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SEX DIFFERENCES IN ADVERSE DRUG EVENTS FROM CARDIOVASCULAR MEDICINES IN ROUTINE CARE

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SEX DIFFERENCES IN ADVERSE DRUG EVENTS FROM CARDIOVASCULAR MEDICINES IN ROUTINE CARE
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

In preventive drug treatment of cardiovascular disease, adverse drug effects often lead to suboptimal compliance with a risk of disability and shorter life expectancy. The overall aim of this thesis was to assess the nature and extent of adverse drug events (ADEs) from cardiovascular drugs in both women and men treated in routine care. A special focus was on bleeding events from antithrombotic treatment, in particular warfarin. Better understanding of potential differences in adverse drug effects between women and men could contribute to more successful prevention. Different sources of information were used in order to obtain information about sex differences in ADEs from cardiovascular drugs: spontaneous reporting of ADEs in routine care, a cross sectional study conducted at an Emergency Ward setting, data from national pharmacovigilance and prescription databases, medical files, and the national patient register.

Study I describes the prevalence, preventability and reporting of adverse drug reactions (ADRs) in an emergency medicine ward. 40% of the patient population had at least one possible ADR, in 18% ADRs were the reason for or had contributed to admission, and 24% of these ADRs were preventable. The most common ADRs were cardiovascular and the under-reporting of ADRs was 99%.

Study II presents sex differences in spontaneous reports on bleeding events from clopidogrel, low-dose aspirin and warfarin (1999-2010 and 2005-2010). We found that more men were dispensed clopidogrel although the reported bleeding event risk was higher in women. For low-dose aspirin, the reported bleeding event risk was lower in women while no sex difference was found for warfarin.

Study III presents sex differences in spontaneous reports on ADEs from common antihypertensive drugs (2005-2012). In six out of ten groups of antihypertensives (angiotensin converting enzyme inhibitors (ACE-Is), ACE-I-combinations, angiotensin receptor blocker (ARB)-combinations, thiazides, diuretics and potassium sparing agents and dihydropyridine (DHP) calcium channel blockers), women had a higher prevalence of ADE-reports with a potential linkage to dose exposure. Aldosterone antagonists was the only group with a higher prevalence of ADE-reports in men but without any sex difference in dose exposure.

Study IV describes sex differences in severe bleeding events during warfarin treatment. Women had a lower incidence of bleeding which corresponded to a lower overall risk of severe bleeding in women, even after adjusting for age, comorbidity and co-medication. Women had a lower risk of CNS and urogenital bleeding. However, in the age groups 40-49 and 50-59 as well as in patients with renal failure, women had a higher risk of severe bleeding than men.

LIST OF SCIENTIFIC PAPERS

I. **Rydberg DM,** Holm L, Engqvist I, Fryckstedt J, Lindh JD, Stiller CO, Asker-Hagelberg C
Adverse drug reactions in a tertiary care emergency medicine ward – prevalence, preventability and reporting
PLoS One 2016 Sep 13;11(9): e0162948

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 Jan;70(1):117-26

III. **Rydberg DM,** Mejyr S, Loikas D, Schenck-Gustafsson K, von Euler M, Malmström RE
Sex differences in spontaneous reports on adverse drug events for common antihypertensive drugs
Eur J Clin Pharmacol 2018 Sep;74(9):1165-117

IV. **Rydberg DM,** Linder M, Malmström RE, Andersen M
Sex differences in bleeding events during warfarin treatment. A population-based cohort study using Swedish health care registers
In manuscript

CONTENTS

LIST OF ABBREVIATIONS

CVD	Cardiovascular disease
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
ACE	Angiotensin Converting Enzyme
ACE-I	Angiotensin Converting Enzyme Inhibitor
ARB	Angiotensin Receptor Blocker
DHP	Dihydropyridine
EMA	European Medicines Agency
MPA	Medical Products Agency
SWEDIS	Swedish Drug Information System
BiSi	Biverkningar och Signaler
SPC	Summary of Product Characteristics
WHO	World Health Organization
WHO-UMC system	World Health Organization Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, Sweden) system
GFR	Glomerular Filtration Rate
RAAS	Renin Angiotensin Aldosterone System
BP	Blood Pressure
HRT	Hormone Replacement Therapy
MI	Myocardial Infarction
DRP	Drug Related Problem
AF	Atrial Fibrillation
TdP	Torsades de Pointes
NOAC	Non-vitamin K Oral Anticoagulant
RCT	Randomized Controlled Trial
PDR	Prescribed Drug Register
NBHW	National Board of Health and Welfare
OTC	Over The Counter
ATC	Anatomical Therapeutic Chemical classification

PIN	Personal Identity Number
ICD	International Classification of Diseases
ICD-10	10^{th} version of the ICD
NPR	National Patient Register
DDD	Defined Daily Dose
CI	Confidence Interval
RR	Risk Ratio
OR	Odds Ratio
VKA	Vitamin K Antagonist
OD	Once Daily
INR	International Normalized Ratio
TTR	Time in Therapeutic Range
DAT	Dual Antiplatelet Therapy
TDM	Therapeutic Drug Monitoring
SPAF	Stroke Prevention in Atrial Fibrillation

1 INTRODUCTION

Cardiovascular disease (CVD) is a major cause of premature death and disability worldwide [1]. In recent years, the mortality rates have decreased and most of the reduction in mortality rates from CVD is considered to be attributable to preventive treatment [2]. Good compliance to drug treatment is key for achieving successful prevention and if the patient experiences an adverse effect of the drug treatment there is a risk of suboptimal compliance. The threshold for tolerable adverse drug effects tends to be lower in preventive drug treatment with a higher risk of discontinuing the treatment [3]. It is not known if women or men experience more adverse events and are more likely to discontinue treatment. Better understanding of differences in adverse drug effects from cardiovascular treatment between women and men may provide important information for a successful prevention of cardiovascular disease.

Sex difference is defined as the biological difference between women and men, as compared to gender difference being the psychosocial differences between women and men. In clinical cardiovascular pharmacology, both sex and gender differences play important roles with biological differences accounting for most of the pharmacokinetic and pharmacodynamic differences while gender is essential in the choice and administration of therapy and could therefore influence the potential adverse drug effects from cardiovascular treatment [4].

Potential differences in adverse drug effects between women and men could derive from differences in physiology, genetics, morbidity and therapeutic traditions, demographics and the propensity of reporting adverse drug events. In the literature, there are findings which indicate sex differences in physiological, pharmacodynamic or pharmacokinetic outcomes, but studies with findings which could be translated into clinically relevant differences in safety of drug treatment in general are sparse [5]. Accordingly, we need to gain a better knowledge and understanding of differences in adverse effects from drug treatment of CVDs among women and men.

This thesis presents the prevalence, preventability, and reporting of adverse drug reactions (ADRs) in a tertiary care emergency medicine ward setting. Of special interest were sex differences in spontaneous reports from cardiovascular treatment, specifically adverse bleeding events from antithrombotic treatment and adverse drug events (ADEs) from common antihypertensive drugs. Furthermore, sex differences in bleeding events during warfarin treatment and the influence of comorbidities and co-medication on bleeding risk were explored.

