currently, there are no evidence-based recommendations for the management of PSE [178, 180, 181].

3 AIMS

The overall aim of this thesis was to study sex- and gender differences in drug utilization in the Swedish population using observational data from different registers combined with qualitative data trying to identify prescribers' perceptions of sex and gender aspects in medical treatment.

The thesis includes five studies with the following aims:

Study I To describe and analyze differences in the prevalence and incidence between men and women of drugs dispensed to the Swedish population.

Study II To explore if sex differences are found in spontaneously reported adverse events for clopidogrel, low-dose aspirin and warfarin treatment in routine care.

Study III To explore general practitioners' perceptions of sex and gender aspects in medical treatment.

Study IV To examine sex differences in thromboprophylaxis in patients with atrial fibrillation before and after the introduction of non-vitamin K oral anticoagulants.

Study V To describe the use and persistence of antiepileptic drugs when initiating treatment in men and women with post-stroke epilepsy.

4 METHODS AND METHODOLOGICAL CONSIDERATIONS

This thesis includes five studies with various designs, study populations and data sources. An overview of the materials and methods used in the studies is presented in Table 4.

Table 4. Overview of the studies included in this thesis.

	Study I	**Study II**	**Study III**	**Study IV**	**Study V**
Setting	Sweden	Sweden	Urban and rural areas in Sweden	Stockholm region	Stockholm region
Design	Cross-sectional	Cross-sectional	Qualitative	Cross-sectional	Cross-sectional
Data source(s)	Swedish Prescribed Drug Register (SPDR)	Swedish Drug Information System (SWEDIS), Swedish Prescribed Drug Register (SPDR)	Focus group discussions	Region Stockholm administrative health data register (VAL)	Region Stockholm administrative health data register (VAL)
Study population	All individuals in Sweden	Bleeding event reports and individuals with ≥1 purchased prescription of warfarin, clopidogrel and/or low-dose aspirin	Physicians at five health centres in Sweden	All residents in the Stockholm region with a diagnosis of atrial fibrillation	All residents in the Stockholm region with post-stroke epilepsy and antiepileptic drug treatment
Study period	2010	1999-2010 and 1 July 2005 - 31 December 2010	2012-2013	2007-2011 and 2011-2015	2012-2019
Analyses	Descriptive statistics	Descriptive statistics	Thematic analysis	Descriptive statistics	Descriptive statistics, logistic regression analysis

4.1 SETTINGS

All studies in this thesis were conducted in Sweden where the health system is publicly funded, primarily through taxes, and accessible to all residents. Patients are covered by a high-cost protection and usually only pay a small patient fee for outpatient and inpatient care [182]. The maximum fee for outpatient care during a 12-month period is 1 150 SEK in 2021. Children and adolescents (up to 18 years of age in some regions and up to 20 years of age in other regions) as well as individuals aged 85 years or older are exempt from patient fees for outpatient care [183].

The majority of outpatient visits take place in primary care and for most medical problems the first contact with healthcare is with a general practitioner (GP) at a health centre. However, primary care has a limited gatekeeping function as patients may seek specialist services for first-contact care. The health centres are often multidisciplinary with physicians and nurses, and sometimes also physiotherapists, psychologists, midwives and gynecologists [182].

Most prescription drugs are covered by the pharmaceutical benefit scheme and are subsidized to patients. The high-cost protection for prescription drugs means incrementally reduces patient costs and a maximum fee of 2 350 SEK during a 12-month period. From January 1, 2016, all prescription drugs included in the benefits scheme is free of charge for children up to 18 years of age [184]. A prescription is valid up to 1 year from the date it was issued and may be filled with a maximum of a three-month supply at each refill.

In Sweden, healthcare professionals and pharmaceutical companies should report all suspected ADRs to the Swedish MPA, and it is also possible for patients and consumers to report suspected ADRs. This can be done via electronic form, paper form or in some cases directly from the medical record system [114].

4.2 STUDY DESIGNS

Most of the studies in this thesis are of a cross-sectional design (Table 4).

A cross-sectional study is a type of observational study that can be seen as a "snapshot" of the study population status, collecting all information, including information about exposure and outcome variables, at a specific point in time [185]. It is the most relevant study design when assessing prevalence and it is commonly used to present drug utilization patterns and can also be used in studies investigating drug use in relation to specific diagnoses or conditions [63]. Cross-sectional studies can be either descriptive or analytical. Generally, since there is no time dimension in cross-sectional studies and no information on whether the exposure precedes or follows the studied outcome, the study design should not be used to draw cause-and-effect conclusions [186].

A cohort study is another type of observational study. It has an analytical study design investigating causal relationships between a risk factor and an outcome. In a cohort study, individuals who are exposed or unexposed (or less exposed) to a presumed risk factor are followed over a period of time and the incidence of a specific outcome is measured and compared between groups [185]. The cohort study design can be used in persistence studies to assess discontinuation rates and factors associated with discontinuation [63]. In these studies, discontinuation is considered as the "outcome" and the factors associated with discontinuation, e.g. patient sex and age, comorbidities, socioeconomic characteristics of the patient, and concomitant drugs, are considered as "exposure". In many cases these patient characteristics are adjusted for with a multivariate analysis, to identify which characteristics that are associated with poor persistence.

In study V, we followed individuals exposed to different AEDs over time and measured the occurrence of discontinuation of treatment and identified factors associated with discontinuation. Thus, the study has elements of a cohort study. However, since the main objective of the study was descriptive, and since we did not assess whether there were any changes in comorbidities during follow up of drug treatment, we chose to label it as a cross-sectional study. It should be noted, though, that the study has a more analytical approach than

many cross-sectional studies that have no opportunity to distinguish between patient characteristics occurring before or after the drug therapy was initiated.

An ecologic study is a special type of observational study that investigates associations between exposure and outcome at the population or group level, rather than individual level. It is relatively easy to conduct but since there is no individual linkage between the exposure data and outcome data, any associations found cannot directly be interpreted as associations at individual level. Hypotheses generated from ecologic studies must be tested in more advanced analytical studies [63]. Study II can be defined as an ecologic study because there is no individual linkage between the different datasets on exposure (drug dispensations) and outcome (ADRs). However, it should be emphasized that all adverse events were reported from Sweden, thus constituting a sample from the source population including all people being dispensed these medicines.

In study III, where we wanted to explore physicians' perceptions of sex and gender aspects regarding medical treatment, we used a qualitative research approach since this methodology is ideally suited for studying experiences and perceptions. Also, qualitative methodology is advantageous when material and basic understanding of a topic is missing and when several outcomes and angles are possible [187].

4.3 DATA SOURCES

Four studies in this thesis were register-based. In Sweden, we have great registers and thus great opportunities for such studies. Also, the use of unique personal identification numbers enables individual-level linkage between different registries, and follow-up over time [188].

Although Swedish registers provide excellent opportunities for epidemiological research, such studies may only answer some of all questions related to differences between men and women in drug utilization, and especially the gender aspects may be difficult to study with register data. Qualitative research methods may be used to provide a deeper understanding of the subjective aspects of prescribing, dispensing and use of drugs, and also the interaction between healthcare providers and patients. One study in this thesis was qualitative.

4.3.1 Registry data

In healthcare as well as in other societal bodies, large amounts of data are routinely collected for administrative purposes. These data, as well as medical records and other data already collected by someone else with no specific research purpose, that can be accessed by researchers are referred to as secondary data [189, 190]. Secondary data can offer large national or regional datasets containing many different variables, Also, in many datasets the same data has been collected for a long time.

4.3.1.1 Drug utilization data

In drug utilization studies, a common approach is to use dispensing data as the main data source. Data on dispensed drugs are registered at pharmacies for both administrative and

clinical reasons. Normally, all dispensations are registered, regardless of reimbursement status [191]. Among available registry data, data on dispensed drugs will provide the most accurate picture of the actual drug use in the population although it does not reveal whether the patient took the medicine or not. Dispensing data can be used as a proxy for both the prescriber and the patient perspective of drug use. Another possibility is to use prescription data, however these data are more difficult to access [192]. Which data is best mainly depends on the research question. Prescription data may better reflect the physicians' intentions while dispensing data are closer to the truth about what drugs individuals are taking.

After a drug has been prescribed, dispensation at a pharmacy is expected. However, not all prescriptions are being dispensed, i.e. primary nonadherence. When using pharmacy dispensing data, one needs to reflect on what conclusions can be drawn from it. If there are for instance sex differences in drug use, are they due to drugs being prescribed differently to men and women or it is because men and women purchase drugs to different extents? It should also be noted that the nature of dispensing data is heavily dependent on the reimbursement system and comparisons between countries may therefore be difficult.

When using dispensing data in registry studies, it is commonly assumed that patients only take the drugs registered in the database. This may lead to an underestimation of drug use. However, at present it is not possible to get an overall picture of a patient´s drug use as medicines given in inpatient care are not included in the national drug register. Also, some drugs can be purchased over-the-counter (OTC), abroad, or even illegal. It also happens that individuals share medicines, such as siblings share asthma medication [107].

4.3.1.2 The Swedish Prescribed Drug Register (SPDR)

SPDR was created in 1999 to be used for monitoring the use of medicines, among other things. It is held by the National Board of Health and Welfare and contains all prescribed drugs dispensed at pharmacies, dispensed medical devices, and medical consumables within the pharmaceutical benefits scheme, for example foods for nutritional use by children.

SPDR includes detailed information about the dispensed product (for example drug name, strength, quantity, date of prescription, date of expedition and cost), the prescriber (work title, education code and specialist education code, type of care according to the work-place), and the patient (age, sex and place of residence) [193]. Since July 2005, also the patient's personal identity number is registered. Hence, drug dispensation can be analyzed at an individual level, including number of drugs, dispensation intervals, concomitant treatment and possible drug-drug interactions [194]. Dispensed drugs are coded according to the ATC classification system [195].

The register does not include drugs administered at hospitals or nursing homes, vaccines and OTC drugs. For those pharmacological groups and drugs exclusively prescribed, the register holds the whole truth. However, for pharmacological groups and drugs mainly used in inpatient care or sold OTC, the registry does not provide the full picture.

A major shortcoming of the data in SPDR is that there is no structured information on purpose of the prescription; on what indication a drug is prescribed. Indication, when specified, is written in a free text field and is thus difficult to handle as a data variable. To get more information and to be able to draw conclusions about why a particular drug is used, individual drug dispensing data can be linked to other population-based registers and clinical data from medical records [196].

4.3.1.3 Diagnosis data

For each visit to outpatient care and after hospital discharge, one or more diagnoses are registered. One primary diagnosis is mandatory and should correspond to the disease or symptom that was the main reason for the care contact. Also, one or more conditions other than the primary diagnosis that have been assessed, investigated or treated during the care contact/period can be registered as secondary diagnoses.

4.3.1.1 VAL

The administrative health data register of the Stockholm healthcare region (called VAL) contains pseudonymized data on all individuals in the region of Stockholm regarding age, sex, diagnoses, procedures, hospitalizations and other healthcare consultations, dispensed prescription drugs, migrations and death. Over the past decade, it has been used as data source in a number of scientific studies [70, 197-203].

VAL contains all hospitalizations and consultations in secondary care from 1997 and all consultations in primary care from 2003. Data on diagnoses in inpatient- and outpatient care is the same as in the National Patient Register [204], and additionally VAL also includes diagnoses in primary care. Diagnoses are coded according to the Swedish international classification of diseases (ICD) system. The 10th revision of the classification system (ICD-10) has been used since 1997. Individual-level pharmacy dispensing data have been included in VAL since July 2010 and corresponds to the data in SPDR, except for the free text field with dosage, use and purpose, that is missing in VAL.

4.3.1.2 Data on adverse drug reactions

Unlike the data on dispensed drugs, data on ADRs is based on manual reporting. Underreporting is a known problem in the spontaneous reporting of ADRs [205, 206], also for serious and fatal reactions [207]. Thus, the data only represent a proportion of the incidence and not the true incidence rate.

A limitation with data in VigiBase and in data from other pharmacovigilance datasets, are that data comes from a variety of sources, both regulated and voluntary, and the reporters can be healthcare professionals, pharmaceutical companies and patients. Thus, the probability that the suspected ADR is caused by a drug differs between the cases. It cannot be proven that an ADR was caused by a specific drug, rather than for example underlying illness or other concomitant drug use [115].

4.3.1.3 The Swedish Drug Information System (SWEDIS)

In Sweden, reports of suspected ADRs should be sent to the MPA. At the time when study II was conducted, physicians, dentists and nurses were supposed to report serious ADRs, ADRs that were not mentioned in the summary of product characteristics (SPC), ADRs related to new drugs (≤2 years after the authorization) except ADRs labeled as common in the SPC, and ADRs that appeared to increase in incidence. The spontaneous ADR reports were stored in the national database SWEDIS (Swedish Drug Information System), which was established in 1965 [208]. Reported ADRs were assessed whether they were serious or non-serious, and regarding causality.

Serious ADRs are defined by WHO as ADRs that cause death or are life-threatening, result in hospital admission or prolonged hospitalization, cause persistent or significant disability or incapacity, or is a congenital anomaly or defect [209]. Basically, the same criteria applied at the time of the study, except for the congenital causes. The causality between the suspected drug(s) and the adverse reaction(s) was assessed using the following WHO definitions: certain, probable, possible, unlikely, unclassified, or unclassifiable [210].

SWEDIS contain information about the patient, the administered drug, diagnoses of suspected ADRs, causality assessment, and outcome. Also, type of report and source are registered. In SWEDIS, all reports were provided by healthcare professionals. Consumer reporting started 2008 in Sweden, but these reports were saved in another database [208].

4.3.2 Qualitative data

Although registers contain large amounts of structured data, including many variables, there may still be various variables missing depending on the research question, and sometimes the answers you seek cannot be found in numbers. The common feature of qualitative studies is that they do not primarily attempt to provide quantified answers to research questions. Instead, the goal is to gain an increased understanding of a specific topic or phenomena [211].

There are several different data collection methods used in qualitative research, including questionnaires with open answer, interviews, focus group discussions (FGDs), and observations. In study III, we used FGDs as data collection method. The main reason for that was that FGDs works well to find out the participants' (called informants) knowledge and opinions regarding a specific topic [187, 212], which agrees well with the purpose of the study. Moreover, FGDs are particularly useful when the knowledge about the topic is limited or when discussing an unreflected issue [212], as sex and gender aspects in drug treatment turned out to be. Also, FGDs is a relatively fast method but still provides a lot of data [187, 212].

4.3.2.1 Focus group discussions

FGDs are a form of interviews in groups with a moderator that use relatively open questions to conduct the discussion forward [212, 213]. In FGDs, the interaction is important. The informants will interact and help each other to explore and concretize ideas and to find

common experiences and variations, that may not had been expressed in a separate context [212, 213]. In contrast to a series of individual interviews, participants in a focus group will hear each other's responses and can give additional comments and develop and supplement their answers [187]. Also, when informants share their experiences and thoughts, it contributes to the development of the subject and gives the researchers the depth and context they need to deepen their understanding [214].

Data collection

In the conduct of the FGDs in study III, the moderator led the informants in the discussion and ensured that they discussed the questions with each other and not just answered the moderator, and that all informants had the opportunity to speak. In addition to the moderator, an observer was also present at the FGDs taking notes about the informants' behavior and the interaction in the groups. The observer also supported the moderator with catching questions in the discussions [212]. Since there were two researchers present during the FGDs we had the opportunity to have a field debrief, a short conversation after each focus group, sharing spontaneous impressions of the discussion and what we perceived as the most important issues and arguments [214].

We used a semi-structured interview guide. Semi-structured interviews have a certain degree of structure, allowing for changes in the order of the questions, reformulation of questions and probing to gain a better understanding and clarification [187]. The interview guide was developed and pre-tested to guarantee that no integrity questions was used.

Since two of the researchers were moderator and observer respectively, having preunderstandings and preconceptions about the research questions, and the fact that the topic sex and gender equality might be seen as controversial among some people, it was important trying not to let this affect the interaction within the FGDs. Therefore, the questions were openly formulated and without valuation. The informants' answers were never questioned, instead the moderator asked "what"- and "how"-questions and the informants were asked to give concrete examples from their own practice [187].

Sample size

Saturation is commonly used for determining sample size in qualitative studies. However, saturation is a complex and contested concept [215]. In general, it means that no additional data are being found, but saturation can have different meanings depending on study design and the underlying approach to analysis. It can be used to determine when to stop data collection or when to stop analysis of materials. Saturation was first defined in the context of grounded theory, where theoretical saturation relates to the development of theoretical categories and the point when sampling more data is not considered to lead to further development. The process of saturation can also be considered as mainly linked to the data collection, often referred to as data saturation. After a while, new data tends to be redundant

from data already collected, and data saturation is being reached when the researcher hears the same things repeatedly. Then it is time to stop data collection and start analyzing [215].

At least three focus groups are generally considered needed to achieve saturation, meaning that no new information will be added if additional focus group discussions are carried out [212]. Therefore, initially three FGDs were performed where the third FGD did not give any additional information regarding the research questions. These FGDs were carried out at health centres in an urban area of Sweden. To see if there were other perspectives and ideas among physicians in other, non-urban, areas of Sweden, two more FGDs were performed. Since no new information was obtained, we presume that saturation was reached.

Sample selection and setting

In qualitative research, unlike quantitative research, the purpose is not to have a random or representative sample from a population, but rather to identify information-rich cases, i.e. people who have the best possible knowledge, experience or overview with respect to the study's research topic [211]. This is referred to as a strategic or purposeful sample selection [187]. Since a large part of healthcare and medical treatment is carried out in primary care, we chose to include physicians working at health centres. They meet patients with a large variety of symptoms and diagnoses [201].

The focus groups consisted of physicians from the same health centre. This was mainly for practical reasons, but also there are several advantages with a pre-existing group such as shared experiences and a more open climate where they dare to question each other's opinions [212]. Nevertheless, there can be a risk that the informants adapt their answers based on what they think the moderator wants to hear, or because they do not want to stand out. Also, it is important to be aware of that hierarchy within a group may affect the data [187, 212]. The informants may choose to agree with a certain person or with the majority, even though they have a different opinion, to avoid conflicts within the group or because they do not have the courage to express their opinion.