2 AIMS

The overall aim of this thesis is to identify possible sex differences in ADEs from cardiovascular medicines in routine care.

- **D**escribe the prevalence and preventability of ADRs and the frequency of formal reporting of ADRs according to current legislation in Emergency Medicine.

- **S**tudy if sex differences are found in spontaneously reported adverse events for clopidogrel, low-dose aspirin, and warfarin treatment in routine care.

- **E**xplore if sex differences are found in spontaneously reported adverse events for antihypertensive drug treatment with betablockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), diuretics, and/or dihydropyridine calcium channel blockers (DHPs) in routine care.

- **I**nvestigate if there are sex differences in the risk of bleeding during warfarin treatment in routine care and if such differences could be explained by different distribution of risk factors among women and men.

3 BACKGROUND

3.1 ADVERSE DRUG EFFECTS

3.1.1 Definitions

Adverse effects from pharmacological treatment constitute significant health and quality of life problems, especially in the elderly [6]. An adverse drug reaction (ADR) is defined as harm directly caused by the drug at normal doses and during normal use compared to an adverse drug event (ADE) with a wider definition, including ADRs, overdoses, dose reductions, and discontinuations of drug therapy [7]. However, many authors do not seem to follow these strict definitions for ADR and ADE. In this thesis, the term ADR was used in the emergency care ward setting study in which we had information on dosing through patient records. In the studies using register prescription data which lack information on dosing, the term ADE was more appropriate.

3.1.2 Pharmacovigilance

Drug-related risks are not always apparent until a drug is used in large numbers of patients, many of whom are older, more likely to be female, and have more comorbidities than the participants in the clinical trials. Randomized clinical trials often do not include adequate numbers of older patients to identify important safety issues in the general elderly patient population and this is especially the case for older women [8].

The purpose of pharmacovigilance legislation is to collect safety information on drug use in normal health care settings for many patients who may differ from the study population. In EMA (European Medicines Agency) guidelines it is mandatory for health care professionals to report all suspected ADEs to the national competent authority. This feedback loop leads to improved safety information and may lead to increased pharmacovigilance regarding certain side effects (Black box warning, black triangle) or contribute to withdrawal of market authorization [9].

3.1.2.1 Reporting

Since 2012 spontaneous adverse drug event reports are registered in Sweden in the national pharmacovigilance database (BiSi, “Biverkningar och Signaler”), managed by the Swedish Medical Products Agency (MPA) [10].

The previous MPA register was called SWEDIS (Swedish drug information system) before the change of legislation in 2012 [11]. In SWEDIS, physicians, dentists, and nurses were supposed to report serious ADEs; ADEs not mentioned in the Summary of Product Characteristics (SPC), ADEs related to the use of new drugs (≤2 years after authorization) except those already labeled as common in the SPC; and ADEs that seem to be increasing in incidence, to regional pharmacovigilance centers [11].

3.1.2.2 Causality assessment

The reported, suspected ADRs sent to the Swedish MPA are assessed using the WHO-UMC system, the World Health Organization Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, Sweden) for standardized case causality assessments [12]. This assessment for case reports is the most widely used and accepted causality assessment scale in clinical practice (Table 1) alongside the Naranjo ADR Probability Scale [13].

Table 1. WHO-UMC causality categories [12]

Causality term	***Assessment criteria***
Certain	• Event or laboratory test abnormality with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory if necessary
Probable/ **Likely**	• Event or laboratory test abnormality with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ **Unclassified**	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Non-assessable/ **Unclassifiable**	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

The reports of the suspected ADRs sent to the Swedish MPA are also assessed as being serious or not. An ADR was assessed as serious if it fulfilled the World Health Organization (WHO) criteria for a serious adverse drug reaction, that is, if it was lethal, life-threatening, permanently disabling, lead to hospital admission, prolongation of hospital stay, or classified as an "important medical event" [14, 15].

Another causality assessment scale, the Naranjo ADR probability score was used when assessing the causality of the ADRs in the Emergency ward study. This scale assigns the

ADR to a probability category; definite, probable, possible, or doubtful. Ten questions are to be answered with a “yes”, “no” or “do not know” being worth a certain point and the total score puts the ADR in a probability category; definite ≥9, probable 5 to 8, possible 1 to 4, doubtful ≤0 (Table 2) [13].

Table 2. Naranjo ADR probability score [13]

	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued and a specific antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
			Total score	

3.1.2.3 Preventability assessment

In the emergency ward study, the preventability of ADRs was assessed using the Hallas' avoidability criteria [16]. These include four categories, "definitely avoidable", "possibly avoidable", "not avoidable", and "unevaluable". *Definitely avoidable*; the drug event was clearly unrealistic or due to a drug treatment procedure inconsistent with present day knowledge of good medical practice, taking the known circumstances into account. *Possibly avoidable*; the drug event could have been avoided by an effort exceeding the obligatory demands. *Not avoidable*; the drug event could not have been avoided by any reasonable means, or it was an unpredictable event of a treatment fully in accordance with good medical practice. *Unevaluable*; the data for rating could not be obtained or the evidence was conflicting.

3.2 SEX AND GENDER DIFFERENCES IN ADVERSE DRUG EVENTS FROM CARDIOVASCULAR MEDICINES

In recent years, the importance of sex (determined by genetics) and gender (related to social factors) in the response to drug treatment has been recognized with increasing amount of data showing sex differences in physiology, pharmacokinetics, and pharmacodynamics [17]. These sex and gender differences may be due to therapeutic traditions, the propensity of ADE-reporting, morbidity, and demographic differences. Thus, there is a need for more information on how these differences translate into clinically relevant sex differences in ADEs [5].

3.2.1 Physiological differences

3.2.1.1 Bioavailability, distribution and elimination of drugs

There are numerous factors affecting the bioavailability and distribution of drugs such as the ratio of lean to fat tissue, circulating plasma volume, and the amount of plasma proteins binding the drug [18]. Since women have lower body mass and higher lipid levels [19, 20], lipid soluble drugs may have a greater volume of distribution in women [21].

Furthermore, the circulating plasma volume is generally reduced in women with variations throughout the menstrual cycle [18], and with sex hormones affecting gastrointestinal motility leading to a slower transit time reported in women [22, 23]. Sex hormones also affect plasma levels and excretion of drugs with narrow therapeutic indexes, such as warfarin and digoxin, leading to significant clinical effects [24]. Additionally, the glomerular filtration rate (GFR) is directly proportional to weight and therefore generally higher in men. For digoxin, there are reports of increased mortality in women where reduced GFR has led to higher drug serum concentrations in the upper normal range due to reduced distribution volume and lower drug elimination [18].

3.2.1.2 Cardiovascular medicines and physiological differences

There are reports indicating differences between women and men in response to cardiovascular treatment [25]. Since sex hormones affect the renin angiotensin aldosterone system (RAAS) different response to ACE-Is and ARBs may be anticipated [26]. Estrogens increase the availability of angiotensinogen and plasma levels of angiotensin II, but decrease renin and angiotensin converting enzyme (ACE) activities and the expression of angiotensin receptor I. In contrast, androgens up-regulate the RAAS system. If these hormonal influences impact efficacy and safety of drug treatment involving the RAAS is not clear [27]. Furthermore, there are sex differences in the response to the DHP amlodipine with a larger blood pressure (BP) reduction and a higher incidence of edema in women, despite dose adjustments for body weight, and with an adjustment for the use of hormone replacement therapy (HRT) [28]. A better response to antithrombotic treatment with aspirin (acetylsalicylic acid) in women may be due to higher bioavailability, slower clearance and a longer half-life of aspirin [25]. Aspirin seems to inhibit spontaneous platelet aggregation in men only [24], a finding that may explain aspirin resistance, which is more frequently found in women. Additionally, the aspirin-induced inhibition on platelet aggregation has been found to be induced by testosterone, while estradiol was found to have no impact on aspirin-induced inhibition [17]. For clopidogrel, no differences have been found in plasma levels of the main metabolite between women and men [25] and there are no other findings in the literature pointing to sex differences in the physiological responses to clopidogrel treatment.

3.2.2 Genetic differences

3.2.2.1 Drug metabolizing cytochrome P450 enzymes

Sex differences have been found for some of the drug metabolizing cytochrome P450 enzymes [24]. The higher expression of CYP2D6 in men leads to an increased drug clearance compared to women [29]. Women have a higher incidence of ADE and higher plasma concentration of beta blockers, metabolized by CYP2D6 [30]. Women have a higher expression of CYP3A4 and an increased clearance of several CYP3A drug substrates [24]. It has been hard to present data supporting the clinical relevance of these sex differences [29].

3.2.2.2 ACE gene and bradykinin receptor

ACE gene polymorphism has been demonstrated and genetic variants with high expression of ACE have been linked to increased plasma levels of ACE and a major risk for cardiovascular disease. In addition, the renoprotective effect of ACE-Is has been reported to be greater in women with the D/D genotype of the ACE-1 enzyme compared to men with the same genotype [26]. Cough and angioedema are more frequent in women compared to men during ACE-I treatment. ACE-I related cough seems to be associated with polymorphism of the bradykinin B_2 receptor with some evidence pointing to the effect of the polymorphism being

sex-specific [31]. Most women discontinue treatment with ACE-Is because of cough while most men stop treatment due to hypotension [26].

3.2.3 Differences in morbidity, demography and therapeutic traditions

3.2.3.1 CVD risk and sex and gender differences

There are several notable differences between women and men in CVD incidence, mortality, risk-factor profiles, outcomes and clinical presentation. In all age groups, except the oldest, CVD prevalence, incidence and mortality rates tend to be higher in men compared to women. Women experience their first cardiovascular events, e.g. myocardial infarction (MI) and stroke later in life than men. The protective effect of estrogen on the development of CVD risk factors, such as hypertension and dyslipidemia, is the most cited reason for these sex and gender differences. However, HRT in postmenopausal women does not reduce the CVD risk and is not recommended for primary or secondary prevention of CVD. Additionally, oral contraceptives are associated with an increased risk of hypertension. During pregnancy and the postpartum period women have an increased risk of stroke. Women also experience poorer outcomes when they have a CVD event (post MI or stroke), partly due to delayed treatment start. Another cited reason is that women tend to be older with more comorbidity than men at the time of the CVD event [32]. These sex and gender differences in CVD risk should be taken into consideration when exploring sex differences in ADEs from cardiovascular medicines.

3.2.3.2 ADE-related hospital admissions and sex and gender differences

The rate of ADEs is higher in women, both in hospital and community settings [33]. However, data on sex and gender differences in ADE-related hospital admissions are found with female gender has been identified as an independent risk factor for ADE-related hospital admissions in the general population by some authors [34-39] but not by others [40-46]. Among older Swedish patients receiving home healthcare, very old women with impaired renal function were associated to the ADR-related hospital admissions to a high extent [47]. In older Italian patients from geriatric and internal medicine wards, female sex, as well as the number of concomitant drugs and alcohol were associated with ADR-related hospitalizations. Furthermore, older age and frailty were found to be predictors for severe ADRs and with cardiovascular medicines causing approximately 45 percent of the ADR-related hospitalizations [48].

3.2.3.3 ADEs, cardiovascular medicines and sex and gender differences

Women have a higher incidence of ADEs from cardiovascular medicine with drug-induced arrhythmias, e.g. supraventricular tachycardia (SVT) and QT syndrome [49], with an increased incidence of developing severe arrhythmia, Torsades de Pointes (TdP), from QT-prolonging drug therapy [50]. Sotalol was the most frequently suspected drug in the reports of

drug-induced TdPs in a review of the Swedish pharmacovigilance database with female gender being one of the risk factors [51].

Furthermore, there are reports on ADEs from ACE-Is with drug-induced cough being significantly more reported in women compared to men [52] and beneficial effects from ACE-Is being more frequent in men while women experienced more side effects from ACE-Is [53]. The most prominent ADE of aldosterone antagonist is gynecomastia, which only affects men and when given to patients as an add-on treatment in heart failure, excessive hypotension is more prevalent in women [54]. In the case of ADEs from antithrombotic medicines such as warfarin, there are conflicting data in whether there is a sex difference. Most interventional and some observational studies did not find any difference in bleeding risk between women and men during warfarin treatment [55-61]. However, an increased risk for severe bleeding in male patients was reported in a Swedish observational study on patients with several different indications for warfarin [62]. An observational study from Canada on AF patients presented an increased risk of major bleeding in women on warfarin [63]. There is also conflicting data on sex differences in the bleeding risk from low-dose aspirin with some studies finding no sex difference in the bleeding risk [64, 65], while in another study on aspirin-treated patients, a higher risk of major bleeding was found in men compared to women [66].

3.2.3.4 Therapeutic traditions and gender differences

Differences between women and men in therapeutic traditions have been found in the literature. According to a Swedish population-based drug utilization study anticoagulants were dispensed to a larger extent to men compared to women, indicating underuse of anticoagulants in women with atrial fibrillation (AF) [67]. In 2011 (at time of the introduction of the non-vitamin K oral anticoagulants, NOACs) the use of oral anticoagulants (mostly warfarin) was less frequent in women and more women were treated with aspirin only compared to men. Similar use patterns were presented in Canadian patients with new-onset AF, i.e. older women were twice as likely to receive low-dose aspirin and half as likely to receive warfarin compared to men in the same age group [63]. In 2015 the previous sex difference regarding use of oral anticoagulants (warfarin and NOAC) disappeared. However, when comparing warfarin treated patients of the same stroke risk, more men than women were treated with warfarin [68].

Differences between women and men in therapeutic traditions are also found for the RAAS-agents with ACE-Is being dispensed to a higher degree in men, probably due to a higher frequency of drug-induced cough in women. The ARBs, on the other hand, have been found to be dispensed to the same extent in both sexes, with a suggested underuse of RAAS-agents in women [67]. Furthermore, there are other findings on gender disparities in antihypertensive treatment, with men receiving more ACE-Is and women more frequently treated with diuretics [69, 70] and at the same time less likely to be treated with beta blockers, calcium antagonists, compared to men [71, 72].