In one of the FGDs, we felt that there was a hierarchy. It was mainly one of the informants who led the discussion while the others confirmed her opinions. The moderator tried to respond to this with various strategies, such as asking for the others opinions [212]. Although the others in the group did not speak as much, they expressed their own opinions and thoughts. However, in the other FGDs we experienced that the informants felt comfortable and did not seem to hesitate to express conflicting opinions. The FGDs were carried out at the health centre or another place selected by the group where they felt comfortable. During the discussions, the participants were offered lunch or "fika" (coffee and cake), so that their allocated time could be used as efficiently as possible. No other compensation was paid.

4.4 STUDY POPULATIONS

In study I and II, as well as in study IV and V, one purchase of the studied drug/substance was enough for an individual to be regarded as treated. This is a simple and common way to

calculate the period prevalence of drug use [216]. However, the use will be overestimated since all patients do not take medicines regularly. An alternative for chronic medications is to require two or more dispensations over a period to be counted as use.

In study IV, individuals in the region of Stockholm with a diagnosis of atrial fibrillation at least once in any level of healthcare during a 5-year period were included in the study population. Atrial fibrillation is clearly defined by an ICD-10 code, which was used for identification in VAL. It is a chronic disease and since chronic disease diagnoses may not be registered at every healthcare visit, we used a 5-year period for diagnosis detection. That is a time window previously shown to identify the majority of all patients with chronic disease [217].

In study V, we wanted to study individuals with PSE. However, PSE has no specific ICD-10 code and there is no uniform definition. Our inclusion criteria included a seizure and epilepsy-related diagnosis (ICD-10 code G40, G41, R25 or R56) and one AED (ATC-code beginning with N03). Individuals in the region of Stockholm with a stroke diagnosis (ICD-10 I60, I61 or I63) as primary diagnosis in inpatient care, a first purchase of any AED up to two years after the stroke diagnosis, and an epilepsy-related diagnosis recorded in in- or outpatient care after the stroke and before the first AED purchase constituted the study population.

The definition of PSE varies between studies. In the Swedish study by Larsson et al. [218] PSE was defined as "patients with an epilepsy-related diagnosis (ICD-10 G40, G41 or R56.8) registered at least seven days after the date of the index stroke", and patients with a prior seizure-related diagnosis were excluded. We used a very similar definition. A Swedish study by Redfors et al. [219] of PSE after ischemic stroke also included patients with a stroke diagnosis and an epilepsy-related diagnosis. However, they also confirmed all events by reviewing medical records. Besides, they checked the indications for the prescribed and dispensed AEDs in the medical records.

A Taiwanese study on late-onset post-stroke epilepsy [220] identified new incidences of stroke as hospitalized patients who had a primary diagnosis of stroke, with no stroke diagnosis at least three years prior to the index stroke. Of these, patients who presented with seizures that occurred more than 14 days after stroke were included. In the study by Redfors et al. [219] one unprovoked seizure occurring more than 7 days after stroke was defined as PSE We also applied a limit of more than 7 days to exclude acute symptomatic seizures. In a systematic review by Zhang et al. [172] including studies on stroke and seizure outcomes, most studies on late seizures defined it as seizure onset more than 7 days after stroke, some used a 14-day-criteria and a few used a 30-day-criteria. A meta-analysis on incidence of PSE [221] compared definitions in published studies and concluded that 14 days is the ideal cut-off time point. The incidence density was about three times higher when using the definition of PSE as seizure occurring 7 days after stroke, than as seizure occurring 14 days after stroke.

According to a review [222], the majority of PSE occur within 6 to 12 months after the stroke. A Swedish study by Hassani et al. [223] showed that most events occurred during the

first year, and median time to PSE from stroke-onset was 237 days (IQR 33-688). The Swedish study by Redfors et al. [219] showed that most patients developed PSE the first year after the index stroke, and the median time from index stroke to PSE was 9.8 months (IQR 5.5–20.6). In our study, we chose to include patients who purchased an AED within two years after their stroke diagnosis. Notably, the median time from stroke diagnosis to first purchase of AED was 211 days (IQR 75-442) and 184 days (IQR 81-364) for men and women, respectively.

Because the VAL-database only contains data on healthcare consumption for residents in Stockholm, depending on what question to be studied, it may be important to have historical data relative to the studied event(s). In study IV, data on selected comorbidities and procedures were collected from the same 5-year-period as the atrial fibrillation diagnosis. Individuals who had moved to Stockholm during the study period or were not residents in Stockholm the last day of the study period were excluded, so that all individuals would have the same amount of available history in the database. In study V, we excluded individuals who had moved to Stockholm less than two years before their index stroke. In this way, we got a period of two years to collect data on comorbidities and procedures. The reason why we chose two years here instead of five years was to increase the number of eligible individuals to the study population, as these were significantly fewer than in study IV.

In study IV, we collected data for diagnoses and drugs during a 5-year period without establishing a chronological order between diagnosis and drug treatment. That is, we have not ensured that the patients were diagnosed with atrial fibrillation before they received their oral anticoagulant. However, these drugs have limited use and it is highly likely that in patients diagnosed with atrial fibrillation and who purchased a prescribed oral anticoagulant, the anticoagulant is used for the treatment of atrial fibrillation. On the contrary, in study V concerning antiepileptics that can be used for a variety of indications, it was essential to establish the order of diagnosis before treatment. Therefore, we set requirements in the inclusion criteria for the order in which events would occur. This made the procedure of inclusion of individuals more complicated.

4.5 MEASUREMENTS AND ANALYSIS METHODS

Baseline characteristics of the study populations were presented stratified by sex using descriptive statistics. We did not analyze whether there were any significant sex differences in baseline characteristics, but perhaps we should have done so.

In total, the quantitative studies have included calculation of proportions, prevalence, incidence and persistence. Sex differences have been analyzed by comparing proportions and calculating risk ratios (RR) of women/men with 95% confidence intervals (CIs). Also, logistic regression analysis and multinomial logistic regression analysis have been used.

4.5.1 Prevalence and incidence

Prevalence and incidence are two common measures in epidemiological studies, and two different ways of measuring occurrence. Prevalence refers to the proportion of cases in the population at a given time or during a given time period, often 1-year, whereas incidence refers to proportion or rate of new cases, i.e. individuals who develop a certain condition during a given time period [224].

In study I, we analyzed differences between men and women in the prevalence and incidence of dispensed drugs in Sweden 2010. Period prevalence was defined as the proportion of the population that purchased at least one prescribed drug in 2010 and was measured by the number of individuals (patients) per 1000 inhabitants (PAT/TIN). The period prevalence represents an indeterminable mix of prevalent and incident drug users. Some individuals are already using one or more medications in the beginning and some individuals become new users during the studied period.

Incidence, defined as the proportion of the population that purchased at least one prescribed drug in 2010 after a run-in period with no drug purchased, was measured by the number of patients per 1000 person-years (PAT/1000 PYs). As incidence refers to the occurrence of new cases, there is a need of a run-in period to establish an individual as new, during which an individual is not allowed to have purchased prescriptions for the drug in question to be classified as a new user. The appropriate length of the run-in period depends on the therapeutic area [216]. We used a 1-year run-in period, which corresponds to the validity of a prescription.

In study V, incident use of AED was a criterion to be included in the study population. Incident use was defined as having a first purchase of an AED after not having purchased any AED up to one year before stroke diagnosis. For individuals in the study population, the chronological order would be a stroke diagnosis first, followed by an epilepsy-related diagnosis and then a purchase of any AED. The stroke diagnosis was the beginning and thus we checked for occurrence of comorbidities and other drug treatment in relation to the stroke diagnosis. Since the time between stroke diagnosis and first AED purchase varied between individuals, also the time interval defining incidence, the run-in period, varied. Usually when studying a drug, the run-in period is fixed, for example 1-year. The alternative would have been to check for comorbidities and drug treatment in relation to the first AED purchase, and up to one year before AED. However, that had also led to differences in time periods.

4.5.2 Bleeding event reports adjusted for drug use

When interpreting ADR reports it is important to consider prescribing practice since differences in reporting rates to a significant extent can be explained by differences in prescribing [225]. However, the choice of denominator can be difficult.

One denominator that has been used are number of dispensed defined daily doses (DDDs), but it is inappropriate, particularly in children, since prescribed DDDs varies largely between

ages [226]. Another denominator that has been used are number of treated individuals [227]. It is clearer and enables comparisons between populations. However, available data represents drug purchase and not actual drug intake, which may overestimate the number of treated individuals and consequently underestimate the rates of ADR reports per 1000 treated individual. Furthermore, exposure time is not considered and an individual who has purchased a drug once is equated with an individual who has used a drug for several years. Furthermore, individual-level drug utilization data are in most countries only available for prescription drugs and not for those medicines used in the hospital setting or sold as OTC.

In study II, we analyzed the total number of bleeding event report for clopidogrel, low-dose aspirin and warfarin and adjusted for drug use in the population of each drug during the same time period. Two different time periods were studied, 1999-2010 and 1 July 2005 to 31 December 2010. The latter period was included because then there was individual-level drug dispensing data available. Drug use were measured through the number of prescriptions and the number of DDDs for the time period 1999-2010, and for the time period 2005-2010 also through the number of individuals with at least one purchased prescription, reflecting the number of exposed individuals. We believe that using number of individuals as denominator is more accurate since it can be compared to the safety population in a RCT.

4.5.3 Persistence

Persistence, time from treatment initiation until discontinuation, is often measured in drug utilization research [228]. Persistence is an integrated measure of tolerability and efficacy, not possible to discriminate between the two, and discontinuation of drug treatment may be due to low efficacy and/or adverse effects. However, other factors may also be important such as patient beliefs and motivation to take the medicine. Persistence can be measured in different ways [228, 229], and this, as well as dissimilarities in the underlying study populations and the availability of comparable data, makes it difficult to compare results across persistence studies.

In study V, we wanted to compare persistence of different AEDs. Due to large variations in the dosage of certain AEDs it was not possible to assume approximate daily doses, which is needed to calculate the number of days supplied by each drug purchase. Instead, we used the refill-sequence model, in which time from the first purchase to the point where an unacceptable gap between two refills occur is calculated [229]. A period of 120 days between two refills is commonly used and was therefore used.

Drug persistence is also known as drug survival, and the length of drug survival can be considered as a measure of treatment success. Since persistence concerns time-to-event data it should be analyzed using standard survival analysis. Kaplan-Meier curves and proportions of patients persistent at a defined time point are commonly used [87]. In study V, persistence was plotted using Kaplan-Meier curves.

4.5.3.1 Kaplan-Meier curves

Kaplan-Meier curves are used to illustrate the probability of an event over time, in this case, discontinuation of drug treatment. New users are followed until their treatment stops, that is, when an unacceptable gap between two refills occur. If a patient drops out during follow-up or if the follow-up ends before discontinuation has occurred, the true persistence value will be replaced by a censored value [230, 231]. In our study, we censored at longer hospitalization (>1 month), migration, death or at the end of follow-up.

To compare the survival between two or more groups, the log-rank test is the most popular method. It takes the whole follow-up period into account and provide a comparison of the groups' total survival experiences, which is an advantage since the differences in survival can be greater at some time points and be zero at some points. Another significant advantage with the log-rank test is that it makes no assumptions regarding the shape of the survival curves (distribution of survival time). However, the test only shows if there is a difference. To estimate the size of the difference between the groups, regression models for survival analysis should be used, such as the Cox model [232].

4.5.4 Logistic regression analysis

Regression analysis investigates the relationship between a dependent (response) variable and one or more independent variables (predictors). Basic linear regression is the simplest model, estimating the relationship between one dependent and one independent variable, both continuous, using a straight line. Many variables of interest in epidemiological research are, however, dichotomous. For example, a patient may or may not get a certain disease or medicine, or may or may not survive/die during a given time period. Logistic regression analysis is used to examine the relationship between a dichotomous dependent variable and independent variables (categorical or continuous) [233].

In study V, logistic regression analysis was used to identify factors associated with treatment discontinuation within 90 days, thus a dichotomous dependent variable (or dummy variable) with only two possible values: 0=absence of outcome, in this case continuing treatment; and 1=presence of outcome, in this case discontinuation of treatment. All baseline patient variables and year of first AED purchase were selected as independent variables. Continuous variables were split by tertiles into three categories. In univariable models, only a few variables demonstrated p-values <0.1 level, and we chose to include all variables in the final model. The $p<0.1$ level was used since it served as a criterion for a possible role as confounder, and not as a risk factor per se.

In situations where the response variable has more than two response values, i.e. a multiple response outcome, a regression model with categorical response variables is needed. Ordered logistic regression is often used when there is a natural order of the values of the response variable. If the response values are not ordered, multinomial logistic regression is used [234].

In study V, we wanted to identify factors associated with choice of AED. Thus, choice of AED was the response variable with five response values: levetiracetam, carbamazepine, lamotrigine, valproic acid, and other AED/combination. Since there is no natural order in the response values, multinomial logistic regression was used. Levetiracetam, the most common AED, was set as the reference value. The same variables as in the logistic regression analysis were selected as independent variables. Variables with a univariate $p<0.1$ were included in the final model.

Variables included in the regression models were exclusively patient information. However, it would have been interesting to also include information about the prescribing physician. Physician information such as workplace, education year and years of work experience, and also the physician's sex may have influenced the results.

4.5.5 Qualitative analysis

Unlike quantitative analysis, qualitative analysis is largely dependent on the researcher. A good analysis requires skills in analysis as well as understanding of the research topic and of the social context from where the data is collected. In the analysis of qualitative data, it is important to reflect on the impact of oneself as a researcher. What impact did I have on the informants/those I observed? What impact does my pre-understanding and experiences have on how I perceive/categorize data?

All FGDs was audio-recorded and transcribed word for word. That is the most time-consuming way to transcribe but gives the best basis for a systematic and thorough analysis. The transcripts were made by the moderator and controlled by the observer, or vice versa. It is a great advantage as a researcher to transcribe the material yourself, since the first thoughts on further analysis often comes during that process [214].

4.5.5.1 Thematic analysis

The transcripts from the FGDs were analyzed with an inductive thematic analysis without any predetermined categories [187, 213, 235]. The inductive thematic analysis provides a flexible approach where the researcher is open to the entirety of the material and explore the presence of different topics and facts, without trying to fit data into a pre-existing coding frame or any preconceived hypothesis.

Thematic analysis provides a useful research tool for sorting and analyzing qualitative material. It works well when you are not interested in creating a theory or a model explaining a phenomenon (grounded theory) or identify phenomena through how they are perceived (phenomenology) or studying the variation of ways people experience a phenomenon (phenomenography). Thematic analysis does not depend on a specific theoretical or epistemological position unlike other qualitative methods, including those mentioned above [236].

The analysis process was performed in six steps, as described in paper III [237]. The process is described linearly but was performed iteratively moving back and forth between the steps [187]. I had the main responsibility for carrying out the analysis and had regular meetings with the research group during the process, describing and discussing my way through the steps. Categories and subcategories were created and changed, material was restructured, new categories and subcategories were created, material was restructured again, subcategories were moved under a different category and so on. My co-researchers have occasionally gone back to the transcripts to verify that the categories and the condensation of the material to the summary text is correct, mainly looking for similarities and differences in the informants' statements.

5 ETHICAL CONSIDERATIONS

Study I, II, IV and V are based on register data and were approved by the Regional Ethical Review Board in Stockholm.

An advantage of register-based research is that data is already collected. This saves time and resources. However, the data is not collected with the (main) purpose of being used for research. This raises some questions for me. How aware is the population of the large amount of data that is registered in various registers, and that this data may be used in research? Do they think it is quite acceptable if their data is used in research?

Often no informed consent is required for pure register studies. This is decided by the Ethical Review Board based on the risk of violation of the personal integrity of those whose registered information is used. However, I believe that there may be a difference between what the ethical review board and what the individual considers to be an invasion of privacy. Some individuals feel offended only by being registered at all. It is my wish and hope that an overwhelming majority of the registered individuals, if asked, would allow their data to be used for research purposes.

Furthermore, it is not practically applicable or reasonable to obtain informed consent in every individual register-based epidemiological study. If any individuals should feel offended that their data has been used in a study, I hope they can still feel that the purpose of the study was important and that its benefits (for the larger group) outweigh the dissatisfaction of the individual.

In registry-based studies, to not risk offending anyone, it is important to present results in ways that no individual can be identified. With the ability to link data from several different registers, advanced mapping can be done by an individual. The more data combined and the more detailed the data, the greater risk of identification. However, this is not a problem in my studies. In study I and II, aggregated data on national level was used and it is therefore impossible to identify any one individual. Data in study IV and V was pseudonymized individual-level data with encrypted personal identification number. Theoretically, it would be possible to identify an individual based on sex, age and drug treatment and/or diagnosis in master data. However, all results are analyzed and presented on a more comprehensive level where an individual cannot be identified.

Study III did not include the processing of such personal data as is referred to in the Swedish Act concerning the Ethical Review of Research Involving Humans [238]. Nonetheless, an ethics application was sent to the Regional Ethical Review Board in Stockholm and they had no objection to the study. During the study, participants were guaranteed confidentiality on behalf of the researchers. It was fundamental that all participation was voluntary and that each participant may at any time withdraw their participation. The participants received information in several steps, both oral and written, regarding the study purpose, the process of implementation and how the results would be used. The interview guide we used was pre-tested on three people to ensure that no intrusive questions were asked. All participants gave

their written informed consent before participating in the FGDs. All material was anonymized when transcribed.

In paper III, some citations from the FGDs are included and individuals may recognize their own or their colleagues' answers. Some participants may feel uncomfortable exposing their lack of knowledge. On the other hand, no one forced anyone to say anything, and there was the possibility of not speaking. The moderator made sure to have an open mind and not be judgmental in any way. In the end of each FGD, the participants were given the opportunity to comment on the discussion and no complaints were received.

The purpose of research should be to provide important knowledge. A benefit of my studies is to gain knowledge about whether there are unjustified differences between men and women in drug utilization in Sweden. It is important to highlight any inequalities so that they can be remedied and prevented. For example, the study results can form the basis for initiatives that can improve healthcare and drug utilization in society.