3.2.4 Reporting differences

There are studies showing that women seek healthcare more often than men [73, 74] which could lead to a higher reporting rate of adverse drug events in women. There are few studies on sex and/or gender differences in ADEs reported to pharmacovigilance centers. In an ambulatory medical population, women generally reported more symptoms compared to men [75, 76]. Differences between women and men in the onset and description of symptoms influenced the reporting of ADEs [77]. In a German pharmacovigilance database study, women more frequently experienced ADEs associated with diuretics compared to men, which could not be explained by women being prescribed more diuretics [78]. Results from a Swedish pharmacovigilance database study indicate that healthcare professionals more frequently reported ADEs for the oldest patients and for women [79].

4 METHODS

4.1 STUDY DESIGNS

In paper I, the electronic patient records of patients admitted to an emergency ward were reviewed in this prospective cross sectional study. In paper II and III, we analyzed ADE-reports and dispensed prescriptions in women and men respectively (cross sectional analyses). In paper IV, women and men with warfarin treatment fulfilling the eligibility criteria were included in this cohort study.

4.2 DATA SOURCES

4.2.1 National pharmacovigilance database

4.2.1.1 The Swedish Drug Information System

Spontaneous ADE reports are registered in the national pharmacovigilance database managed by the Swedish MPA. Before 2012, this database was called SWEDIS, established in 1965 and contained ADEs reported with the former legislation [11]. SWEDIS contains data from 1965 until October 2013, with more than 130 000 reports at the end of 2012. The severity criteria were introduced in SWEDIS 1998 and from 2006 reports on ADEs were also registered as serious if they were assessed as "important medical events". In 2008, consumer reporting started in Sweden with the reports being collected in a separate database and therefore not included in the studies with ADE-report data from SWEDIS (paper II and III).

4.2.2 National health registers

4.2.2.1 The Prescribed Drug Register

The Prescribed Drug register (PDR) was established in 1999 and is held by the National Board of Health and Welfare (NBHW) [80] and since July 2005 patient identity data on all dispensed drugs is available. The register has a coverage of >99 % with unique identifiers of all drugs dispensed to the entire Swedish population [81]. All medications in the PDR are classified by the Anatomical Therapeutic Chemical classification (ATC) codes [82]. The dispensed prescription data in the PDR holds details on the sex and age of the patient, the profession, and workplace of the prescriber and includes medications prescribed in primary and specialized care. Over-the-counter (OTC) medications and medications used in hospitals for inpatient care are not included [81]. The PDR has a high validity where >99.7% of all prescriptions have a personal identity number (PIN) recorded [83]. Dispensed prescription data from the PDR was used in paper II, III, and IV.

4.2.2.2 The National Patient Register

The National Patient Register (NPR) contains nationwide data on primary and secondary diagnoses and surgical procedures recorded at Swedish hospitals. Since 1987, inpatient care data is provided and data on outpatient encounters from both public and private caregivers is provided since 2001. Diagnoses are recorded by the international classification of diseases (ICD) system [84], with the 10th version (ICD-10) available since 1997 [85-89]. The register also holds information on hospital surgical procedures using the Nordic classification of surgical procedures [90]. Data from the NPR was used in paper IV.

4.2.2.3 The Cause of Death Register

The Cause of Death Register is held by the NBHW and contains information, since 1961 and onwards, on dates and primary and contributing causes of death for all deceased residents in Sweden [91]. The date of death was retrieved from this register in paper IV.

4.2.2.4 The National Population Register

The National Population Register includes information on date of birth, sex, death, and burial site, migration, residency and civil status of all Swedish residents since 1961 [92]. A central database at the Swedish Tax Agency distributes the information in the register to central and regional authorities who use the data [93]. Data from this register was used in paper IV.

4.2.2.5 The National Cancer Register

For both the physician detecting the cancer and the verifying pathology departments it is mandatory to register the diagnosis in the National Cancer Register (established in 1958). The register has high coverage [94, 95] and it contains data on cancer diagnosis using the ICD classification [84]. Data from this register was used in paper IV.

4.3 PAPER I

4.3.1 Study design and analyses

706 patients admitted to one of the emergency wards (AVA 1) at Karolinska University Hospital Solna, Stockholm were periodically included during the study period (September 2008 -September 2009). The electronic patient records were reviewed for severity, causality, and the preventability of ADRs, as well as the contribution to hospital admission. The ADRs were classified using the Naranjo ADR probability score [13]. The ADRs that were assessed as having caused and contributed to admission were additionally assessed for preventability by using the Hallas' avoidability criteria [16]. The formal reporting of the ADRs to the national authority, according to current legislation, was noted. Additionally, by using the CKD-EPI formula [96], the impact of decreased GFR was assessed. The influence of age, the number of concomitant drugs, and sex in relation to the probability of presenting with an ADR were investigated. The association between age, sex, and ADRs was calculated separately for women and men in different age groups. For these calculations, descriptive statistics were used with $p<0.05$ considered statistically significant.

4.4 PAPER II

4.4.1 Study design and analyses

For clopidogrel, low-dose aspirin, and warfarin, differences between women and men concerning bleeding event reports were analyzed separately. As the primary analysis, the total number of bleeding event reports from SWEDIS were adjusted for dispensed prescriptions in the PDR. The drug exposure was analyzed during two different time frames, 1999-2010 and 2005-2010, in women and men respectively. The total number of dispensed prescriptions and defined daily doses (DDDs) of each substance were obtained for the period 1999-2010. The number of individuals with at least one dispensed prescription (individuals exposed) and the total number of dispensed prescriptions and DDDs were obtained from 2005-2010. As a secondary analysis, the total number of serious reports adjusted for prescription data were calculated. For low-dose aspirin, the mean doses in women and men respectively were assessed by analyzing the distribution between different dispensed tablet strengths, i.e., 75 mg or 160 mg. Other antithrombotic treatment chosen as co-medication in the bleeding reports and dispensed co-prescriptions were also analyzed. The descriptive statistics data were presented as proportions and risk ratios (RRs) with 95% confidence intervals (CI).

4.5 PAPER III

4.5.1 Study design and analyses

For ACE-Is and ARBs, with or without thiazide, diuretics (thiazide, potassium sparing agents, sulfonamides, aldosterone antagonists), selective beta blockers, and DHPs, the total

number of ADE-reports in SWEDIS was adjusted to exposed individuals and dispensed DDDs in the PDR among women and men respectively (2005-2012). The total amount of serious reports for the ten different groups of antihypertensives were also adjusted to prescription data as a secondary analysis. Additionally, the most frequently reported type of ADEs were collected. For the selected group of antihypertensives, the most frequently reported antihypertensive co-medications (classified as suspected in the report) and the most frequently dispensed co-prescribed antihypertensives were collected. To estimate dose exposure, both DDDs per individuals exposed and DDDs per dispensed prescription per year were calculated in women and men respectively divided by age group (0-49 years, 50-74 years, ≥75 years). Descriptive statistics were used with 95% CIs when presenting proportions and sex differences as odds ratios (ORs).

4.6 PAPER IV

4.6.1 Study design and analyses

During the study period (2007 -2011), women and men (≥18 years) with a dispensed prescription of warfarin were included in the study cohort. The first date of warfarin dispensing during this period was the index date and only patients with no VKA (vitamin K antagonist) use 1 year prior to index date (new users) were included. Subjects not resident in Sweden the year before and including index date were excluded. The cohort patients were all followed for the occurrence of bleeding events until 12 months (maximum) after the index date, death, or emigration, whichever occurred first, see flow chart (Fig 1).

The indications for warfarin included in the analyses were identified through the main and secondary discharge diagnosis, as well as the outpatient visit diagnosis in the NPR (Supplementary Table 1). For comorbidities, hospital admissions, and outpatient contacts were identified up to 10 years before index date and a modified HAS-BLED score [97, 98] was used for classifying the risk of bleeding (Tables 1 and 2). Additionally, co-medication and clinically relevant interacting drugs were considered and adjusted for in the analysis (Tables 1 and 2).

Descriptive statistics are presented as numbers and proportions. Hazard ratios (HR) for severe bleeding comparing women to men, and the association of bleeding with indications, comorbidities/risk factors, and co-medication were estimated using multiple Cox regression adjusted for age (except for age-stratified analyses) and presented with a 95% CI. Effect modification for each covariate by sex was investigated. In additional regression models, age as a continuous variable was used for adjustments and co-medications that could lead to drug interactions with warfarin were included.

4.7 ETHICAL CONSIDERATIONS

Ethical considerations in research are primarily focused on the safety and autonomy of the individual, the individual's perspective. In Sweden, with publicly funded health care, there is also a group perspective to be considered where the resources should be spent in a utilitarian manner with maximal "benefit" for society. The goal in publicly funded health care is also to be equal and needs-based. All included studies were approved by the Regional Ethical Review Board in Stockholm.

In Paper I, the patient treatment was according to clinical routine and this was not an interventional study. This was an observational study that was performed with informed consent for most patients. Patients unable to give informed consent were also included after permission from the Regional Ethical Review Board in Stockholm since the benefit of complete data collection, especially for this high-risk group, was assessed as superior to the invasion of privacy (Dnr 2008/982-31/3 and 2009/2130-32).

Paper II and III are both register studies with data extracted from the former Swedish pharmacovigilance database SWEDIS and the PDR with no risk for the participants to be identified. The ADE-reports are analyzed on a group level and specific individual reports are not described or detailed in publications. No risk or benefit for the individual in this case but benefits for patients in general and society with gained knowledge of possible sex differences in ADE reporting (Dnr 2010/788-31/5 and 2012/1581-32).

In Paper IV, with data from the NPR, the PDR, and the National Population Register, there could be a potential risk for the individual to be identified with the analyses of specific diagnoses and dispensed drugs. In this case, all data analyzed are anonymous and grouped so that no individual can be identified. There are benefits for the patients, health care, and society with more knowledge of possible sex differences in bleeding complications from warfarin treatment (Dnr 2013/1850-31/1 and 2014/2215-32).

5 RESULTS

5.1 PAPER I

Women (n=351) and men (n=355) were evenly represented in the total patient population (n=706) and the median age was slightly higher in women (Table 1). The patients with ADRs (n=284) were older, had a higher percentage of women (54% vs 46%), a higher number of drugs, lower GFRs, and longer duration of hospital stay compared to the non-ADR-population.

Table 1. Patient characteristics. *Modified from Paper I* [99]

	All patients (n=706)	**Women (n=351)**	**Men (n=355)**	**ADR-patients (n=284)**	**Non-ADR-patients (n=422)**
Age (years[1])	71 (58-82)	72 (59-84)	69 (57-81)	75 (63-84)	68 (53-81)
Number of drugs[1]	6 (2-11)	7 (3-12)	6 (2-10)	8 (4-13)	5 (2-10)
Duration of hospital stay (days[1])	2 (2-4)	2 (2-4)	2 (2-3)	3 (2-4)	2 (2-3)
GFR (mL/min[1,2])	72 (46-93)	72 (44-97)	71 (48-91)	65 (37-87)	75 (52-98)

[1]median (inter quartile range), [2] CKD-EPI formula

Approximately 40 % of the entire patient population had at least one possible ADR (n=284). Preventability assessment was restricted to the ADRs causing or contributing to admission (n=129) and 24% (31/129) were considered avoidable.

ADR-admissions seemed to be more common in older women above 75 years compared to the same age group of men (Fig 1). In the multivariable regression model, sex was not significantly associated with the risk for ADRs (p=0.27), while age and number of concomitant drugs were ($p<0.01$ and $p<0.001$).

Cardiovascular ADRs were both the most frequent ADRs and the most frequent preventable ADRs, followed by electrolyte disturbances and hemorrhage. Antihypertensives were responsible for the cardiovascular ADRs while hemorrhages were assessed as the most frequent serious ADRs and mainly caused by low-dose aspirin.

During the study, only two reports were sent to the MPA although 146 patients had at least one ADR which should have been reported to the MPA according to current legislation.