6 RESULTS AND DISCUSSION

6.1 STUDY I: AN OVERVIEW OF DRUG USE IN MEN AND WOMEN IN SWEDEN

In Sweden, 59 percent of all men and 76 percent of all women purchased at least one prescribed drug in 2010. The numbers are in line with previous Swedish studies [239, 240]. Similar studies from other countries have also shown that women generally use medicines more often than men [241-243].

The pattern of drug dispensing in the Swedish population divided by age and sex (Figure 1) shows great similarities with the pattern over GP consultation rates by age and sex described in other studies [77, 79]. In general, women had more prescription drugs as well as more consultations with GPs than men between the ages of about 15 and 60 years, but not at younger and older ages.

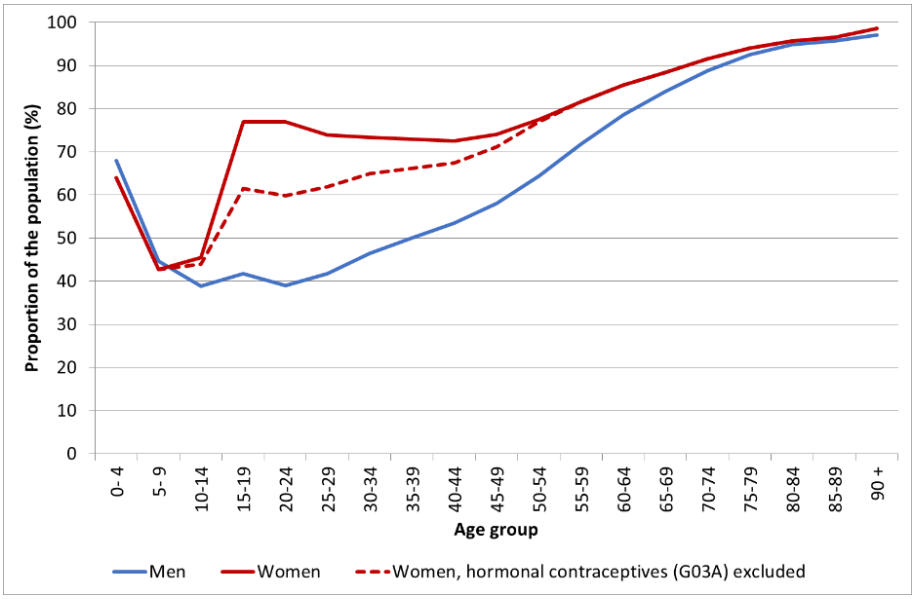

Figure 1. Proportions of the Swedish population that purchased at least one prescribed drug in 2010, by age group and sex. Modified from paper I [244] and Loikas et al. 2011 [245].

More women seeking healthcare is often explained by women's visits regarding contraception, pregnancy and childbirth. Also, higher drug utilization in women is sometimes explained by their use of contraceptives and hormone replacement therapy. Thus, it is interesting to see that when excluding such diagnoses [79] and pharmacological groups, the sex difference remains, however not as large.

A Swedish study performed in the county of Östergötland in Sweden [240] concluded that the use of anti-conception drugs and drugs used to treat some specific diseases more common in women may explain a large part of the sex difference in prescription drug use. The authors stressed the importance of considering the presence of sex-specific drugs and to exclude anti-conception drugs when analyzing differences in drug use between men and women. For this

reason, we divided our data for women into two curves in the result graph, one with total drug use and one with hormonal contraceptives excluded (Figure 1).

A large sex difference was seen for antibiotics, which were more common in women. Probably this is largely since women more often than men seek healthcare but could also be due to a higher incidence of urinary tract infection and related antibiotic prescribing in women. In a meta-analysis evaluating differences between men and women in antibiotic prescribing in primary care [246], women were more likely than men to receive a prescription for antibiotics. The largest sex differences were found for cephalosporins and macrolides, whereas antibiotics commonly used to treat urinary tract infections were almost equally common among men and women. A study from the English primary care exploring the causes of differences in antibiotic prescribing between men and women [247], concluded that the gap between the sexes in antibiotic prescribing to a large extent can be explained by consultation behavior. With some exceptions, men and women were equally likely to be prescribed antibiotics when seeking care for common conditions.

Study I contains speculations about possible reasons behind showed sex differences, mainly based on biological differences between men and women in underlying morbidity. However, some sex differences were more difficult to explain on medical grounds and may be due to gender aspects such as perceived expectations from society on men and women. It may be the patient who seeks care for a certain condition and requests treatment, or it may be the physician who prescribes a particular drug in the belief that the patient expects or want it. Furthermore, patients can choose not to dispense a prescribed drug based on perceived expectations from society.

Sex differences in some pharmacological groups are easier to speculate about than others. The wider use and the more possible indications, the more difficult to derive sex differences to differences between men and women in prevalence of disease. Other possible explanations behind the observed sex differences are disparities in incidence of side effects.

The results from study I should be seen as an overview of drug use in Sweden, and it gives an indication in which areas there may be differences between men and women worth investigating further. To be able to deeper analyze what showed sex differences may be due to, more background information about the patients is needed, mainly regarding diagnoses. The prevalence and incidence in men and women of the diseases that the drugs are used in must be considered when evaluating sex difference. This study focused on pharmacological groups with large sex differences, but not to forget, in groups where there were no sex differences, maybe there should be.

6.2 STUDY II: ADVERSE BLEEDING EVENTS OF WARFARIN, CLOPIDOGREL AND LOW-DOSE ASPIRIN

Bleeding event reports accounted for a high proportion of the total number of ADR reports in SWEDIS during the time period; 89 percent for low-dose aspirin, 74 percent for warfarin, and 57 percent for clopidogrel. A total of 1386 reports with bleeding events were registered for warfarin in 1999-2010, and corresponding figures for clopidogrel and low-dose aspirin were 219 and 676, respectively. Sex differences in bleeding event reports were found for all three substances (Table 5).

Table 5. Bleeding event reports and exposure data in men and women. Modified from paper II [248].

	Bleeding event reports	**Dispensed prescriptions (dp)**	**Exposed individuals (ei)**	**RR women/men (95 % CI)**
Clopidogrel 1999-2010	M: 126 W: 93	M: 970 467 W: 824 138	N/A	RR(dp) 0.87 (0.66-1.14)
Clopidogrel 2005-2010	M: 75 W: 64	M: 601 266 W: 516 199	M: 97 684 W: 59 495	RR(dp) 0.99 (0.71-1.39) RR(ei) 1.40 (1.00-1.96)
Low-dose aspirin 1999-2010	M: 383 W: 293	M: 18 079 512 W: 21 100 226	N/A	RR(dp) **0.66 (0.56-0.76)**
Low-dose aspirin 2005-2010	M: 239 W: 178	M: 9 985 355 W: 11 987 930	M: 561 151 W: 521 201	RR(dp) **0.62 (0.51-0.75)** RR(ei) **0.80 (0.66-0.97)**
Warfarin 1999-2010	M: 768 W: 618	M: 3 059 924 W: 2 053 435	N/A	RR(dp) **1.20 (1.08-1.33)**
Warfarin 2005-2010	M: 415 W: 302	M: 1 769 378 W: 1 171 801	M: 157 376 W: 113 627	RR(dp) 1.10 (0.95-1.27) RR(ei) 1.01 (0.87-1.17)

M = men. W = women. N/A = not available. RR = risk ratio, women/men. CI = confidence interval. RR(dp) = risk ratio calculated on bleeding event reports adjusted for dispensed prescriptions. RR(ei) = risk ratio calculated on bleeding event reports adjusted for exposed individuals. Bold figures indicate statistically significant findings.

For low-dose aspirin there were significantly more bleeding event reports in men, regardless of whether the figures were adjusted for dispensed prescriptions or exposed individuals. Two sex-specific meta-analyses [249, 250] have shown that aspirin treatment in primary prevention is associated with a similar increased risk of major bleeding in both men and women, whereas another meta-analysis [251] has showed an increased risk of extracranial (mainly gastrointestinal) major bleedings in men. The higher strength of aspirin, 160 mg, were more commonly dispensed in men. You can therefor assume that men generally received higher doses, with potentially higher risk of ADRs. Another factor might be that aspirin resistance is more frequent in women [50] decreasing the risk of bleeding.

For clopidogrel, bleeding event reports seemed to be more common in women when adjusting for exposed individuals, however the sex difference was not significant. This is in agreement with a large meta-analysis [252] which showed that the risk of major bleeding from clopidogrel treatment was similar in men and women. Unfortunately, in paper II [248], the above-mentioned signal of a higher incidence of bleeding event reports in women were referred to as significant although the confidence interval includes one (1).

For warfarin, bleeding event reports were more common in women when adjusting for dispensed prescriptions for the time period 1999-2010, otherwise no sex difference was seen.

In several studies, including a large meta-analysis, the major bleeding risk with warfarin was similar between men and women [253-255]. A RCT also found similar major bleeding rates between the sexes, however women experienced more bleeding (minor/major) overall [256]. In a multicenter study in Canada [257], women on warfarin were three times more likely to experience major bleeding compared to men on warfarin. Another multicenter study [258] showed that male sex and use of potentially interacting drugs were the only independent risk factors of severe bleeding during warfarin treatment, and a Swedish cohort study [259] found an overall lower risk of severe bleeding in women on warfarin than in men on warfarin.

In a Norwegian study including all reports of adverse effects for warfarin and NOACs from 2013-2015 [260], 66 percent of warfarin reports were related to men, and 60 percent of the total number of warfarin users were men. In our study, in 2005-2010, 58 percent of warfarin reports, and 58 percent of warfarin users were men. Furthermore, 97 percent of the adverse reaction reports for warfarin were classified as serious in the Norwegian study [260], corresponding to 94 percent in our study (93 % in men and 96% in women).

In contrast to most drugs, warfarin has individualized dosing. Several studies have showed that women require a lower warfarin dose than men [261-263]. Garcia et al. [262] studied warfarin maintenance dosing patterns in clinical practice and found that the warfarin dose was strongly associated with patient sex and inversely related to age. Younger men required the highest doses and older women required the lowest doses. For atrial fibrillation, the median daily dose was 5.4 mg in men below 50 years of age and 3.1 mg in women aged 80 years or older. The often-recommended initiation dose of 5 mg warfarin daily would be too high for a majority of both men and women older than 70 years, leading to over-anticoagulation and increased risk of bleeding. This could be a plausible explanation for bleeding event reports being more common in women. Other studies have also showed that age is associated with warfarin dose, but although women required a lower warfarin dose than men the difference were not statistically significant [263, 264]. Nevertheless, women with atrial fibrillation are generally older than men.

In this study, all results were presented sex-disaggregated and for the two different study periods. Differences between men and women were calculated as risk ratios (RRs). Bleeding is a severe ADR, and we assumed a high reporting rate from physicians with no difference between male and female patients. However, we did not account for any potential gender differences affecting the tendency to report ADRs. Most bleeding event reports were serious, and a previous Swedish study have shown that healthcare professionals more often file serious reports for men [121].

Due to the incomplete and unsystematic nature of the data, spontaneous reports of ADRs can only be used as signals and further investigation is required. In this case, Diana et al. [259] has studied sex differences in bleeding events further in a cohort of individuals initiated on warfarin treatment. The study showed that women had a lower incidence of severe bleeding, even after adjustment for age, comorbidity and co-medication.

6.3 STUDY III: EXPERIENCES AND EXPRESSED KNOWLEDGE AMONG PHYSICIANS ABOUT SEX AND GENDER ASPECTS IN MEDICAL TREATMENT

The thematic analysis of the material from five FGDs, conducted with physicians working at health centres in Sweden, resulted in three main categories and eight subcategories.

The first main category "Experiences of sex and gender differences in diagnosing and assessment of clinical findings" included the physician's experiences of differences between men and women in symptomatology, diseases, morbidity, and healthcare seeking behavior. Also, how the physician-patient interaction was affected by the patient's sex and the physician's sex was addressed.

The second main category "Medical treatment in men and women" emphasized factors that influenced treatment decisions, including individual factors and guidelines to a great extent, perceived sex differences in patients' attitudes to medicines, and the physicians' non-awareness of or consideration of sex differences in ADRs.

The third main category "Knowledge of sex differences in drug therapy" reflected the physicians' perceived lack of knowledge and their expressed need of more knowledge regarding sex differences in pharmacological treatment.

Initially, we were set on discussing sex and gender aspects in drug treatment. However, it turned out that the physicians had lots of other things to discuss regarding the patients' visits. Large parts of the FGDs were not about drug treatment specifically. The patient's sex comes into the picture much earlier, sometimes even before the patient enters the room as a name in the time book. Perceptions of men and women affected how physicians thought about diseases and how likely various differential diagnoses were. For example, the physicians described that because men more rarely than women seek healthcare, a man who comes to the health center for urgent medical needs are regarded as more likely to have genuine health problems. Furthermore, the physicians had thoughts on how male and female patients think about treatment and their attitudes to drug treatment. Also, their own perceptions about men and women may affect treatment. Any drug prescribing takes place at the end of the visit and represents only a small proportion of the total visit.

At the moment of prescribing, the physician reflects on the patient's sex (man/women), or not. Patient sex should be one factor that is considered when prescribing drugs, while gender perhaps mainly influence the path to diagnosis and treatment decisions together with the physician's perceptions of the patient based on other factors including for example socioeconomic factors.

Thoughts, beliefs and/or knowledge about men and women were there all the way, from interpretation of symptoms to decision on treatment, and the physicians gave several examples of that. For instance, the physicians perceived a more diffuse symptomatology expressed in women complicating the diagnosis, especially in cardiovascular diseases. Also, the physicians described sex differences in ADRs for certain substances, for example statins

and ACE inhibitors. But when it came to the choice of drug to prescribe, they mostly followed a recommendation list. Particularly the recommendation list from the local Drug and Therapeutics Committee (DTC) was mentioned.

The physicians talked a lot about personalized medicine, but in practice they said they mostly follow a recommendation list. Often, following a recommendation list is a good choice as it will suit most patients. However, more reflection may be needed to make a personalized choice and patient sex is then one of the factors to consider.

The physicians expressed that they had very little knowledge about sex differences in drug treatment and that they had received no or very little training in it. The lack of education in this area was perceived as there is nothing to know and nothing to take into consideration. There was a circular reasoning on that if sex differences in drug treatment were important training would be given, and the physicians said that they do not know much about the topic because there is not so much knowledge. However, in contrast to their expressed lack of knowledge, during the discussions the physicians brought up several sex differences and even gave some examples of how they took them into consideration when deciding on drug treatment. For instance, the physicians mentioned avoidance of beta-blockers in men due to risk of sexual dysfunction and avoidance of diuretics to prevent prostate problems, while diuretics sometimes were chosen to women who needed antihypertensive treatment and also had swollen feet.

The concept gender can be perceived as a complex concept. In some FGDs, gender was mentioned, but mainly sex differences were discussed. However, sometimes we thought it was really more about gender differences, even if the physicians did not use the word "gender". For example, several physicians mentioned that personality is more important than sex, and here we believe that gender has a matter.

During the FGDs, the concept "gender equality" was used in the initial questions. Afterwards, we realized that it was not such a good idea to use a political concept. It may have been interpreted differently by the physicians and it is generally difficult to discuss a political concept. Sweden is considered to be equal and it is not politically correct to talk about sex differences, except possibly for reproduction. One should not make any difference between men and women. This may be one reason for the physicians not having reflected that much about sex differences in drug treatment. In contrast, they talked more about equality in society. Furthermore, it is unclear what equal drug treatment really means. Our interpretation was that an equal drug treatment, to the physicians, initially meant that men and women should be treated equally, equally as with the same drug in the same dose. But after some discussion and further considerations, the physicians were more assured that men and women should be treated equally well, and that can imply different dosages or even different drugs.

6.4 STUDY IV: ANTICOAGULANT TREATMENT IN ATRIAL FIBRILLATION

The proportion of patients with atrial fibrillation treated with anticoagulants increased substantially between 2011 and 2015 in both men and women (Figure 2). This increase is probably due to a combined effect of several factors including the introduction of NOACs, the change from $CHADS_2$ to CHA_2DS_2-VASc score with an additional point for female sex, and guidelines emphasizing the higher risk of stroke in women with atrial fibrillation. The introduction of new treatment options increases the focus on the disease/diseases that they should be used to treat. Thus, we also saw an increasing number of individuals diagnosed with atrial fibrillation in Stockholm during the same time.

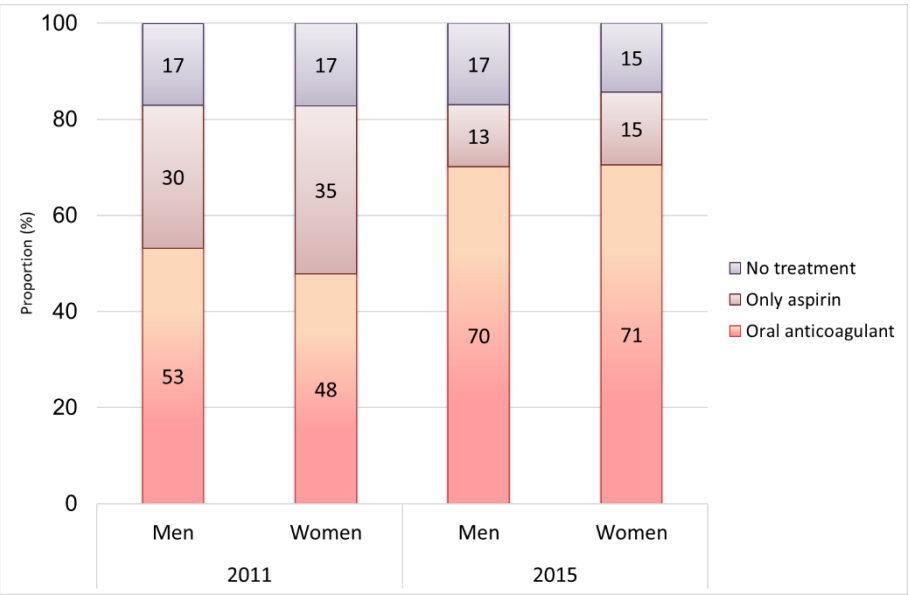

Figure 2. Proportions of patients with nonvalvular atrial fibrillation in the Stockholm region 2007-2011 and 2011-2015 dispensed anticoagulant treatment in 2011 and 2015, the aggregate for all age groups by sex. No treatment refers to neither oral anticoagulants nor aspirin.

A total increase in OAC treatment after the introduction of NOACs has also been seen in studies in the U.S. [265, 266] and in Australia [153], and the proportion warfarin decreases while the proportion NOACs increases.

In our study, the sex difference in the total proportions of patients receiving anticoagulant treatment seen in 2011 had disappeared in 2015. However, other studies have showed that women were still less likely to receive OAC compared to men even after the introduction of NOACs [153, 267], and regardless of risk/number of risk factors [266, 268]. In a large global cohort study of patients with atrial fibrillation [154], overall rates of anticoagulant use were not different between men and women. Further, in an American study comparing OAC use for atrial fibrillation in the pre- and post-NOAC eras [265], women were more likely than men to receive OAC treatment during both periods.

An American study analyzing trends in oral anticoagulant use from 2010 to 2014 in patients with atrial fibrillation [266] suggested that female sex was not sufficiently emphasized as a risk factor, since female sex was associated with relatively lower use of OAC than the other

risk factors in the CHA_2DS_2-VASc score, except vascular disease. Other studies have also discussed the under-recognition of female sex as a thromboembolic risk factor [266] and physicians downplaying of the risk in women [268].

Some additional reasons that have been discussed regarding why women are less likely than men to receive anticoagulant treatment are; different application of clinical guidelines in men and women, physicians' perception of a higher bleeding risk in women, more female patients deciding against anticoagulation therapy, prescribing low-dose aspirin instead of an OAC in women, and higher age at the time of diagnosis in women [148, 153, 266, 268].

In 2015, there were still fewer women using OAC in patients above 80 years of age and in patients with complicated comorbidity. The physicians may think that they want to be careful with the elderly and not give them high risk medicines, but not treating them with anticoagulants may expose them to even greater risk. The fact that it is older women who are not treated may be due to the gender stereotype that women are weaker than men.

The fact that women are undertreated with OAC has also been shown to influence outcome. An American retrospective cohort study [268] analyzed whether observed sex differences in OAC treatment mediated any observed differences in outcomes. Women were less likely than men to receive OAC treatment, and this partly mediated the observed increased risk of ischemic stroke and the decreased risk of intracranial bleeding in women.

Another study in patients with atrial fibrillation in Stockholm [147] showed that the increased use of OAC between 2012 and 2017 contributed to a marked decrease of ischemic strokes, without increased bleeding rates. The stroke reduction was largest in elderly patients with the highest risks for stroke and bleeding.

Not all patients with atrial fibrillation are suitable for treatment with OACs due to contraindications and treatment risks. The National Board of Health and Welfare in Sweden state that a level of at least 80 percent of patients with atrial fibrillation with a clear indication (i.e. CHA_2DS_2-VASc$\geq$2) being treated with an OAC is clinically reasonable [269]. In our study, 70 percent of men and 71 percent of women were treated with OAC in 2015. In patients with complicating comorbidity, the proportions were slightly lower.

In our study, the proportion of patients treated with only low-dose aspirin decreased significantly between 2011 and 2015. However, there were still notable proportions of patients using low-dose aspirin, and remarkably it was mainly individuals with the highest risk (CHA_2DS_2-VASc 5-9). According to treatment recommendations from The Swedish National Board of Health and Welfare, patients with atrial fibrillation and increased stroke risk (i.e. CHA_2DS_2-VASc $\geq$1) should not be treated with low-dose aspirin, mainly because the effect of treatment is worse compared to treatment with NOAC or warfarin [269]. Low-dose aspirin in monotherapy is not recommended for stroke prevention in international treatment guidelines of atrial fibrillation [137, 138].

The use of low-dose aspirin in atrial fibrillation treatment is particularly high in Asia, as it is considered a safer alternative to warfarin [155-157]. In a qualitative study from Hong Kong examining barriers to use OACs among long-term low-dose aspirin users with atrial fibrillation [157], most patients had no knowledge of other OACs than low-dose aspirin, there was concerns about the bleeding complications from OACs, and the lifestyle changes with warfarin, including a more complicated dosing regimen, INR monitoring and diet restrictions, were seen as barriers.

In our study, the study population characteristics were presented separately for men and women and the results were presented stratified by sex and age group or CHA_2DS_2-VASc score. Women in the study population were on average six years older than men, and had 1-1,5 points higher CHA_2DS_2-VASc score. This is in agreement with results from other studies [154, 267, 268, 270].

As female sex gives one point in the CHA_2DS_2-VASc score, it is somewhat confusing how to make comparisons between women and men with different CHA_2DS_2-VASc score.

6.5 STUDY V: ANTIEPILEPTIC DRUG TREATMENT IN POST-STROKE EPILEPSY

Levetiracetam was the most used antiepileptic drug in both men and women when initiating treatment for PSE, and it also had the highest persistence. Several factors were associated with the choice of AED including patient sex, age, renal impairment, hospitalization due to epilepsy, inpatient bed-days, number of consultations in specialist care, number of days from stroke to initiation of an AED, and year of first AED purchase. Lamotrigine was more common in women than in men, and valproic acid was less common in women than in men.

Levetiracetam had the highest persistence in both men and women. Factors associated with risk of treatment discontinuation within 90 days were choice of AED, oral anticoagulant use and percutaneous endoscopic gastrostomy tube delivery of the drug (PEG).

The Kaplan-Meier plots in paper V show sex-disaggregated results with one curve for men and one curve for women in the same plot, one plot for each analyzed drug. An alternative way of presenting the results is to have one plot for men and one plot for women with curves for the different drugs in the same plot. Then it becomes clearer which drug has the longest persistence in men and women, respectively. In men, there was no significant difference in time to treatment discontinuation between levetiracetam, carbamazepine, lamotrigine and valproic acid (Figure 3). However, for women the time to treatment discontinuation was significantly longer with levetiracetam (Figure 4).

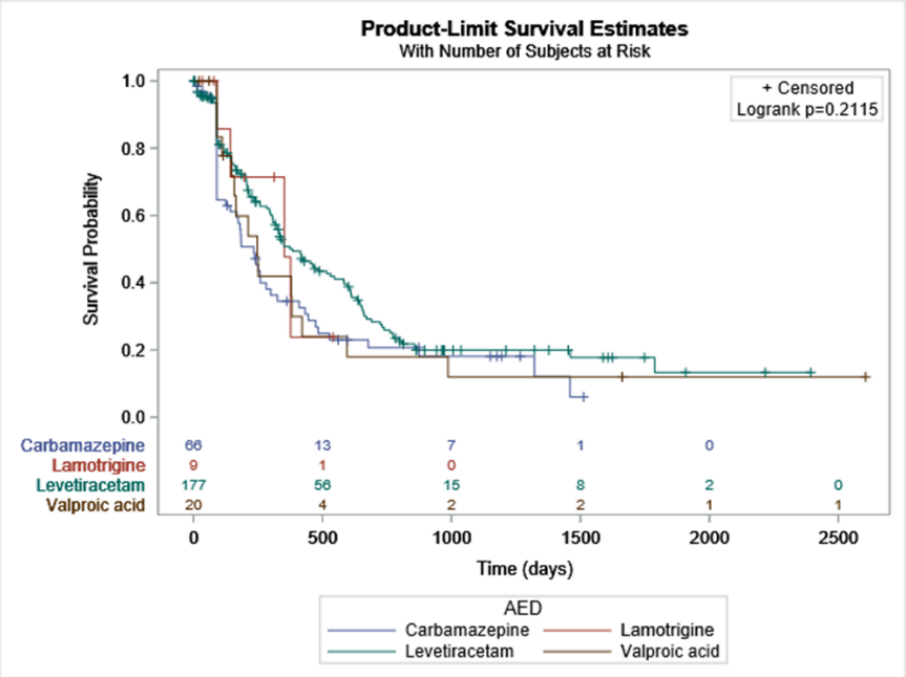

Figure 3. Kaplan-Meier plot with curves for the four most used AEDs for initiation of therapy in PSE. Time to treatment discontinuation in **men** treated with levetiracetam (median: 384 days, 95% CI 308-531), carbamazepine (median: 234 days, 95% CI 124-299), lamotrigine (median: 352 days, 95% CI 90-.), and valproic acid (median: 247 days, 95% CI 148-421)

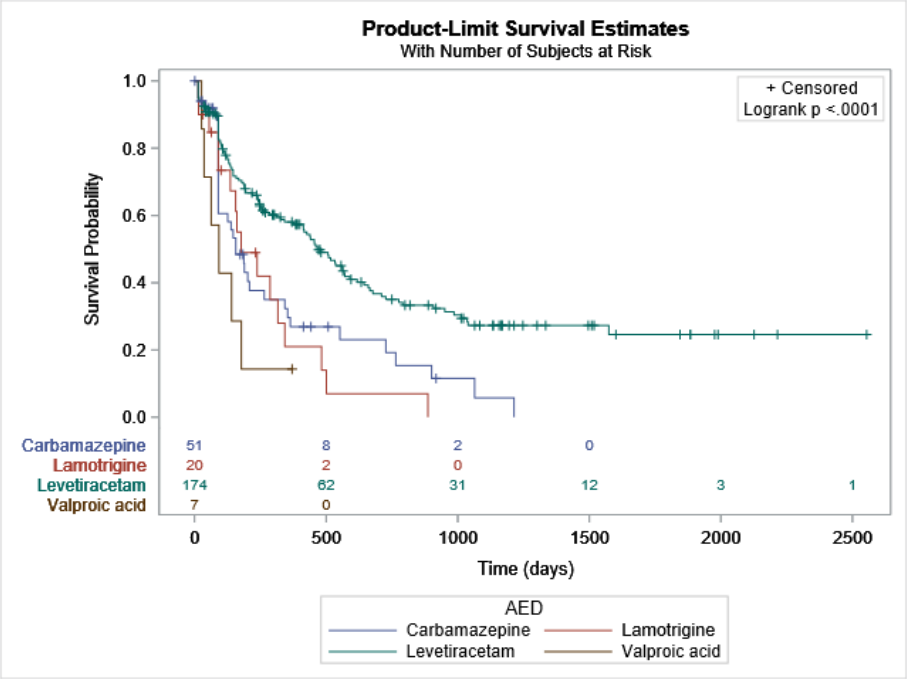

Figure 4. Kaplan-Meier plot with curves for the four most used AEDs for initiation of therapy in PSE. Time to treatment discontinuation in **women** treated with levetiracetam (median: 471 days, 95% CI 376-571), carbamazepine (median: 157 days, 95% CI 90-265), lamotrigine (median: 177 days, 95% CI 90-343), and valproic acid (median: 93 days, 95% CI 27-178).

In the regression analysis we identified factors associated with discontinuation within 90-days. The time span of 90 days is rather short and most likely reflects lack of tolerability rather than lack of efficacy. AED doses are commonly increased slowly, and the target dose may not be reached until the middle or latter part of the 90 days [163]. Moreover, as the drugs are used to prevent an occurrence that may not be very frequent, a longer period would be needed to evaluate effect. Among the studied variables, no data regarding adverse effects was available and included.

Furthermore, it is important to note that discontinuation with one substance do not necessarily mean discontinuation of antiepileptic treatment. It most likely means that the patient has switched to another substance, however we have not studied that. In a small descriptive study on switching of AED treatment in PSE [271], up to 40 percent of patients needed to switch their first prescribed AED, mostly due to side effects in lower dosage ranges.

In the study population, comorbidity was common. Atrial fibrillation occurred in about 40 percent and neuropathic pain occurred in just over 40 percent. Many patients had several of the studied comorbidities (Figure 5 and 6). This study focused on AED and PSE, however in the individual patient there may have been other diseases that were more in focus affecting the PSE treatment.

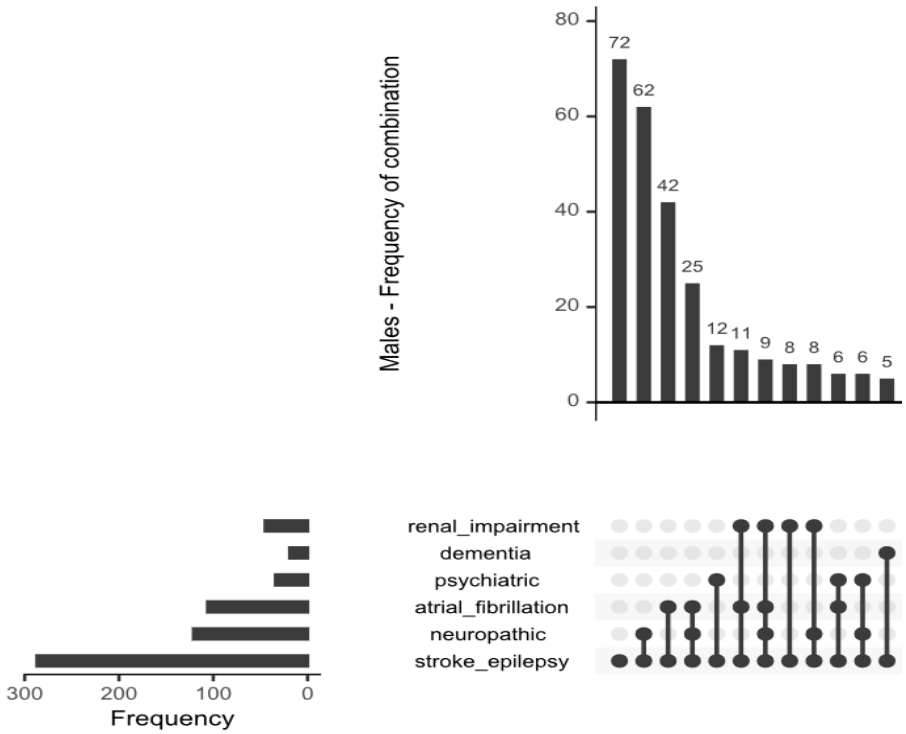

Figure 5. UpSet plot showing the combined comorbidity in men. Each column corresponds to a set of diagnoses. Psychiatric = psychiatric conditions. Neuropathic = neuropathic pain. (For details on diagnosis codes (ICD-10 codes), see paper V.)

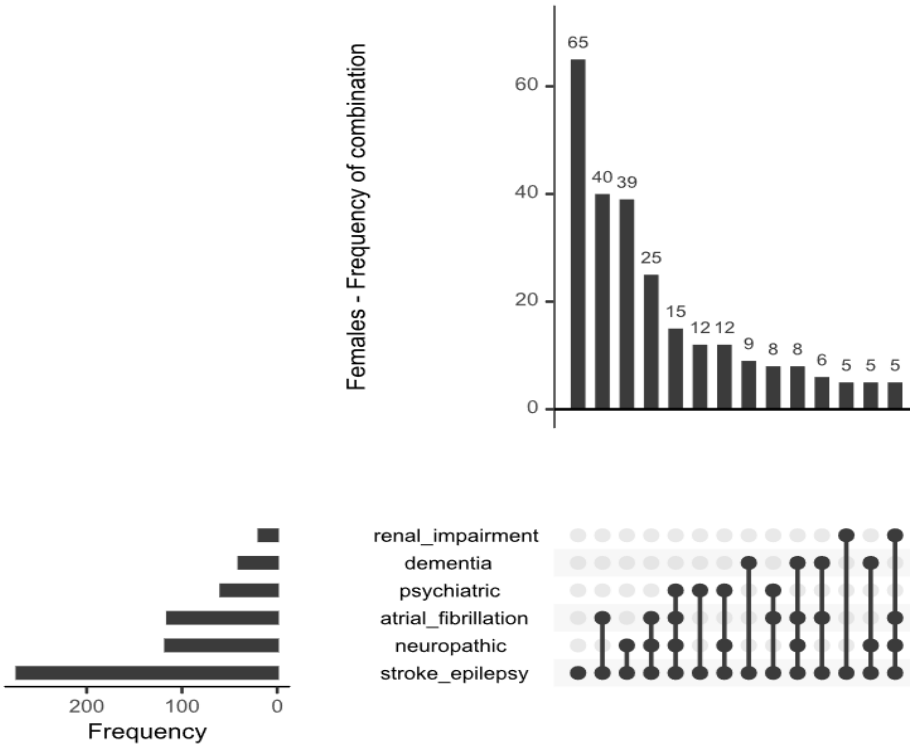

Figure 6. UpSet plot showing the combined comorbidity in women. Each column corresponds to a set of diagnoses. Psychiatric = psychiatric conditions. Neuropathic = neuropathic pain. (For details on diagnosis codes (ICD-10 codes), see paper V.)

In this study, the study population characteristics were presented separately for men and women as well as the description of first dispensed AED. Due to the relatively low number of women and men in this study, it was not ethically appropriate to stratify the results per age group, which otherwise would have been interesting. In the regression analysis, patient sex was one of several variables. It would have been interesting to do sex-disaggregated regression analyzes to see which factors affecting the choice of AED and persistence in men and women, respectively. However, this was limited due to the relatively small number of men and women in the study population.

To further study whether there was any impact of patient sex on the results we tested if there were any interactions between patient sex and any of the other independent variables. In the persistence analysis, there was an interaction between sex and stroke type, meaning that the relationship between stroke type and the risk of treatment discontinuation within 90 days is different between different sexes and that the relationship between sex and the risk of treatment discontinuation within 90 days depends on stroke type. However, this interaction effect was difficult to interpret and was therefore not included in the final analysis.

6.6 ANALYSING SEX AND/OR GENDER DIFFERENCES

6.6.1 Terminology

There is a conceptual confusion regarding the terms sex and gender, and the use and misuse of the concepts in medical research articles has complicated the literature search. Finding relevant articles was sometimes difficult because it was not always easy to understand what the authors had studied and analyzed. I have read many articles where the terms sex and gender were used synonymously, and I have read even more articles where gender was incorrectly used instead of sex. In many articles, it felt like the authors were unaware of the meanings of the terms. I have also read articles where sex-disaggregation was equated with gender analysis. Furthermore, there seems to be a trend in how the terms are used. Also, some journals seem more careful than others about the use of the concepts, while others do not discriminate between the terms.