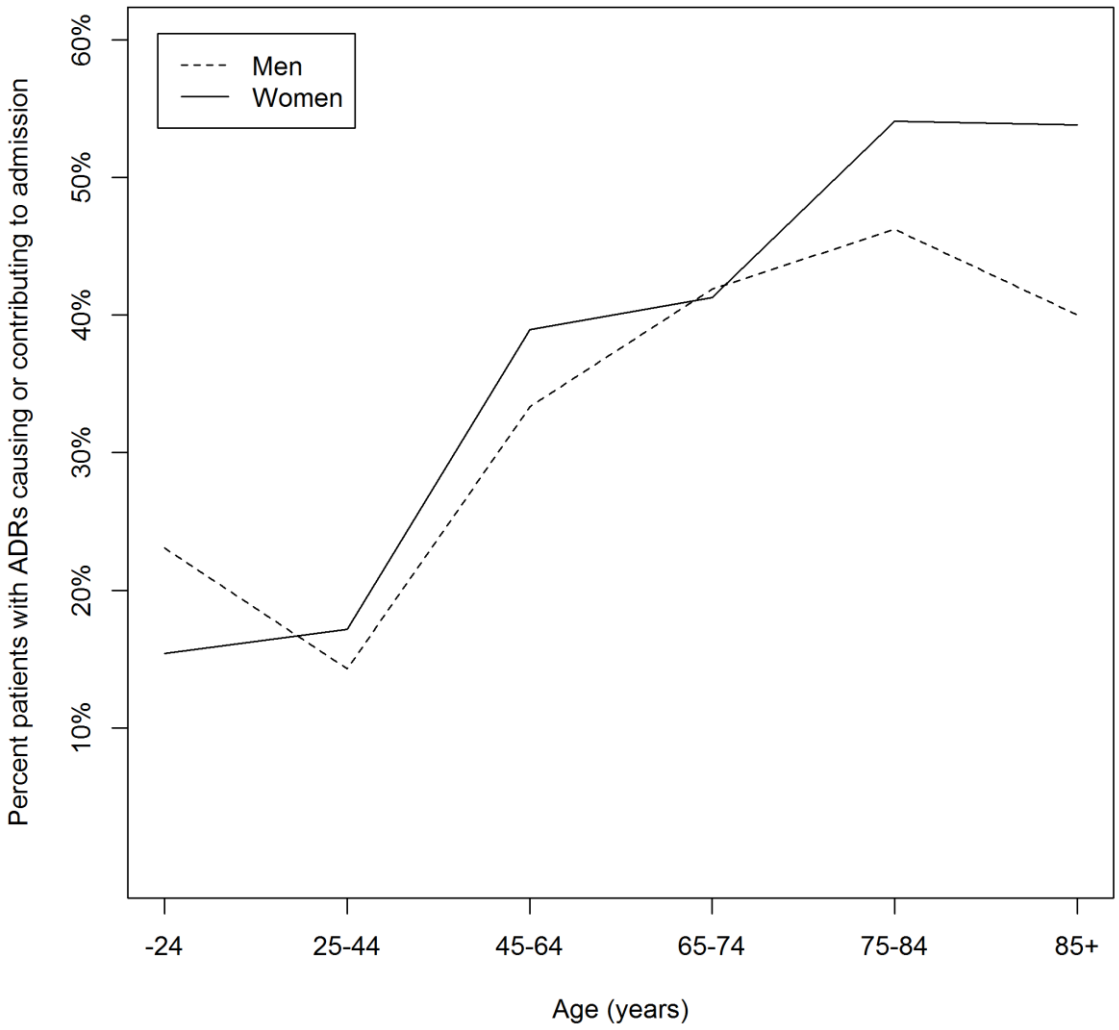

Fig 1. The distribution, in different age groups, of ADRs causing or contributing to admission, in women and men. *Modified from Paper I* [99]

5.2 PAPER II

For clopidogrel (standard dose of 75 mg once daily, OD), the number of dispensed prescriptions was higher in men but the risk of reported bleeding events was significantly higher in women when adjusting for the number of exposed individuals (RR 1.40; 95%CI 1.00-1.96, Table 1).

For low-dose aspirin (75-320 mg OD), the risk of reported bleeding events was significantly lower in women, both when adjusting for exposed individuals (RR 0.80; 95% CI 0.66-0.97, Table 2) and the number of dispensed prescriptions during both time periods (Table 2). In men, the proportions of patients dispensed 160 mg once or twice daily was higher compared to women with a ratio of 1.2.

For warfarin (individualized dosing), no difference in bleeding event reports was found between women and men when adjusting for the number of exposed patients (RR 1.01; 95% CI 0.87-1.17, Table 3). However, when adjusting for the number of dispensed prescriptions women had a higher risk of reported bleeding events (Table 3).

Overall, the RRs for serious bleeding events were in line with the total bleeding reports. For all three substances, the proportion of reports on CNS and GI bleedings were higher in men. Additionally, bleeding reports constituted 89, 74 and 57 percent of the total reports for low-dose aspirin, warfarin, and clopidogrel respectively during 1999-2010.

Table 1. Reports and exposure data for clopidogrel. *Modified from Paper II [100]*

	Number of prescription (Rx)	**Individuals exposed**	**Total reports with bleeding events[1]**	**RR adjusted for nr of Rx[2] (CI[3])**	**RR adjusted for individuals exposed[2] (CI[3])**	**Serious reports with bleeding events**	**RR adjusted for nr of Rx[2] (CI[3])**	**RR adjusted for individuals exposed[2] (CI[3])**
1999-2010								
Total	1 794 605	NA	219			194		
Women	824 138	NA	93			78		
Men	970 467	NA	126			116		
RR[2]				0.87 (0.66-1.14)	NA		0.79 (0.59-1.06)	NA
2005-2010								
Total	1 117 465	157 179	139			120		
Women	516 199	59 495	64			53		
Men	601 266	97 684	75			67		
RR[2]				0.99 (0.71-1.39)	1.40 (1.00-1.96)		0.92 (0.64-1.32)	1.30 (0.91-1.86)

[1] For details on reported events, see Table 4., [2] RR women vs men, [3] 0.95 Confidence Interval

Table 2. Reports and exposure data for low-dose aspirin. *Modified from Paper II [100]*

	Number of prescription (Rx)	**Individuals exposed**	**Total reports with bleeding events[1]**	**RR adjusted for nr of Rx[2] (CI[3])**	**RR adjusted for individuals exposed[2] (CI[3])**	**Serious reports with bleeding events**	**RR adjusted for nr of Rx[2] (CI[3])**	**RR adjusted for individuals exposed[2] (CI[3])**
1999-2010								
Total	39 179 062	NA	676			625		
Women	21 100 226	NA	293			270		
Men	18 079 512	NA	383			355		
RR[2]				0.66 (0.56-0.76)	NA		0.65 (0.56-0.76)	NA
2005-2010								
Total	21 973 285	1 082 352	417			372		
Women	11 987 930	521 201	178			156		
Men	9 985 355	561 151	239			216		
RR[2]				0.62 (0.51-0.75)	0.80 (0.66-0.97)		0.60 (0.49-0.74)	0.78 (0.63-0.96)

[1] For details on reported events, see Table 5., [2] RR women vs men, [3] 0.95 Confidence Interval

Table 3. Reports and exposure data for warfarin. *Modified from Paper II [100]*

	Number of prescription (Rx)	**Individuals exposed**	**Total reports with bleeding events[1]**	**RR adjusted for nr of Rx[2] (CI[3])**	**RR adjusted for individuals exposed[2] (CI[3])**	**Serious reports with bleeding events**	**RR adjusted for nr of Rx[2] (CI[3])**	**RR adjusted for individuals exposed[2] (CI[3])**
1999-2010								
Total	5 113 359	NA	1386			1334		
Women	2 053 435	NA	618			598		
Men	3 059 924	NA	768			736		
RR[2]				1.20 (1.08-1.33)	NA		1.21 (1.09-1.35)	NA
2005-2010								
Total	2 941 179	271 003	717			677		
Women	1 171 801	113 627	302			290		
Men	1 769 378	157 376	415			387		
RR[2]				1.10 (0.95-1.27)	1.01 (0.87-1.17)		1.13 (0.97-1.32)	1.04 (0.89-1.21)

[1] For details on reported events, see Table 6., [2] RR women vs men, [3] 0.95 Confidence Interval

5.3 PAPER III

Women had a higher prevalence of ADE-reports in six of the ten subgroups of antihypertensives; ACE-Is (OR 1.21; 95% CI 1.09-1.35), ACE-I with thiazide combinations (OR 1.61; 1.44-1,79), ARB with thiazide combinations (2.12; 1.47-3.06), thiazides (1.78;1.33-2.39), diuretics with potassium sparing agents (1.62; 1.22-2.17), and DHPs (1.40; 1.17-1.67). For these groups, we also found a potential linkage to a sex difference in dose exposure.

In men, a higher prevalence of ADE-reports was observed for aldosterone antagonists (0.75; 0.59-0.97, Table 8) but no difference in dose exposure between women and men was found. Overall, the ORs for the reports of serious ADEs were higher than expected for thiazides and diuretics with potassium sparing agents (Table 5 and 6).