In paper I and III, we shortly defined the two terms in the introduction, with sex differences referring to biological differences, and gender differences referring to sociocultural differences. In paper II, IV and V, we did not use the word gender, except from in the title of study IV which begins with "Sex and Gender Differences…", which may seem a little strange. However, to some extent we still discussed differences related to gender in these studies. Several times, through all papers, we chose to write "men and women" to avoid define whether it was sex and/or gender that influenced.

6.6.2 Analysis

Sex-disaggregated data in healthcare research is needed to identify differences or similarities between the sexes, and an important first step in addressing potential inequities. However, it is important to further analyze whether sex, gender or both, and what other factors are behind the current results. Furthermore, it is also important to look at whether the differences have any consequences.

Although it is important knowing about differences between men and women, there is criticism of using the male/female dichotomy since it exaggerates sex differences and treat men and women as if they were two completely separate groups instead of groups with common characteristics [272]. Also, there is a risk that research focusing on differences between men and women may perpetuate dichotomies that do not reflect the diversity that exists between different groups of men and women. Besides, it provides limited space for moving beyond two definable sexes and genders [21].

It can be precarious and directly incorrect to generalize because differences between men and women do not necessarily mean that there are differences between all men and women. There can be large differences in subgroups. Likewise, it is important knowing differences in between women and in between men. Regarding biological differences there can be large inter-individual differences for example in comorbidities, and in sex hormone levels in between women at different ages, and during pregnancy and lactation [51]. Regarding gender

differences there can be large inter-individual differences based on for example socioeconomic status, race/ethnicity, and (dis)ability, and other important social locators [272].

In Swedish healthcare data registers, patient sex is a dichotomous variable referring to the set of sex chromosomes. Thus, in the studies based on register data included in this thesis, we had information about patient sex in the format man or woman and we could draw conclusions about differences between men and women related to biological sex. However, we could speculate about gender differences and how gender may have influenced the outcome, and that was what we have done. In other parts of the world there is greater opportunity for individuals to identify themselves as neither exclusively male or female [27], but this is probably used very little in medical research.

We have presented sex-disaggregated data, and in some studies, we have also disaggregated data at other levels to study differences/similarities in subgroups. However, we have applied the male/female dichotomy and we have not studied differences in between women and in between men in any structured way, which are limitations in the studies. Nor have we included any social characteristics or performed any proper gender analysis, mainly because we did not have access to data or enough knowledge.

Tackling analyzing sex and gender requires expertise in both biomedical and social science. Of these two, I master the biomedical part much better than the social part, which is reflected in the studies. Also, my main data source has been administrative healthcare registers which has been a limitation. Nowatzki and Grant [272] mean that research based exclusively on administrative data cannot show the importance of the social determinants of health, and that administrative data need to be supplemented by other types of data and indicators that captures how gender, and not just sex, plays a role.

Gender is not a stand-alone variable, but it must be understood in relation to other variables, i.e. biological or social factors, and their impact on health. The influence of gender may be more easily captured by qualitative studies, and valuable considerations of sex and gender can be provided by mixing qualitative and quantitative research methods [273].

There are several important dimensions that affect health and illness, including sex/gender, race/ethnicity, and class, and it can be seen as a limitation that we have focused only on one dimension. From an intersectionality perspective, the prioritization of sex/gender above other dimensions of social identity undermine efforts of understanding the complexity of health outcomes [21].

6.7 STRENGTHS AND LIMITATIONS

In the register studies, we have used datasets from healthcare utilization databases with national or regional coverage of entire populations for long periods of time. This offers large datasets containing many different variables, with reduced likelihood of recall bias and non-response bias. Using existing data is likely both time- and cost-saving, as compared to studies where you collect your own data, primary data. However, it is not certain that collected data fully meets the needs of the researcher, e.g. contains all desired variables. Then it may be necessary to collect primary data.

Another advantage of healthcare utilization databases is there representativeness of routine clinical care. However, this is also a disadvantage since data is not primarily collected for research purposes and the detail and accuracy of data are not under the control of the researcher. The data collection method, how things are measured, codes and/or classification may have changed, which complicates comparisons over time.

Two important factors that affect the quality of secondary data are the completeness in the registration of individuals, and the accuracy of the recorded data [189].

Swedish pharmacy dispensing data includes all drugs dispensed to the entire Swedish population and data are recorded automatically when a prescribed drug is dispensed. Data should not be biased, however random errors may exist. A disadvantage of using pharmacy dispensing data is that we have no information about if and how the patients took their medication. Thus, there is a risk of misclassification, i.e. to classify a patient as exposed when not. Furthermore, pharmacy dispensing data includes no information about drugs used in inpatient care or purchased OTC. In study I, because of this, we included only pharmacological groups with at least 75 percent of the total sales volume purchased on prescription. Study II, IV and V concerned drugs mainly purchased on prescription, not sold OTC.

Hospital diagnoses are generally well validated [204, 274], while diagnoses in primary care are less validated [70, 197]. Since some patients occur only within primary care, it is a great advantage to have access to diagnoses from primary care. In a previous study in patients with atrial fibrillation in the region of Stockholm, for 12 percent of the patients the diagnosis was found only in primary care [70].

Routines for diagnosis registration may differ between regions and between different healthcare providers. Also, it has been shown that the use of compensation models for health centres based on registered diagnoses leads to over-registration and many irrelevant diagnostic registrations [275]. Moreover, to make a diagnosis and to register a diagnosis is not the same. Diagnoses in free text in the medical records are translated to ICD-10 codes, and it is not certain that the codes in the registers fully correspond to the diagnoses made by healthcare professionals.

Data on ADRs are based on manual reporting and underreporting is its major limitation [205-207]. Also, there are several other limitations of spontaneous ADR reports including a) confounding by indication, i.e. patients taking a certain drug may have a condition that is associated with a higher incidence of the adverse event, b) questionable representativeness of patients, c) effects of media attention on the numbers of reports, d) attribution of the adverse event to a single drug when multiple drug exposure has occurred [276]. However, the available data are important to be able to study the prevalence of ADRs in larger materials, and it is desirable that reporting is improved.

More strengths and limitations are addressed in the various sections of chapter 4 *Methods and methodological considerations* and in section 6.6. *Analyzing sex and/or gender differences*.

6.7.1 Generalizability

The generalizability of drug utilization studies derived from healthcare utilization data can be limited by difference in study population, guidelines and recommendations, healthcare organizations and regional reimbursement systems.

In study IV and V, the study populations consisted of individuals from Stockholm and the results may not be generalizable to the Swedish population since the general population in Stockholm is younger, have higher educational level and a higher mean income [277]. Furthermore, there are more healthcare providers in Stockholm and easier access to specialist care.

Study II and IV included treatment with warfarin. The effectiveness and safety of warfarin treatment is associated with time in therapeutic range (TTR) of INR of 2.0-3.0. A high TTR is associated with a lower risk of stroke and bleeding. Due to large variations in mean TTR between centers and countries, there are difficulties in comparing results between different study populations. In Sweden, warfarin treatment quality is high with TTR over 75 percent [278], and data from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial shows that of 44 countries Sweden had the highest mean TTR [279].

6.7.2 Trustworthiness

The trustworthiness of qualitative studies concerns how believable the results are given the methods used to produce it. The aim of trustworthiness is to support the argument that the study findings are "worth paying attention to" [280]. Several definitions and criteria of trustworthiness exists, and four of the commonly used are credibility, dependability, confirmability and transferability [280-282]. A short description of each concept together with notes of what we have done to try to achieve trustworthiness are presented in Table 6.

Table 6. Description of four criteria of trustworthiness [280-282] and how we tried to meet them in study III.

Concept	**Description of concept**	**Implemented arrangements in study III to meet the criterion**
Credibility	The ability of the researcher to convey how the research process affects the validity of the formed knowledge. The analysis must be true to the collected data and include critical reflection. A clear and comprehensive description of the research process, from data collection to analysis, is needed.	Several researchers were involved in the analysis process, and also validated material against raw data (audio records and transcripts). The findings were presented to a physician working at a health centre to validate whether they were understandable in the clinical setting in which they were collected, and the physician recognized the findings. Quotes from the FGDs were used in the paper to illustrate the findings.
Dependability/ consistency	The stability of data over time and over conditions, which is facilitated by a logical, traceable, and clearly documented analysis process.	The research process is clearly documented throughout all steps. We used the same person as moderator in the first four FGDs, and in the fifth FGD, the person who had been observed in all previous discussions was the moderator. This led to the last FGD being conducted in a very similar way as the foregoing.
Confirmability	The objectivity of data and the level of confidence that finding are grounded in the data and not based on potential researcher biases. The researcher's background and preconceptions about the research questions may affect the angle of investigation and the interpretation of data. Reflexivity is commonly used to achieve objectivity and to counter the biases the researcher may bring to her research [283].	Reflexivity was applied throughout our study process meaning that the researchers reflected on their own beliefs, judgements and actions during all steps in the research process, and how these may have influenced the results. It was a strength to be several researchers with different backgrounds and perspectives, who went through and interpreted the material and could complement and question each other's statements.
Transferability	To what degree the results can be applicable to other contexts or settings. It is left to the readers to assess if the findings can be applied to their own setting. The researcher is responsible for providing "thick descriptions" to enable assessment, including a detailed description of the informants and the research setting.	By describing the study thoroughly, it is left to the reader to decide if the results are transferable to a similar context.

7 CONCLUSIONS

In this thesis, drug use in men and women have been described and analyzed within various areas using different data sources and methods. The focus has been on sex differences, however to some extent, also gender differences have been addressed.

Focus group discussions to explore general practitioners' perceptions of sex and gender differences with a focus on medical treatment revealed that individual factors appeared to be taken in account more often than the patient's sex when deciding on treatment. Furthermore, the physicians expressed that they had little knowledge of sex differences in drug treatment. However, they gave several examples of how they considered this in drug treatment indicating the opposite.

In 2010, when data for the first paper was collected, we found substantial differences in dispensed drugs between men and women. Most differences seemed reasonable and may be explained by differences in the incidence or prevalence of disease, or frequency of adverse drug reactions, whereas other differences appeared more difficult to explain on medical grounds and may be due to sex and gender differences in health and healthcare.

In some areas, these differences have diminished over time as we could show for oral anticoagulant (OAC) use in patients with atrial fibrillation. In men and women with atrial fibrillation, thromboprophylactic treatment improved considerably over time. A time when non–vitamin K oral anticoagulants (NOACs) were introduced, and sex-specific risk factors were included in guidelines on atrial fibrillation treatment. The proportions of patients with OACs have increased and the use of less efficient therapy with low-dose aspirin has decreased. Fewer women used OACs in 2011, however the sex difference had disappeared in 2015, except in elderly women and in patients with complicated comorbidity. A shift in most used antiepileptic drug (AED) in both men and women with post-stroke epilepsy (PSE) was seen compared to other, earlier studies. In 2012-2019, levetiracetam was the most used AED when initiating treatment in men and women with PSE. Also, levetiracetam had the highest persistence in both men and women. Albeit only examples, this illustrates that differences between men and women in drug use and in choice of drugs may change over time.

Adverse event reporting is sporadic but can be useful as a signal generator. Data on bleeding event reports adjusted for drug use in the population showed no sex difference in the prevalence of bleeding event reports for warfarin, whereas in low-dose aspirin a higher prevalence of bleeding event reports was seen in men than in women. This may be due to a greater proportion of men with a higher aspirin dose and antithrombotic co-medication.

8 IMPLICATIONS AND FUTURE PERSPECTIVES

Improvements have been seen over the years in medical research with an increased focus on sex differences, and more and more studies are conducted analyzing differences between men and women. However, improvements are still needed in many areas.

During the years of my research project, I have been amazed at the number of studies that still do not present sex-disaggregated data, or not even mention possible differences between men and women. Especially in areas where many other studies have shown that there are important differences. When combining results from men and women, the average of the aggregated results may mask differences between the sexes and incorrect conclusions can be drawn. I would like to take the opportunity to urge all researchers who do not have sex-disaggregated data in their analyzes, to redo the analyzes to see if the conclusions remain for men and women separately. It can be just as important to know that there is no difference between men and women as it is to know of differences.

Knowledge of how drugs are prescribed and used in men and women in various diseases can be useful in discussions about rational use of medicines. However, the underlying mechanisms of why things look the way they do may be rather complex. Differences in drug use between men and women may have many different causes. A lot can happen on the way from when an individual decides to seek healthcare for a certain condition, until he or she initiate, implement and persist on drug treatment. In each one of the following steps there may be differences between men and women related to sex and/or gender. If there are, there is a need to explore the cause further.

First, an individual must come to healthcare. Once there, a consultation can result in different examinations, considerations of likely conditions, and diagnosis and treatment decisions. There are guidelines to support treatment decisions, where there in some cases are sex-specific recommendations. Consideration should be given to severity of disease, comorbidity, co-medications, and personal factors such as age, sex and patient preferences. Regarding choice of substance there are regional formularies developed by e.g. DTCs. If a drug is prescribed, it should be purchased, which is not always done, and then it should be continued to be purchased throughout the treatment period, which might be lifelong in chronic conditions. Meanwhile, the patient should take the medicine as prescribed. Many factors may affect if and how patients take their drugs including adverse drug reactions, and treatment can be interrupted on the initiative of the patient and/or healthcare professionals. In addition, the patient's thoughts and opinions about the medical treatment are present at all time, and also society's view on health, diseases and medication. In addition to sex and gender, these steps may be affected by numerous other variables which complicate things even further.

There are many knowledge gaps throughout this process. What happens when the drugs are used by the patients is particularly unstudied.

During the years of my research project, new ideas have developed, and new research questions have been raised. For instance, when conducting study V, we reflected on that

individuals with multi-dose drug dispensing are often excluded in persistence studies. If we would have done this in study V, a large proportion of the study population would have been excluded and substantial bias probably added. It would be of great interest to study how common multi-dose drug dispensing are in different populations, i.e. individuals with different diagnoses and drug treatment, and if there are differences between men and women.

Moreover, I have realized the potential of qualitative studies and how they can enrich quantitative studies. In the registers, you can see what the decisions became, for instance what diagnoses were given, and which drugs were prescribed/dispensed, but you cannot see the thoughts behind the decisions. It may be easy to judge a decision as wrong from an external point of view, but it may be well-founded and based on aspects that are not obvious and difficult to detect in registries. Therefore, it would be interesting to supplement the results from study IV and/or study V with qualitative data, for example from interviews or FGDs with physicians. That could provide new insights and further explanations about why things look the way they do. Also, regarding OAC treatment in patients with atrial fibrillation, it would be interesting to examine patients' thoughts on anticoagulant therapy and to explore whether men and women have different perceptions and expectations.

9 ACKNOWLEDGEMENTS

I am very grateful to have had the opportunity to be a PhD student at Karolinska Institutet. It has been an amazing journey that has taken me to new intellectual heights as well as around the world. However, from time to time I have asked myself – Why am I doing this? It has been hard work, demanding, stressful, and I have received critical comments from reviewers and others. Fortunately, the positives have always prevailed; the excitement and joy of learning new things, gaining knowledge in previously unknown areas, making new contacts, and having rewarding research discussions. Also, the glimmer of hope of being able to make improvements for men and women in health and healthcare.

I would like to thank everyone who has supported me during my PhD journey and made this thesis possible!

I especially want to thank my supervisors for all your time and support during several years. With your extensive knowledge in your respective fields and with your various strengths, you have complemented each other in a good way and formed a great team:

Björn Wettermark, my main supervisor, thank you for inspiring me and inviting me to become a researcher, and for sharing your enthusiasm for drug utilization research. I have really enjoyed that you have included me in many different contexts around drug utilization, including conferences, courses, and supervision of pharmacy students.

Karin Schenck-Gustafsson, my co-supervisor, thank you for introducing me to the fields of gender medicine and cardiology, and for inviting me to many interesting conferences and courses. I envy your fighting spirit and you inspire me to want to spread knowledge about gender inequality in drug utilization.

Mia von Euler, my co-supervisor, thank you for always taking time to answer my questions and read my texts, and for encouragement and good advices (both in working life and in private life). Also, I have appreciated your accuracy and sense of order a lot.

Pia Bastholm Rahmner, my co-supervisor, thank you for introducing me to qualitative research methods, and for helping me to gain insight and knowledge by guiding me in the various concepts of qualitative research.

I also want to express my gratitude to:

My co-authors, for valuable contributions to the original research papers in this thesis. **Linnéa Karlsson Lind**, for support in the qualitative analysis, and I have also appreciated your company at conferences and at the exciting meeting at the FDA. **Karin Hallgren**, for accompanying me on adventures in the world of qualitative research, and for interesting discussions on gender equality. **Diana Rydberg**, for nice chats in the corridor at Klin.farm, and your great enthusiasm and curiosity about drug utilization data. **Tomas Forslund**, for help with data management and analysis, and reflections from primary care. **Anders Sundström**, for help with data analysis, and statistical guidance. **Love Linnér**, for help with

data management and analysis, and for introducing me to UpSet plots. **Ulf Bergman**, for sharing wise opinions from your long experience in drug utilization research, **Paul Hjemdahl**, for sharing your expertise in the cardiovascular field, and wise views in research. **Rickard Malmström**, for valuable input and critical thinking. **Lennart Holm** and **Stefan Mejyr**, for valuable knowledge on adverse drug reaction data.

My current and former colleagues at Region Stockholm: **Elin Dahlén**, for pleasant companionship over the years at work as well as at conferences. It has been good to have someone to discuss all PhD related issues with. **Maria Juhasz Haverinen**, for nice company over the years both at work and at conferences, and for always being there for me. It has meant a lot. **Thomas Cars**, for enjoyable company over the years at work as well as at conferences, and off course for all energy giving pranks. **Sten Ronge**, for nice discussions and lunches. **Pia Frisk** and **Irene Eriksson**, for sharing your experiences in being a PhD student, and interesting research discussions. **Gunnar Ljunggren**, for your support and feedback on my research. And all of you who have shown interest in my research and been supportive, but whom I have not mentioned by name – I have appreciated you all.

My operative managers at Stockholm County Council/Region Stockholm: **Björn Wettermark**, **Anikó Vég**, **Björn Nilsson**, **Gerd Lärfars**, and **Kristina Aggefors**, for allowing me to combine my work with a doctoral education.

Eva Andersén Karlsson, my mentor, for inspiration and wise advice on research.

Axel Carlsson, **Per Wändell**, and my fellow students at the Research School in Family Medicine, KI/SLL 2012-2014, for stimulating discussions and fun times back at school.

Colleagues at **CPE/KEP**, for interesting seminars and discussions, and a special thanks to **Miriam Qvarnström** for encouraged me in my research and for rewarding discussions on issues concerning both research and leisure.

Associates at the **Center for Gender Medicine**, for interesting seminars and conferences, and special thanks to **Britt-Marie Höglund**, **Ingeborg Eriksson**, and **Birgitta Hübinette** for administrative support and encouragement.

The expert panels of Region Stockholm Drug and Therapeutics Committee, for valuable comments on data on sex differences in your respective areas.

All physicians who participated in the focus group discussions, for your time and engagement.

Last but not least, I would like to thank my family:

Elinor and **Tarmo**, my parents, for all love and support throughout life and for always believing in me.

Anne-Marie and **Erik**, my deceased grandparents, who have encouraged me in education and in life.

William, my brother, for overnight stays in Stockholm on your sofa, well needed naprapathic treatment and nice dinners.

Johan, my love, for cheering me on and always being there for me.

Källa and **Lycke**, my beloved daughters, who have not been involved in my research at all but have enriched my life all the other time.

Funding

This research project was partly financed by my employer, the Health and Medical Care Administration, Region Stockholm, and supported by grants provided by the Swedish Association of Local Authorities and Regions (SALAR) within the Sustainable Equality Project (HÅJ) (SKL 08/2254), Region Stockholm (ALF project 20150630 and 20180302), Region Stockholm Drug and Therapeutics Committee, the Swedish Heart-Lung Foundation, and Center for Gender Medicine (Erica Lederhausen Foundation), Karolinska Institutet.

10 REFERENCES

1. Wizemann, T. and M. Pardue, *Exploring the Biological Contributions to Human Health: Does Sex Matter? Board on Health Science Policy*. 2001, Institute of Medicine: Washington, DC.
2. Uhl, K., A. Parekh, and S. Kweder, *Females in clinical studies: where are we going?* Clin Pharmacol Ther, 2007. **81**(4): p. 600-2.
3. Meibohm, B., I. Beierle, and H. Derendorf, *How important are gender differences in pharmacokinetics?* Clin Pharmacokinet, 2002. **41**(5): p. 329-42.
4. Van der Heyden, J.H., et al., *Gender differences in the use of anxiolytics and antidepressants: a population based study.* Pharmacoepidemiol Drug Saf, 2009. **18**(11): p. 1101-10.
5. Stock, S.A., et al., *Sex differences in treatment patterns of six chronic diseases: an analysis from the German statutory health insurance.* J Womens Health (Larchmt), 2008. **17**(3): p. 343-54.
6. Campbell, C.I., et al., *Age and gender trends in long-term opioid analgesic use for noncancer pain.* Am J Public Health, 2010. **100**(12): p. 2541-7.
7. Johnell, K. and J. Fastbom, *Gender and use of hypnotics or sedatives in old age: a nationwide register-based study.* Int J Clin Pharm, 2011. **33**(5): p. 788-93.
8. Johnston, N., K. Schenck-Gustafsson, and B. Lagerqvist, *Are we using cardiovascular medications and coronary angiography appropriately in men and women with chest pain?* Eur Heart J, 2011. **32**(11): p. 1331-6.
9. Klungel, O.H., et al., *Sex differences in antihypertensive drug use: determinants of the choice of medication for hypertension.* J Hypertens, 1998. **16**(10): p. 1545-53.
10. Manteuffel, M., et al., *Influence of patient sex and gender on medication use, adherence, and prescribing alignment with guidelines.* J Womens Health (Larchmt), 2014. **23**(2): p. 112-9.
11. Gyllenberg, D. and A. Sourander, *Psychotropic drug and polypharmacy use among adolescents and young adults: findings from the Finnish 1981 Nationwide Birth Cohort Study.* Nord J Psychiatry, 2012. **66**(5): p. 336-42.
12. Wigzell, O., P. Jonsson, and B. Rosén, *Jämställd vård – olika vård på lika villkor*, in *SOU 1996:133*. 1996, Socialdepartementet: Stockholm.
13. Socialstyrelsen, *Jämställd vård? Könsperspektiv på hälso- och sjukvården*. 2004: Stockholm.
14. McGregor, A.J., et al., *How to study the impact of sex and gender in medical research: a review of resources.* Biol Sex Differ, 2016. **7**(Suppl 1): p. 46.
15. Canadian Institutes of Health Research (CIHR). *What is gender? What is sex?* [cited 2020 Oct 21]; Available from: https://cihr-irsc.gc.ca/e/48642.html.
16. Hyde, J.S., et al., *The future of sex and gender in psychology: Five challenges to the gender binary.* Am Psychol, 2019. **74**(2): p. 171-93.
17. Gahagan, J., K. Gray, and A. Whynacht, *Sex and gender matter in health research: addressing health inequities in health research reporting.* Int J Equity Health, 2015. **14**: p. 12.

18. Miller, V.M., *Why are sex and gender important to basic physiology and translational and individualized medicine?* Am J Physiol Heart Circ Physiol, 2014. **306**(6): p. H781-8.

19. Clayton, J.A. and C. Tannenbaum, *Reporting Sex, Gender, or Both in Clinical Research?* JAMA, 2016. **316**(18): p. 1863-4.

20. Doyal, L., *Sex and gender: the challenges for epidemiologists.* Int J Health Serv, 2003. **33**(3): p. 569-79.

21. Hankivsky, O., *Women's health, men's health, and gender and health: implications of intersectionality.* Soc Sci Med, 2012. **74**(11): p. 1712-20.

22. Mauvais-Jarvis, F., et al., *Sex and gender: modifiers of health, disease, and medicine.* Lancet, 2020. **396**(10250): p. 565-82.

23. Shah, K., C.E. McCormack, and N.A. Bradbury, *Do you know the sex of your cells?* Am J Physiol Cell Physiol, 2014. **306**(1): p. C3-18.

24. Galdas, P.M., F. Cheater, and P. Marshall, *Men and health help-seeking behaviour: literature review.* J Adv Nurs, 2005. **49**(6): p. 616-23.

25. Gough, B. and I. Novikova, *WHO Health Evidence Network Synthesis Reports*, in *Mental health, men and culture: how do sociocultural constructions of masculinities relate to men's mental health help-seeking behaviour in the WHO European Region?* 2020, WHO Regional Office for Europe: Copenhagen.

26. Regitz-Zagrosek, V., *Sex and gender differences in health. Science & Society Series on Sex and Science.* EMBO Rep, 2012. **13**(7): p. 596-603.

27. Wainer, J. and Z. Wainer, *Gender Matters*, in *Handbook of Clinical Gender Medicine*, K. Schenck-Gustafsson, et al., Editors. 2012, Karger: Basel. p. 1-4.

28. Umscheid, C.A., D.J. Margolis, and C.E. Grossman, *Key concepts of clinical trials: a narrative review.* Postgrad Med, 2011. **123**(5): p. 194-204.

29. Pinnow, E., et al., *Increasing participation of women in early phase clinical trials approved by the FDA.* Womens Health Issues, 2009. **19**(2): p. 89-93.

30. Poon, R., et al., *Participation of women and sex analyses in late-phase clinical trials of new molecular entity drugs and biologics approved by the FDA in 2007-2009.* J Womens Health (Larchmt), 2013. **22**(7): p. 604-16.

31. Downing, N.S., et al., *Participation of the elderly, women, and minorities in pivotal trials supporting 2011-2013 U.S. Food and Drug Administration approvals.* Trials, 2016. **17**: p. 199.

32. Chen, A., et al., *Representation of Women and Minorities in Clinical Trials for New Molecular Entities and Original Therapeutic Biologics Approved by FDA CDER from 2013 to 2015.* J Womens Health (Larchmt), 2018. **27**(4): p. 418-29.

33. Ayuso, E., et al., *Evaluation of worldwide clinical trials by gender: An FDA perspective.* Contemp Clin Trials, 2019. **80**: p. 16-21.

34. Feldman, S., et al., *Quantifying Sex Bias in Clinical Studies at Scale With Automated Data Extraction.* JAMA Netw Open, 2019. **2**(7): p. e196700.

35. Scott, P.E., et al., *Participation of Women in Clinical Trials Supporting FDA Approval of Cardiovascular Drugs.* J Am Coll Cardiol, 2018. **71**(18): p. 1960-9.

36. Reusch, J.E.B., et al., *Identifying the Critical Gaps in Research on Sex Differences in Metabolism Across the Life Span.* Endocrinology, 2018. **159**(1): p. 9-19.

37. Clayton, J.A. and F.S. Collins, *Policy: NIH to balance sex in cell and animal studies.* Nature, 2014. **509**(7500): p. 282-3.

38. Tannenbaum, C., et al., *Sex and gender analysis improves science and engineering.* Nature, 2019. **575**(7781): p. 137-46.

39. Anderson, G.D., *Sex and racial differences in pharmacological response: where is the evidence? Pharmacogenetics, pharmacokinetics, and pharmacodynamics.* J Womens Health (Larchmt), 2005. **14**(1): p. 19-29.

40. Heidari, S., et al., *Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use.* Res Integr Peer Rev, 2016. **1**: p. 2.

41. Schiebinger, L., S.S. Leopold, and V.M. Miller, *Editorial policies for sex and gender analysis.* Lancet, 2016. **388**(10062): p. 2841-2.

42. Spierings, N., *The inclusion of quantitative techniques and diversity in the mainstream of feminist research.* European Journal of Women's Studies, 2012. **19**(3): p. 331-47.

43. Soldin, O.P. and D.R. Mattison, *Sex differences in pharmacokinetics and pharmacodynamics.* Clin Pharmacokinet, 2009. **48**(3): p. 143-57.

44. Franconi, F. and I. Campesi, *Pharmacogenomics, pharmacokinetics and pharmacodynamics: interaction with biological differences between men and women.* Br J Pharmacol, 2014. **171**(3): p. 580-94.

45. Farkouh, A., et al., *Sex-Related Differences in Pharmacokinetics and Pharmacodynamics of Frequently Prescribed Drugs: A Review of the Literature.* Adv Ther, 2020. **37**(2): p. 644-55.

46. Franconi, F., et al., *Gender differences in drug responses.* Pharmacol Res, 2007. **55**(2): p. 81-95.

47. Schwartz, J.B., *The influence of sex on pharmacokinetics.* Clin Pharmacokinet, 2003. **42**(2): p. 107-21.

48. Soldin, O.P., S.H. Chung, and D.R. Mattison, *Sex differences in drug disposition.* J Biomed Biotechnol, 2011. **2011**: p. 187103.

49. Zucker, I. and B.J. Prendergast, *Sex differences in pharmacokinetics predict adverse drug reactions in women.* Biol Sex Differ, 2020. **11**(1): p. 32.

50. Tamargo, J., et al., *Gender differences in the effects of cardiovascular drugs.* Eur Heart J Cardiovasc Pharmacother, 2017. **3**(3): p. 163-82.

51. Spoletini, I., et al., *Sex differences in drug effects: interaction with sex hormones in adult life.* Handb Exp Pharmacol, 2012(214): p. 91-105.

52. January, C.T., et al., *2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society.* J Am Coll Cardiol, 2014. **64**(21): p. e1-76.

53. Kirchhof, P., et al., *2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS.* Eur Heart J, 2016. **37**(38): p. 2893-962.

54. Linde, C., et al., *Sex differences in cardiac arrhythmia: a consensus document of the European Heart Rhythm Association, endorsed by the Heart Rhythm Society and Asia Pacific Heart Rhythm Society.* Europace, 2018. **20**(10): p. 1565-1565ao.

55. U.S. Food and Drug Administration. *FDA Drug Safety Communication: FDA approves new label changes and dosing for zolpidem products and a recommendation to avoid driving the day after using Ambien CR.* 2013 [cited 2021 Feb 12]; Available from: http://www.fda.gov/Drugs/DrugSafety/ucm352085.htm.

56. European Medicines Agency. *New advice to minimise risk of next-morning impaired driving ability and mental alertness with zolpidem. EMA/427574/2014*. 2014 [cited 2021 Feb 12]; Available from: https://www.ema.europa.eu/en/medicines/human/referrals/zolpidem-containing-medicines.

57. Hodson, R., *Precision medicine.* Nature, 2016. **537**(7619): p. S49.

58. McGrath, S. and D. Ghersi, *Building towards precision medicine: empowering medical professionals for the next revolution.* BMC Med Genomics, 2016. **9**(1): p. 23.

59. Strom, B.L., *What is Pharmacoepidemiology?*, in *Pharmacoepidemiology*, B.L. Strom, S.E. Kimmel, and S. Hennessy, Editors. 2019, Wiley-Blackwell. p. 1-26.

60. World Health Organization (WHO), *The selection of essential drugs. World Health Organization Technical Report Series No. 615*. 1977: Geneva, Switzerland.

61. Wettermark, B., et al., *Drug utilization research*, in *Pharmacoepidemiology and Therapeutic Risk Management*, A. Hartzema, H. Tilson, and K. Chan, Editors. 2008, Harvey Whitney Books: Cincinnati, OH, USA. p. 159-95.

62. Wettermark, B., et al., *Introduction to drug utilization research*, in *Drug Utilization Research: Methods and Applications*, M. Elseviers, et al., Editors. 2016, John Wiley & Sons, Ltd. p. 3-12.

63. Wettermark, B., M. Di Martino, and M. Elseviers, *Study designs in drug utilization research*, in *Drug Utilization Research: Methods and Applications*, M. Elseviers, et al., Editors. 2016, John Wiley & Sons, Ltd. p. 15-28.

64. Zhao, M., et al., *Sex Differences in Cardiovascular Medication Prescription in Primary Care: A Systematic Review and Meta-Analysis.* J Am Heart Assoc, 2020. **9**(11): p. e014742.

65. Johnston, N., et al., *Do clinical factors explain persistent sex disparities in the use of acute reperfusion therapy in STEMI in Sweden and Canada?* Eur Heart J Acute Cardiovasc Care, 2013. **2**(4): p. 350-8.

66. Wettermark, B., A. Persson, and M. von Euler, *Secondary prevention in a large stroke population: a study of patients' purchase of recommended drugs.* Stroke, 2008. **39**(10): p. 2880-5.

67. Kapral, M.K., et al., *Gender differences in stroke care and outcomes in Ontario.* Womens Health Issues, 2011. **21**(2): p. 171-6.

68. Cho, L., et al., *Gender differences in utilization of effective cardiovascular secondary prevention: a Cleveland clinic prevention database study.* J Womens Health (Larchmt), 2008. **17**(4): p. 515-21.

69. Stramba-Badiale, M., *Women and research on cardiovascular diseases in Europe: a report from the European Heart Health Strategy (EuroHeart) project.* European Heart Journal, 2010. **31**(14): p. 1677-1681D.

70. Forslund, T., et al., *Risk scoring and thromboprophylactic treatment of patients with atrial fibrillation with and without access to primary healthcare data: experience from the Stockholm health care system.* Int J Cardiol, 2013. **170**(2): p. 208-14.

71. Gu, Q., et al., *Gender differences in hypertension treatment, drug utilization patterns, and blood pressure control among US adults with hypertension: data from the National Health and Nutrition Examination Survey 1999-2004.* Am J Hypertens, 2008. **21**(7): p. 789-98.

72. Klungel, O.H., et al., *Sex differences in the pharmacological treatment of hypertension: a review of population-based studies.* J Hypertens, 1997. **15**(6): p. 591-600.

73. Ljungman, C., et al., *Gender differences in antihypertensive drug treatment: results from the Swedish Primary Care Cardiovascular Database (SPCCD).* J Am Soc Hypertens, 2014. **8**(12): p. 882-90.

74. Qvarnstrom, M., et al., *Antihypertensive treatment and control in a large primary care population of 21 167 patients.* J Hum Hypertens, 2011. **25**(8): p. 484-91.

75. Wallentin, F., B. Wettermark, and T. Kahan, *Drug treatment of hypertension in Sweden in relation to sex, age, and comorbidity.* J Clin Hypertens (Greenwich), 2018. **20**(1): p. 106-14.

76. Sketris, I.S., E. Langille Ingram, and H. Lummis, *Optimal prescribing and medication use in Canada: Challenges and opportunities.* 2007: Ottawa, Canada.

77. Banks, I. and P. Baker, *Men and primary care: improving access and outcomes.* Trends in Urology & Men's Health, 2013. **4**: p. 39-41.

78. Vaidya, V., G. Partha, and M. Karmakar, *Gender differences in utilization of preventive care services in the United States.* J Womens Health (Larchmt), 2012. **21**(2): p. 140-5.

79. Wang, Y., et al., *Do men consult less than women? An analysis of routinely collected UK general practice data.* BMJ Open, 2013. **3**(8): p. e003320.

80. Hohn, A., et al., *Do men avoid seeking medical advice? A register-based analysis of gender-specific changes in primary healthcare use after first hospitalisation at ages 60+ in Denmark.* J Epidemiol Community Health, 2020. **74**(7): p. 573-9.

81. Osika Friberg, I., et al., *Sex differences in health care consumption in Sweden: A register-based cross-sectional study.* Scand J Public Health, 2016. **44**(3): p. 264-73.

82. Yousaf, O., E.A. Grunfeld, and M.S. Hunter, *A systematic review of the factors associated with delays in medical and psychological help-seeking among men.* Health Psychol Rev, 2015. **9**(2): p. 264-76.

83. Bertakis, K.D., *The influence of gender on the doctor-patient interaction.* Patient Educ Couns, 2009. **76**(3): p. 356-60.

84. Sandhu, H., et al., *The impact of gender dyads on doctor-patient communication: a systematic review.* Patient Educ Couns, 2009. **76**(3): p. 348-55.

85. Jefferson, L., et al., *Effect of physicians' gender on communication and consultation length: a systematic review and meta-analysis.* J Health Serv Res Policy, 2013. **18**(4): p. 242-8.