Table 5. Reports and exposure data for thiazides (ATC code C03AA) 2005-2012. *Modified from Paper III [101]*

	Individuals exposed	**Number of million DDDs**	**Total reports**	**OR adjusted for individ. exposed[1] (CI[2])**	**OR adjusted for nr of DDDs[1] (CI[2])**	**Serious reports**	**OR adjusted for individ. exposed[1] (CI[2])**	**OR adjusted for nr of DDDs[1] (CI[2])**
Total	419 343	564	222	1.78 (1.33-2.39)	1.69 (1.26-2.26)	137	2.69 (1.77-4.07)	2.55 (1.68-3.86)
Women	248 051	341	160	NA	NA	109	NA	NA
Men	171 292	223	62	NA	NA	28	NA	NA

[1] OR women vs men, [2] 0.95 Confidence Interval

Table 6. Reports and exposure data for diuretics and potassium-sparing agents (ATC code C03EA) 2005-2012. *Modified from Paper III [101]*

	Individuals exposed	**Number of million DDDs**	**Total reports**	**OR adjusted for individ. exposed[1] (CI[2])**	**OR adjusted for nr of DDDs[1] (CI[2])**	**Serious reports**	**OR adjusted for individ. exposed[1] (CI[2])**	**OR adjusted for nr of DDDs[1] (CI[2])**
Total	244373	307	256	1.62 (1.22-2.17)	1.48 (1.11-1.98)	163	2.20 (1.48-3.28)	2.01 (1.35-2.99)
Women	163231	211	196	NA	NA	133	NA	NA
Men	81142	96	60	NA	NA	30	NA	NA

[1] OR women vs men, [2] 0.95 Confidence Interval

Table 8. Reports and exposure data for aldosterone antagonists (ATC code C03DA) 2005-2012. *Modified from Paper III [101]*

	Individuals exposed	**Number of million DDDs**	**Total reports**	**OR adjusted for individ. exposed[1] (CI[2])**	**OR adjusted for nr of DDDs[1] (CI[2])**	**Serious reports**	**OR adjusted for individ. exposed[1] (CI[2])**	**OR adjusted for nr of DDDs[1] (CI[2])**
Total	258 422	104	246	0.75 (0.59-0.97)	0.60 (0.46-0.77)	178	0.78 (0.58-1.05)	0.62 (0.46-0.83)
Women	149 418	66	125	NA	NA	92	NA	NA
Men	109 004	38	121	NA	NA	86	NA	NA

[1] OR women vs men, [2] 0.95 Confidence Interval

In several subgroups involving diuretics, hyponatremia was one of the most frequently reported ADEs. The age groups 50-74 and ≥75 years had the highest number of ADE-reports. There were more reports in women in the oldest age group (≥75 years), but after adjusting for prescription data, the ADE-report prevalence for each subgroup was in line with the main findings.

5.4 PAPER IV

232,624 patients (101,011 women and 131,613 men) were included in the cohort, with the women being older than men (72.2 vs 68.5 years), with an excess of patients in the age group ≥80 years (study flowchart, Fig 1).

Women had a lower incidence rate of severe bleeding compared to men (35 vs 38 events per 1000 person-years) corresponding to a crude HR (95% CI) of 0.94 (0.90- 0.98). After adjustment, the HR was further reduced to 0.85 (0.81-0.89).

Women had a lower adjusted risk of CNS and urogenital bleeding compared to men, but the adjusted GI bleeding risk was similar in both sexes (Table 3). In the group of other bleedings, anemia was more common in women while epistaxis was more frequent in men.

In the stratified analysis, the lower severe bleeding risk in women was independent of indications and HAS-BLED score and women in the age groups 40-49 and 50-59 had a higher risk of severe bleeding than men. Stratifying on comorbidities did not change the general pattern with a lower risk of severe bleeding in women, except for renal failure, COPD, and prior bleeding. In patients with renal failure, effect modification was found with an excessive risk in women compared to men while no significant sex difference in the bleeding risk was found in patients with COPD or prior bleeding.

Fig 1. Study flow chart

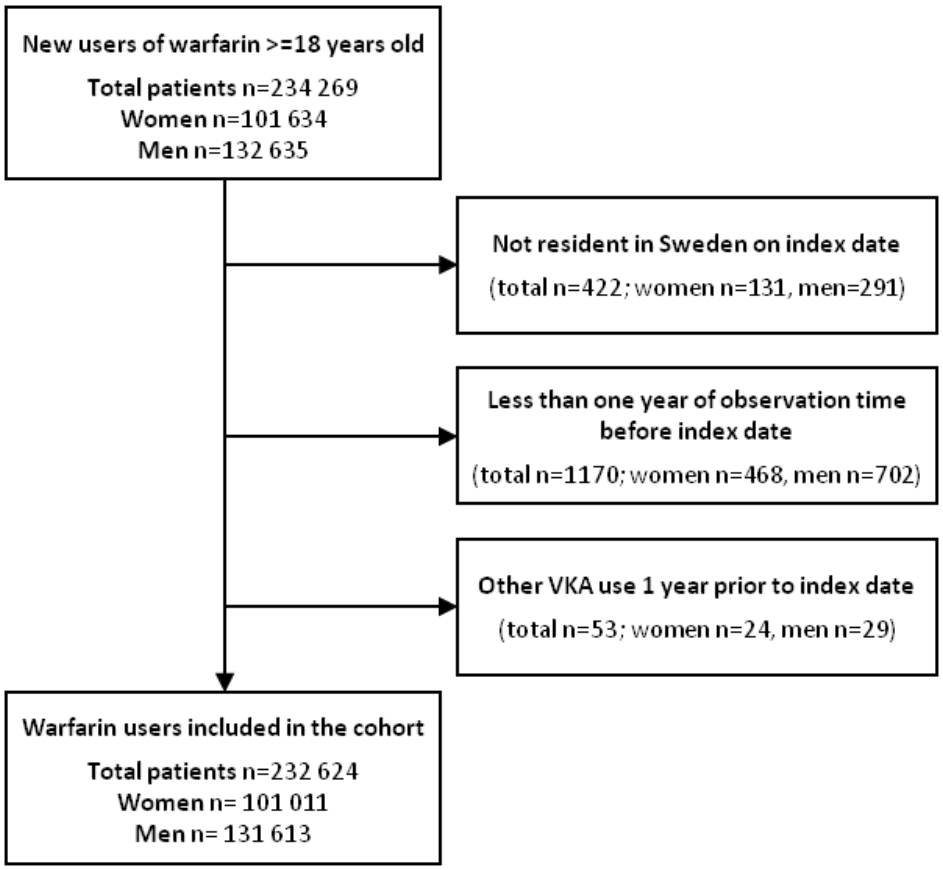

Table 3. Incidence rate (IR) of severe bleeding (per 1000 person years) among women and men on warfarin stratified by bleeding site. Adjusted hazard ratios based on Cox regression.