86. Lee, S.Q., et al., *Reasons for Primary Medication Nonadherence: A Systematic Review and Metric Analysis.* J Manag Care Spec Pharm, 2018. **24**(8): p. 778-94.

87. Vrijens, B., et al., *A new taxonomy for describing and defining adherence to medications.* Br J Clin Pharmacol, 2012. **73**(5): p. 691-705.

88. Lemstra, M., et al., *Primary nonadherence to chronic disease medications: a meta-analysis.* Patient Prefer Adherence, 2018. **12**: p. 721-31.

89. Adams, A.J. and S.F. Stolpe, *Defining and Measuring Primary Medication Nonadherence: Development of a Quality Measure.* J Manag Care Spec Pharm, 2016. **22**(5): p. 516-23.

90. Raebel, M.A., et al., *Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases.* Med Care, 2013. **51**(8 Suppl 3): p. S11-21.

91. Vrijens, B., *An introduction to adherence research,* in *Drug Utilization Research: Methods and Applications,* M. Elseviers, et al., Editors. 2016, John Wiley & Sons, Ltd. p. 355-60.

92. Kardas, P., et al., *Primary nonadherence to medication and its drivers in Poland: findings from the electronic prescription pilot analysis.* Pol Arch Intern Med, 2020. **130**(1): p. 8-16.

93. Ax, F. and A. Ekedahl, *Electronically transmitted prescriptions not picked up at pharmacies in Sweden.* Res Social Adm Pharm, 2010. **6**(1): p. 70-7.

94. Freccero, C., et al., *Primary adherence to antidepressant prescriptions in primary health care: a population-based study in Sweden.* Scand J Prim Health Care, 2016. **34**(1): p. 83-8.

95. Pottegård, A., et al., *Primary non-adherence in general practice: a Danish register study.* Eur J Clin Pharmacol, 2014. **70**(6): p. 757-63.

96. Rolnick, S.J., et al., *Patient characteristics associated with medication adherence.* Clin Med Res, 2013. **11**(2): p. 54-65.

97. Lewey, J., et al., *Gender and racial disparities in adherence to statin therapy: a meta-analysis.* Am Heart J, 2013. **165**(5): p. 665-78, 678 e1.

98. Goldstein, K.M., et al., *Statin Adherence: Does Gender Matter?* Curr Atheroscler Rep, 2016. **18**(11): p. 63.

99. Ingersgaard, M.V., et al., *Reasons for Nonadherence to Statins - A Systematic Review of Reviews.* Patient Prefer Adherence, 2020. **14**: p. 675-91.

100. Ewen, S., et al., *Drug adherence in patients taking oral anticoagulation therapy.* Clin Res Cardiol, 2014. **103**(3): p. 173-82.

101. Biffi, A., et al., *Sex differences in the adherence of antihypertensive drugs: a systematic review with meta-analyses.* BMJ Open, 2020. **10**(7): p. e036418.

102. Thunander Sundbom, L. and K. Bingefors, *Women and men report different behaviours in, and reasons for medication non-adherence: a nationwide Swedish survey.* Pharm Pract (Granada), 2012. **10**(4): p. 207-21.

103. Krivoy, A., et al., *The impact of age and gender on adherence to antidepressants: a 4-year population-based cohort study.* Psychopharmacology (Berl), 2015. **232**(18): p. 3385-90.

104. Qvarnstrom, M., et al., *Persistence to antihypertensive drug treatment in Swedish primary healthcare.* Eur J Clin Pharmacol, 2013. **69**(11): p. 1955-64.

105. Halava, H., et al., *Lifestyle factors as predictors of nonadherence to statin therapy among patients with and without cardiovascular comorbidities.* Cmaj, 2014. **186**(12): p. E449-56.

106. Forslund, T., B. Wettermark, and P. Hjemdahl, *Comparison of treatment persistence with different oral anticoagulants in patients with atrial fibrillation.* Eur J Clin Pharmacol, 2016. **72**(3): p. 329-38.

107. Dahlén, E., *Drug utilization in children with asthma - methodological approaches and practical implications*, in *Department of Medicine, Solna*. 2019, Karolinska Institutet: Stockholm, Sweden.

108. Nebeker, J.R., P. Barach, and M.H. Samore, *Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting.* Ann Intern Med, 2004. **140**(10): p. 795-801.

109. van den Bemt, P. and A. Egberts, *Drug related problems: Definitions and classification.* Eur J Hosp Pharm Pract, 2007. **13**: p. 62-4.

110. Rang, H.P., et al., *Harmful effects of drugs*, in *Pharmacology 5th Edition*. 2003, Churchill Livingstone: Edinburgh. p. 724-37.

111. European Medicines Agency, *From laboratory to patient: the journey of a medicine assessed by EMA*. 2019, European Medicines Agency.

112. Pasquali, S.K., et al., *Status of the pediatric clinical trials enterprise: an analysis of the US ClinicalTrials.gov registry.* Pediatrics, 2012. **130**(5): p. e1269-77.

113. European Medicines Agency. *Pharmacovigilance: Overview*. 2020 [cited 2020 Dec 10]; Available from: https://www.ema.europa.eu/en/human-regulatory/overview/pharmacovigilance-overview.

114. The Swedish Medical Products Agency. *Misstänkt biverkning hos människa*. 2021 [cited 2021 Feb 18]; Available from: https://www.lakemedelsverket.se/sv/rapportera-biverkningar/lakemedel/misstankt-biverkning-hos-manniska.

115. Uppsala Monitoring Centre. *VigiBase*. 2020 [cited 2020 Jan 16]; Available from: https://www.who-umc.org/vigibase/vigibase/.

116. Wiholm, B.-E., et al., *Spontaneous reporting systems outside the US*, in *Pharmacoepidemiology (3rd ed.)*, B. Strom, Editor. 2000, John Wiley & Sons Ltd.: Chichester, UK. p. 175–92.

117. Vaismoradi, M., et al., *Adverse Drug Reactions in Norway: A Systematic Review.* Pharmacy (Basel), 2019. **7**(3).

118. Fjermeros, K., et al., *[Patient reporting of adverse drug reactions in Norway 2010-13].* Tidsskr Nor Laegeforen, 2015. **135**(6): p. 536-40.

119. Nicolson, T.J., H.R. Mellor, and R.R. Roberts, *Gender differences in drug toxicity.* Trends Pharmacol Sci, 2010. **31**(3): p. 108-14.

120. Vinge, E., *[Men and women respond differently to drugs. Hormone-dependent pharmacodynamic differences are rarely studied].* Lakartidningen, 1998. **95**(28-29): p. 3177-82.

121. Holm, L., E. Ekman, and K. Jorsater Blomgren, *Influence of age, sex and seriousness on reporting of adverse drug reactions in Sweden.* Pharmacoepidemiol Drug Saf, 2017. **26**(3): p. 335-43.

122. Martin, R.M., et al., *Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: analysis of 48 cohort studies.* Br J Clin Pharmacol, 1998. **46**(5): p. 505-11.

123. Watson, S., et al., *Reported adverse drug reactions in women and men: Aggregated evidence from globally collected individual case reports during half a century.* EClinicalMedicine, 2019. **17**: p. 100188.

124. D'Incau, P., et al., *No differences between men and women in adverse drug reactions related to psychotropic drugs: a survey from France, Italy and Spain.* Fundam Clin Pharmacol, 2014. **28**(3): p. 342-8.

125. Park, H.H., et al., *Gender differences in the adverse events associated with cardiovascular drugs in a spontaneous reporting system in South Korea.* Int J Clin Pharm, 2021.

126. Zoni-Berisso, M., et al., *Epidemiology of atrial fibrillation: European perspective.* Clin Epidemiol, 2014. **6**: p. 213-20.

127. Friberg, L. and L. Bergfeldt, *Atrial fibrillation prevalence revisited.* J Intern Med, 2013. **274**(5): p. 461-8.

128. Kavousi, M., *Differences in Epidemiology and Risk Factors for Atrial Fibrillation Between Women and Men.* Front Cardiovasc Med, 2020. **7**: p. 3.

129. Ko, D., et al., *Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis.* Nat Rev Cardiol, 2016. **13**(6): p. 321-32.

130. Emdin, C.A., et al., *Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies.* BMJ, 2016. **532**: p. h7013.

131. Wagstaff, A.J., et al., *Is female sex a risk factor for stroke and thromboembolism in patients with atrial fibrillation? A systematic review and meta-analysis.* Qjm, 2014. **107**(12): p. 955-67.

132. Poli, D. and E. Antonucci, *Epidemiology, diagnosis, and management of atrial fibrillation in women.* Int J Womens Health, 2015. **7**: p. 605-14.

133. Marzona, I., et al., *Sex differences in stroke and major adverse clinical events in patients with atrial fibrillation: A systematic review and meta-analysis of 993,600 patients.* Int J Cardiol, 2018. **269**: p. 182-91.

134. Amaraneni, A., V. Chippa, and A.C. Rettew, *Anticoagulation Safety*, in *StatPearls*. 2020: Treasure Island (FL).

135. Camm, A.J., et al., *2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial*

fibrillation--developed with the special contribution of the European Heart Rhythm Association. Europace, 2012. **14**(10): p. 1385-413.

136. Pisters, R., et al., *A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey.* Chest, 2010. **138**(5): p. 1093-100.

137. Hindricks, G., et al., *2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS).* Eur Heart J, 2020.

138. January, C.T., et al., *2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons.* Circulation, 2019. **140**(2): p. e125-e151.

139. NHFA CSANZ Atrial Fibrillation Guideline Working Group, et al., *National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation 2018.* Heart Lung Circ, 2018. **27**(10): p. 1209-66.

140. Lip, G.Y., et al., *Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation.* Chest, 2010. **137**(2): p. 263-72.

141. Nielsen, P.B., et al., *Female Sex Is a Risk Modifier Rather Than a Risk Factor for Stroke in Atrial Fibrillation: Should We Use a CHA2DS2-VA Score Rather Than CHA2DS2-VASc?* Circulation, 2018. **137**(8): p. 832-40.

142. Friberg, L., et al., *Assessment of female sex as a risk factor in atrial fibrillation in Sweden: nationwide retrospective cohort study.* BMJ, 2012. **344**: p. e3522.

143. Zhu, W., et al., *The HAS-BLED Score for Predicting Major Bleeding Risk in Anticoagulated Patients With Atrial Fibrillation: A Systematic Review and Meta-analysis.* Clin Cardiol, 2015. **38**(9): p. 555-61.

144. Kuruvilla, M. and C. Gurk-Turner, *A review of warfarin dosing and monitoring.* Proc (Bayl Univ Med Cent), 2001. **14**(3): p. 305-6.

145. Ruff, C.T., et al., *Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials.* Lancet, 2014. **383**(9921): p. 955-62.

146. Vazquez, S.R., *Drug-drug interactions in an era of multiple anticoagulants: a focus on clinically relevant drug interactions.* Hematology Am Soc Hematol Educ Program, 2018. **2018**(1): p. 339-47.

147. Forslund, T., et al., *Improved Stroke Prevention in Atrial Fibrillation After the Introduction of Non-Vitamin K Antagonist Oral Anticoagulants.* Stroke, 2018. **49**(9): p. 2122-8.

148. Gallu, M., et al., *Female Sex as a Thromboembolic Risk Factor in the Era of Nonvitamin K Antagonist Oral Anticoagulants.* Cardiovasc Ther, 2020. **2020**: p. 1743927.

149. Gelosa, P., et al., *Pharmacokinetic drug interactions of the non-vitamin K antagonist oral anticoagulants (NOACs).* Pharmacol Res, 2018. **135**: p. 60-79.

150. Tan, C.S.S. and S.W.H. Lee, *Warfarin and food, herbal or dietary supplement interactions: A systematic review.* Br J Clin Pharmacol, 2021. **87**(2): p. 352-74.

151. Ogilvie, I.M., et al., *Underuse of oral anticoagulants in atrial fibrillation: a systematic review.* Am J Med, 2010. **123**(7): p. 638-45 e4.

152. Alamneh, E.A., L. Chalmers, and L.R. Bereznicki, *Suboptimal Use of Oral Anticoagulants in Atrial Fibrillation: Has the Introduction of Direct Oral Anticoagulants Improved Prescribing Practices?* Am J Cardiovasc Drugs, 2016. **16**(3): p. 183-200.

153. Bezabhe, W.M., et al., *Factors influencing oral anticoagulant use in patients newly diagnosed with atrial fibrillation.* Eur J Clin Invest, 2020: p. e13457.

154. Lip, G.Y., et al., *Does sex affect anticoagulant use for stroke prevention in nonvalvular atrial fibrillation? The prospective global anticoagulant registry in the FIELD-Atrial Fibrillation.* Circ Cardiovasc Qual Outcomes, 2015. **8**(2 Suppl 1): p. S12-20.

155. Guo, Y., et al., *Time Trends of Aspirin and Warfarin Use on Stroke and Bleeding Events in Chinese Patients With New-Onset Atrial Fibrillation.* Chest, 2015. **148**(1): p. 62-72.

156. Huisman, M.V., et al., *The Changing Landscape for Stroke Prevention in AF: Findings From the GLORIA-AF Registry Phase 2.* J Am Coll Cardiol, 2017. **69**(7): p. 777-85.

157. Ng, V.W.S., et al., *Understanding the barriers to using oral anticoagulants among long-term aspirin users with atrial fibrillation - a qualitative study.* BMC Health Serv Res, 2020. **20**(1): p. 1084.

158. Wiffen, P.J., et al., *Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews.* Cochrane Database Syst Rev, 2013(11): p. CD010567.

159. Ovsiew, F., *Antiepileptic drugs in psychiatry.* J Neurol Neurosurg Psychiatry, 2004. **75**(12): p. 1655-8.

160. Bagnato, F. and J. Good, *The Use of Antiepileptics in Migraine Prophylaxis.* Headache, 2016. **56**(3): p. 603-15.

161. Perucca, E., *Antiepileptic drugs: evolution of our knowledge and changes in drug trials.* Epileptic Disord, 2019. **21**(4): p. 319-29.

162. Abou-Khalil, B.W., *Update on Antiepileptic Drugs 2019.* Continuum (Minneap Minn), 2019. **25**(2): p. 508-36.

163. Kumlien, E., H. Sundelin, and K. Söderberg Löfdal, *Principer för farmakologisk behandling.* Information från Läkemedelsverket. **2019;30**(3): p. 7-9.

164. Tomson, T., et al., *Management of epilepsy in pregnancy: a report from the International League Against Epilepsy Task Force on Women and Pregnancy.* Epileptic Disord, 2019. **21**(6): p. 497-517.

165. European Medicines Agency. *CMDh agrees to strengthen warnings on the use of valproate medicines in women and girls*. 2014 [cited 2021 Jan 25]; Available from: https://www.ema.europa.eu/en/news/cmdh-agrees-strengthen-warnings-use-valproate-medicines-women-girls.

166. Svalheim, S., et al., *Interactions between antiepileptic drugs and hormones.* Seizure, 2015. **28**: p. 12-7.

167. Salpekar, J.A. and M. Mula, *Common psychiatric comorbidities in epilepsy: How big of a problem is it?* Epilepsy Behav, 2019. **98**(Pt B): p. 293-7.

168. Dussaule, C. and V. Bouilleret, *Psychiatric effects of antiepileptic drugs in adults.* Geriatr Psychol Neuropsychiatr Vieil, 2018. **16**(2): p. 181-8.

169. Zaccara, G. and E. Perucca, *Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs.* Epileptic Disord, 2014. **16**(4): p. 409-31.

170. Fisher, R.S., et al., *ILAE official report: a practical clinical definition of epilepsy.* Epilepsia, 2014. **55**(4): p. 475-82.

171. *Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy.* Epilepsia, 1993. **34**(4): p. 592-6.

172. Zhang, C., et al., *Risk factors for post-stroke seizures: a systematic review and meta-analysis.* Epilepsy Res, 2014. **108**(10): p. 1806-16.

173. Zhao, Y., et al., *The Progress of Epilepsy after Stroke.* Curr Neuropharmacol, 2018. **16**(1): p. 71-8.

174. Brodie, M.J., A.T. Elder, and P. Kwan, *Epilepsy in later life.* Lancet Neurol, 2009. **8**(11): p. 1019-30.

175. Sarecka-Hujar, B. and I. Kopyta, *Poststroke epilepsy: current perspectives on diagnosis and treatment.* Neuropsychiatr Dis Treat, 2019. **15**: p. 95-103.

176. Zelano, J., *Poststroke epilepsy: update and future directions.* Ther Adv Neurol Disord, 2016. **9**(5): p. 424-35.

177. Doria, J.W. and P.B. Forgacs, *Incidence, Implications, and Management of Seizures Following Ischemic and Hemorrhagic Stroke.* Curr Neurol Neurosci Rep, 2019. **19**(7): p. 37.

178. Wang, J.Z., et al., *Incidence and management of seizures after ischemic stroke: Systematic review and meta-analysis.* Neurology, 2017. **89**(12): p. 1220-8.

179. Feyissa, A.M., T.F. Hasan, and J.F. Meschia, *Stroke-related epilepsy.* Eur J Neurol, 2019. **26**(1): p. 18-e3.

180. Holtkamp, M., et al., *European Stroke Organisation guidelines for the management of post-stroke seizures and epilepsy.* 2017. **2**(2): p. 103-15.

181. Sykes, L., E. Wood, and J. Kwan, *Antiepileptic drugs for the primary and secondary prevention of seizures after stroke.* Cochrane Database Syst Rev, 2014(1): p. Cd005398.

182. Anell, A., A.H. Glenngard, and S. Merkur, *Sweden health system review.* Health Syst Transit, 2012. **14**(5): p. 1-159.

183. Sveriges Kommuner och Regioner *Patientavgifter i öppen hälso- och sjukvård år 2021*. 2021.

184. The Dental and Pharmaceutical Benefits Agency (TLV). *What is the high cost threshold?/How it works*. 2021 [cited 2021 Feb 18]; Available from: https://www.tlv.se/in-english/medicines/what-is-the-high-cost-threshold/how-it-works.html.

185. Rothman, K.J., *Types of Epidemiologic Study*, in *Epidemiology : an introduction*. 2002, Oxford University Press Inc.: New York. p. 57-93.

186. Kesmodel, U.S., *Cross-sectional studies - what are they good for?* Acta Obstet Gynecol Scand, 2018. **97**(4): p. 388-93.

187. Patton, M., *Qualitative Research & Evaluation Methods*. Vol. 3 ed. 2002: SAGE.

188. Ludvigsson, J.F., et al., *The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research.* Eur J Epidemiol, 2009. **24**(11): p. 659-67.

189. Sorensen, H.T., S. Sabroe, and J. Olsen, *A framework for evaluation of secondary data sources for epidemiological research.* Int J Epidemiol, 1996. **25**(2): p. 435-42.

190. Harpe, S.E., *Using secondary data sources for pharmacoepidemiology and outcomes research.* Pharmacotherapy, 2009. **29**(2): p. 138-53.

191. Eriksson, I. and L. Ibáñez, *Secondary data sources for drug utilization research*, in *Drug Utilization Research: Methods and Applications*, M. Elseviers, et al., Editors. 2016, John Wiley & Sons, Ltd. p. 39-48.

192. Coorevits, P., et al., *Electronic health records: new opportunities for clinical research.* J Intern Med, 2013. **274**(6): p. 547-60.

193. National Board of Health and Welfare. *The Swedish Prescribed Drug Register*. 2020 [cited 2020 Sep 21]; Available from: https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/the-swedish-prescribed-drug-register/.

194. Wettermark, B., et al., *The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months.* Pharmacoepidemiol Drug Saf, 2007. **16**(7): p. 726-35.

195. WHO Collaborating Centre for Drug Statistics Methodology. *ATC/DDD Index 2020*. 2020 [cited 2020 Nov 4]; Available from: https://www.whocc.no/atc_ddd_index/.

196. Furu, K., et al., *The Nordic countries as a cohort for pharmacoepidemiological research.* Basic Clin Pharmacol Toxicol, 2010. **106**(2): p. 86-94.

197. Carlsson, A.C., et al., *High prevalence of diagnosis of diabetes, depression, anxiety, hypertension, asthma and COPD in the total population of Stockholm, Sweden - a challenge for public health.* BMC Public Health, 2013. **13**: p. 670.

198. Zarrinkoub, R., et al., *The epidemiology of heart failure, based on data for 2.1 million inhabitants in Sweden.* Eur J Heart Fail, 2013. **15**(9): p. 995-1002.

199. Cars, T., et al., *Healthcare Utilisation and Drug Treatment in a Large Cohort of Patients with Inflammatory Bowel Disease.* J Crohns Colitis, 2016. **10**(5): p. 556-65.

200. Dahlen, E., et al., *Eliminated patient fee and changes in dispensing patterns of asthma medication in children-An interrupted time series analysis.* Basic Clin Pharmacol Toxicol, 2019. **125**(4): p. 360-9.

201. Wandell, P., et al., *Most common diseases diagnosed in primary care in Stockholm, Sweden, in 2011.* Fam Pract, 2013. **30**(5): p. 506-13.

202. Brostedt, E.M., et al., *Health care use, drug treatment and comorbidity in patients with schizophrenia or non-affective psychosis in Sweden: a cross-sectional study.* BMC Psychiatry, 2017. **17**(1): p. 416.

203. Karlsson Lind, L., et al., *Valproic acid utilization among girls and women in Stockholm: Impact of regulatory restrictions.* Epilepsia Open, 2018. **3**(3): p. 357-63.

204. Ludvigsson, J.F., et al., *External review and validation of the Swedish national inpatient register.* BMC Public Health, 2011. **11**: p. 450.

205. Hazell, L. and S.A. Shakir, *Under-reporting of adverse drug reactions : a systematic review.* Drug Saf, 2006. **29**(5): p. 385-96.

206. Lopez-Gonzalez, E., M.T. Herdeiro, and A. Figueiras, *Determinants of under-reporting of adverse drug reactions: a systematic review.* Drug Saf, 2009. **32**(1): p. 19-31.

207. Backstrom, M., T. Mjorndal, and R. Dahlqvist, *Under-reporting of serious adverse drug reactions in Sweden.* Pharmacoepidemiol Drug Saf, 2004. **13**(7): p. 483-7.

208. Wester, K., et al., *Spontaneously reported fatal suspected adverse drug reactions: a 10-year survey from Sweden.* Pharmacoepidemiol Drug Saf, 2007. **16**(2): p. 173-80.

209. Uppsala Monitoring Centre. *Glossary of pharmacovigilance terms*. 2020 [cited 2021 Feb 9]; Available from: https://www.who-umc.org/global-pharmacovigilance/publications/glossary/.

210. Uppsala Monitoring Centre (UMC). *The use of the WHO-UMC system for standardised case causality assessment*. 2008 [cited 2021 Feb 9]; Available from: https://www.who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf.

211. Pope, C. and N. Mays, *Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research.* BMJ, 1995. **311**(6996): p. 42-5.

212. Krueger, R.A. and M.A. Casey, *Focus groups : a practical guide for applied research*. 4th [updated] ed. 2009, Thousand Oaks, California: Sage Publications.

213. Malterud, K., *Kvalitativa metoder i medicinsk forskning*. Vol. 2 ed. 2009, Lund: Studentlitteratur AB.

214. Wibeck, V., *Fokusgrupper : om fokuserade gruppintervjuer som undersökningsmetod*. 2010, Lund: Studentlitteratur AB.

215. Saunders, B., et al., *Saturation in qualitative research: exploring its conceptualization and operationalization.* Qual Quant, 2018. **52**(4): p. 1893-1907.

216. Hallas, J., H. Støvring, and A. Pottegård, *Individual-level drug utilization analyses*, in *Drug Utilization Research: Methods and Applications*, M. Elseviers, et al., Editors. 2016, John Wiley & Sons, Ltd. p. 68-76.

217. Wirehn, A.B., H.M. Karlsson, and J.M. Carstensen, *Estimating disease prevalence using a population-based administrative healthcare database.* Scand J Public Health, 2007. **35**(4): p. 424-31.

218. Larsson, D., et al., *Retention rate of first antiepileptic drug in poststroke epilepsy: A nationwide study.* Seizure, 2019. **64**: p. 29-33.

219. Redfors, P., et al., *Long-term follow-up of post-stroke epilepsy after ischemic stroke: Room for improved epilepsy treatment.* Seizure, 2020. **76**: p. 50-5.

220. Huang, Y.H., et al., *Efficacy of phenytoin, valproic acid, carbamazepine and new antiepileptic drugs on control of late-onset post-stroke epilepsy in Taiwan.* Eur J Neurol, 2015. **22**(11): p. 1459-68.

221. Chan, L., et al., *Incidence of poststroke seizures: A meta-analysis.* J Clin Neurosci, 2018. **47**: p. 347-51.

222. Xu, M.Y., *Poststroke seizure: optimising its management.* Stroke Vasc Neurol, 2019. **4**(1): p. 48-56.

223. Hassani, M., et al., *Post-stroke epilepsy in an ischemic stroke cohort-Incidence and diagnosis.* Acta Neurol Scand, 2020. **141**(2): p. 141-47.

224. Rothman, K.J., *Measuring Disease Occurrence and Causal Effects*, in *Epidemiology : an introduction*. 2002, Oxford University Press Inc.: New York. p. 24-56.

225. Clark, R.C., et al., *The influence of primary care prescribing rates for new drugs on spontaneous reporting of adverse drug reactions.* Drug Saf, 2007. **30**(4): p. 357-66.

226. Bégaud, B., *Statistical methods of evaluating pharmacovigilance data*, in *Pharmacovigilance*, R. Mann and E. Andrews, Editors. 2002, John Wiley & Sons: Chichester, England. p. 281–9.

227. Wallerstedt, S.M., G. Brunlof, and A. Sundstrom, *Rates of spontaneous reports of adverse drug reactions for drugs reported in children: a cross-sectional study with data from the Swedish adverse drug reaction database and the Swedish Prescribed Drug Register.* Drug Saf, 2011. **34**(8): p. 669-82.

228. Grégoire, J.-P. and J. Moisan, *Assessment of adherence to drug treatment in database research*, in *Drug Utilization Research: Methods and Applications*, M. Elseviers, et al., Editors. 2016, John Wiley & Sons, Ltd. p. 369-80.

229. Caetano, P.A., J.M. Lam, and S.G. Morgan, *Toward a standard definition and measurement of persistence with drug therapy: Examples from research on statin and antihypertensive utilization.* Clin Ther, 2006. **28**(9): p. 1411-24; discussion 1410.

230. Matuz, M., R. Benko, and M. Hoffmann, *Visualization of drug utilization data*, in *Drug Utilization Research: Methods and Applications*, M. Elseviers, et al., Editors. 2016, John Wiley & Sons, Ltd. p. 99-115.

231. Rich, J.T., et al., *A practical guide to understanding Kaplan-Meier curves.* Otolaryngol Head Neck Surg, 2010. **143**(3): p. 331-6.

232. Bland, J.M. and D.G. Altman, *The logrank test.* BMJ, 2004. **328**(7447): p. 1073.

233. Tripepi, G., et al., *How to deal with continuous and dichotomic outcomes in epidemiological research: linear and logistic regression analyses.* Nephron Clin Pract, 2011. **118**(4): p. c399-406.

234. Dupont, W.D., *Statistical Modeling for Biomedical Researchers: A Simple Introduction to the Analysis of Complex Data*. 2009: Cambridge University Press.

235. Braun, V. and V. Clarke, *Using thematic analysis in psychology.* Qualitative Research in Psychology, 2006. **3**(2): p. 77-101.

236. Braun, V. and V. Clarke, *What can "thematic analysis" offer health and wellbeing researchers?* Int J Qual Stud Health Well-being, 2014. **9**: p. 26152.

237. Loikas, D., et al., *Does patient's sex influence treatment in primary care? Experiences and expressed knowledge among physicians--a qualitative study.* BMC Fam Pract, 2015. **16**: p. 137.

238. The Ministry of Education and Cultural Affairs, *The Act concerning the Ethical Review of Research Involving Humans (2003:460)*. 2003, The Ministry of Education and Cultural Affairs: Stockholm.

239. Hovstadius, B., B. Astrand, and G. Petersson, *Dispensed drugs and multiple medications in the Swedish population: an individual-based register study.* BMC Clin Pharmacol, 2009. **9**: p. 11.

240. Skoog, J., et al., *Can gender difference in prescription drug use be explained by gender-related morbidity?: a study on a Swedish population during 2006.* BMC Public Health, 2014. **14**: p. 329.

241. Fernandez-Liz, E., et al., *Identifying how age and gender influence prescription drug use in a primary health care environment in Catalonia, Spain.* Br J Clin Pharmacol, 2008. **65**(3): p. 407-17.

242. Orlando, V., et al., *Gender Differences in Medication Use: A Drug Utilization Study Based on Real World Data.* Int J Environ Res Public Health, 2020. **17**(11).

243. Zhong, W., et al., *Age and sex patterns of drug prescribing in a defined American population.* Mayo Clin Proc, 2013. **88**(7): p. 697-707.

244. Loikas, D., et al., *Differences in drug utilisation between men and women: a cross-sectional analysis of all dispensed drugs in Sweden.* BMJ Open, 2013. **3**(5).

245. Loikas, D., et al., *[Big gender differences in drug utilization. The underlying disease is an insufficient explanation according to a systematic analysis]*. Lakartidningen, 2011. **108**(40): p. 1957-62.

246. Schroder, W., et al., *Gender differences in antibiotic prescribing in the community: a systematic review and meta-analysis.* J Antimicrob Chemother, 2016. **71**(7): p. 1800-6.

247. Smith, D.R.M., et al., *Understanding the gender gap in antibiotic prescribing: a cross-sectional analysis of English primary care.* BMJ Open, 2018. **8**(2): p. e020203.

248. Rydberg, D.M., et al., *Sex differences in spontaneous reports on adverse bleeding events of antithrombotic treatment.* Eur J Clin Pharmacol, 2014. **70**(1): p. 117-26.

249. Berger, J.S., et al., *Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials.* JAMA, 2006. **295**(3): p. 306-13.

250. Xie, M., et al., *Aspirin for primary prevention of cardiovascular events: meta-analysis of randomized controlled trials and subgroup analysis by sex and diabetes status.* PLoS One, 2014. **9**(10): p. e90286.

251. Antithrombotic Trialists, C., et al., *Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials.* Lancet, 2009. **373**(9678): p. 1849-60.

252. Berger, J.S., et al., *The relative efficacy and safety of clopidogrel in women and men a sex-specific collaborative meta-analysis.* J Am Coll Cardiol, 2009. **54**(21): p. 1935-45.

253. Fang, M.C., et al., *Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study.* Circulation, 2005. **112**(12): p. 1687-91.

254. Pancholy, S.B., et al., *Meta-analysis of gender differences in residual stroke risk and major bleeding in patients with nonvalvular atrial fibrillation treated with oral anticoagulants.* Am J Cardiol, 2014. **113**(3): p. 485-90.

255. Poli, D., et al., *Gender differences in stroke risk of atrial fibrillation patients on oral anticoagulant treatment.* Thromb Haemost, 2009. **101**(5): p. 938-42.

256. Gomberg-Maitland, M., et al., *Anticoagulation in women with non-valvular atrial fibrillation in the stroke prevention using an oral thrombin inhibitor (SPORTIF) trials.* Eur Heart J, 2006. **27**(16): p. 1947-53.

257. Humphries, K.H., et al., *New-onset atrial fibrillation: sex differences in presentation, treatment, and outcome.* Circulation, 2001. **103**(19): p. 2365-70.

258. Lindh, J.D., et al., *Incidence and predictors of severe bleeding during warfarin treatment.* J Thromb Thrombolysis, 2008. **25**(2): p. 151-9.

259. Rydberg, D.M., et al., *Risk factors for severe bleeding events during warfarin treatment: the influence of sex, age, comorbidity and co-medication.* Eur J Clin Pharmacol, 2020. **76**(6): p. 867-76.

260. Eek, A.K., et al., *Anticoagulant-associated adverse drug reactions in 2013-15.* Tidsskr Nor Laegeforen, 2018. **138**(12).

261. Absher, R.K., M.E. Moore, and M.H. Parker, *Patient-specific factors predictive of warfarin dosage requirements.* Ann Pharmacother, 2002. **36**(10): p. 1512-7.

262. Garcia, D., et al., *Warfarin maintenance dosing patterns in clinical practice: implications for safer anticoagulation in the elderly population.* Chest, 2005. **127**(6): p. 2049-56.

263. Whitley, H.P., et al., *Effect of patient-specific factors on weekly warfarin dose.* Ther Clin Risk Manag, 2007. **3**(3): p. 499-504.

264. Khoury, G. and M. Sheikh-Taha, *Effect of age and sex on warfarin dosing.* Clin Pharmacol, 2014. **6**: p. 103-6.

265. Brown, J.D., et al., *A Comparison of Oral Anticoagulant Use for Atrial Fibrillation in the Pre- and Post-DOAC Eras.* Drugs Aging, 2016. **33**(6): p. 427-36.

266. Thompson, L.E., et al., *Sex Differences in the Use of Oral Anticoagulants for Atrial Fibrillation: A Report From the National Cardiovascular Data Registry (NCDR((R))) PINNACLE Registry.* J Am Heart Assoc, 2017. **6**(7).

267. Shantsila, E., et al., *Gender differences in stroke prevention in atrial fibrillation in general practice: using the GRASP-AF audit tool.* Int J Clin Pract, 2015. **69**(8): p. 840-5.

268. Yong, C.M., et al., *Sex Differences in Oral Anticoagulation and Outcomes of Stroke and Intracranial Bleeding in Newly Diagnosed Atrial Fibrillation.* J Am Heart Assoc, 2020. **9**(10): p. e015689.

269. Socialstyrelsen, *Nationella riktlinjer för hjärtsjukvård*. 2015.

270. Mikkelsen, A.P., et al., *Substantial differences in initiation of oral anticoagulant therapy and clinical outcome among non-valvular atrial fibrillation patients treated in inpatient and outpatient settings.* Europace, 2016. **18**(4): p. 492-500.

271. Bekelaar, K., et al., *Medication use in poststroke epilepsy: A descriptive study on switching of antiepileptic drug treatment.* Epilepsy Behav, 2019: p. 106434.

272. Nowatzki, N. and K.R. Grant, *Sex is not enough: the need for gender-based analysis in health research.* Health Care Women Int, 2011. **32**(4): p. 263-77.

273. Johnson, J.L., L. Greaves, and R. Repta, *Better science with sex and gender: Facilitating the use of a sex and gender-based analysis in health research.* Int J Equity Health, 2009. **8**: p. 14.

274. Rosen, M., *National Health Data Registers: a Nordic heritage to public health.* Scand J Public Health, 2002. **30**(2): p. 81-5.

275. Engström, S. and K. Lindström, *Ersättningsmodeller för vårdcentraler kan förbättras.* Läkartidningen, 2020. **117:FXPT**.

276. Gibbons, R.D., et al., *Post-approval drug safety surveillance.* Annu Rev Public Health, 2010. **31**: p. 419-37.

277. Statistiska centralbyrån (SCB). *Kommuner i siffror - tabeller och fördjupning*. 2021 [cited 2021 Feb 16]; Available from: https://www.scb.se/hitta-statistik/sverige-i-siffror/kommuner-i-siffror.

278. Björck, F., et al., *Warfarin treatment quality is consistently high in both anticoagulation clinics and primary care setting in Sweden.* Thromb Res, 2015. **136**(2): p. 216-20.

279. Wallentin, L., et al., *Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial.* Lancet, 2010. **376**(9745): p. 975-83.

280. Lincoln, Y. and E.G. Guba, *Naturalistic inquiry*. 1985, Newbury Park, CA: Sage Publications.

281. Hamberg, K., et al., *Scientific rigour in qualitative research--examples from a study of women's health in family practice.* Fam Pract, 1994. **11**(2): p. 176-81.

282. Korstjens, I. and A. Moser, *Series: Practical guidance to qualitative research. Part 4: Trustworthiness and publishing.* Eur J Gen Pract, 2018. **24**(1): p. 120-4.

283. Malterud, K., *Qualitative research: standards, challenges, and guidelines.* Lancet, 2001. **358**(9280): p. 483-8.