	Women		**Men**		**Women vs. Men**
	N	**IR (95% CI)**	**N**	**IR (95% CI)**	**Adjusted HR (95% CI)**
Any severe bleeding*	3406	35.4 (34.2-36.6)	4759	37.8 (36.8-38.9)	0.84 (0.80-0.88)
CNS bleeding	683	7.1 (6.6-7.7)	969	7.7 (7.2-8.2)	0.79 (0.71-0.87)
GI bleeding	1098	11.4 (10.8-12.1)	1303	10.4 (9.8-10.9)	0.98 (0.90-1.06)
Urogenital bleeding	364	3.8 (3.4-4.2)	966	7.7 (7.2-8.2)	0.41 (0.36-0.47)
Other bleeding	1417	14.7 (14.0-15.5)	1731	13.8 (13.1-14.4)	1.03 (0.96-1.11)

* As bleeding from multiple sites may occur, the numbers of site-specific bleeding events exceed the total number of severe bleeding events

6 DISCUSSION

6.1 METHODOLOGICAL CONSIDERATIONS

In the perfect world, the true prevalence and incidence of ADEs may be determined in a randomized, controlled interventional study, with the ability to assess the ADEs through direct patient contact. However, it is almost impossible to achieve a sufficiently large patient population, not to mention the high cost and the personal resources. In order to achieve sufficient statistical power analysis of sex and gender differences require even larger studies. Thus, healthcare registers with large coverage and the possibility of retrieving nationwide and structured data, can be used. Limitations of these registers and the methodological considerations are discussed below.

6.1.1 Spontaneous reporting and pharmacovigilance databases

Sex differences in spontaneous reports (study II and III) are presented as linkage between ADE-reports and drug utilization at the population level rather than the individual level [102]. Thus, an adjustment for potential confounding was not performed. Furthermore, since not all ADEs are reported the data do not represent the real incidence rate, but rather may be considered a proportion of the incidence. In contrast to the large international ADE database of the WHO, Vigibase [103] and other pharmacovigilance databases, the smaller SWEDIS database has a higher quality and reliability, i.e. all reports were provided by health care professionals and causality has been assessed which increases the reliability in comparison to other. The causality subclassification of ADEs into “serious” and “non-serious” in SWEDIS is of great advantage for the scientific evaluation. In general, women report more physical symptoms and use medical services to a larger extent than men [104]. However, the propensity of reporting a serious ADE should not differ between women and men. Spontaneous reports of ADEs are only to be considered as signals requiring further assessment (e.g. temporal relationships, published case reports, biological, and clinical plausibility, clinical trials data, and epidemiological studies in large healthcare databases), and the ADE-reports are not sufficient to establish a causal relationship [105-107]. Thus, research on pharmacovigilance databases has its limitations and the true prevalence of ADEs may not be detected [105].

6.1.2 Emergency care setting and chart reviews

The selection of patients in the emergency care ward (study I) was based on randomization. However, we cannot entirely rule out the risk of selection bias. Clinical pharmacologists assessed all ADRs, if needed a specialized registered nurse working with ADR reporting at the MPA was consulted Established criteria were used when classifying the ADR-symptoms. Furthermore, the study population was not large enough to obtain significant differences

between women and men in the descriptive statistical analyses. In addition, we did not analyze if the correlation between the number of concomitant drugs and if the ADRs were due to comorbidities. Generalization of our results is difficult since the prevalence of ADRs strongly depends on setting and other circumstances. In studies using other methods than medical chart reviews, the prevalence of hospitalizations due to medication is lower [108].

6.1.3 Healthcare register studies

Using Swedish administrative healthcare registers in epidemiological research such as the PDR and the NPR when evaluating effectiveness and safety of drug therapies provides several advantages. These registers consist of already structured data and cover large parts of the healthcare system over a long period. The PIN makes it possible to link data on exposure or treatment from other sources to outcomes in these healthcare data registers [88, 109]. The limitations of using healthcare register studies are discussed below.

6.1.3.1 Selection bias

The two studies on spontaneous reporting (study II and III) have the advantage of the use of nationwide patient identity drug databases, both regarding pharmacovigilance, and dispensed prescription data [110]. In study IV, the use of population-based healthcare registers with full coverage implies that there is no overall selection bias affecting the study population although there is still a risk of bias with a possible sex difference due to selective prescribing.

6.1.3.2 Misclassification and confounding

There are limitations to studies using diagnoses (ICD-10-codes) from healthcare registers because the diagnoses could be inaccurate and information might be missing. A systematic lack of information might lead to misclassification and residual confounding [109]. In study IV, sex and gender differences in receiving a certain diagnosis depend on the physician or patient attitudes and the healthcare consumption of patients which potentially could lead to differences between women and men in the number of patient diagnoses and comorbidities recorded in the registers (differential misclassification).

A confounder is a factor associated with both the exposure and the outcome that does not lie on the causative pathway. A confounder may bias the observed effect of the exposure on the outcome. There are different ways to control for confounding in an observational study, such as stratification and adjusting for confounding variables using a multivariable regression analysis. There may also be exposure-associated unmeasured or poorly measured risk factors of the outcome, referred to as unobserved, unmeasured or misclassified confounders. This may lead to incomplete adjustment and residual confounding [111, 112].

To control for confounding in study IV, the analyses were adjusted for age, indications, comorbidities, and co-medications, and stratified analyses were performed. After adjustment,

the sex difference remained, and was even more accentuated when compared with the crude estimate.

6.1.3.3 Confounding by indication

A major limitation of observational comparative effectiveness and safety studies is confounding by indication of therapy [113]. This is because those who are prescribed a certain drug are generally different from those who are not given this certain drug, according to the medical indication for which the drug was prescribed [114]. The drug prescribing physician is influenced by many different factors and certain types of patients will be prescribed certain types of drugs based on their indications and contraindications. The inability to compensate for differences in patient characteristics between treatment groups when comparing outcomes is called residual confounding.

Both the choice of treatment and the outcomes might be affected by unmeasurable baseline factors, which could lead to confounding by indication. Additionally, different utilization or management of healthcare treatments in the observational study population, compared to a RCT, might also explain unexpected differences in outcomes between treatment groups [113]. Generally, patients in routine care are older with more co-morbidities and a higher discontinuation and lower adherence to treatment, compared to the trial patients.

In study IV, we did not compare treated with untreated neither did we compare two different treatments but we compared two subpopulations e.g. women and men receiving the same treatment. Treatment choice could however be different between women and men and within the study design we could not consider if women and men were given treatment to the same extent. Despite adjustments for comorbidities some potential differences in frailty between men and women may not have been reflected in our confounding variables.

6.1.3.4 Effect modification and interaction by sex

Effect modification is the ability of a third factor (here, sex) to modify or interact with the "main effect" of the exposure (say, treatment) on outcome (usually, disease) [115]. As an example, from study IV, if the association between a certain variable (e.g. indication for warfarin, comorbidity, co-medication) and the outcome (bleeding event during warfarin treatment) were to be stronger for women compared to men, then it is said that sex "interacts" with that variable (e.g., renal failure) to cause bleeding events during warfarin treatment or that sex "modifies" the renal-failure-and-warfarin-induced-bleeding-event association (study IV; Table 4).

6.1.3.5 Validity of diagnoses, treatments and outcomes

The validity of hospital diagnoses in Sweden is well documented [85-89], while primary care diagnoses are less validated [116-118]. We did not have complete information on comorbidities because we lacked primary care diagnoses. The PDR lacks information on indications, and therefore we used diagnoses from the NPR that corresponded to the indications for warfarin treatment.

The prescription data only consists of dispensed prescriptions and therefore we lacked information on patients' compliance to treatment, a limitation study II, III, and IV all have in common. Also, when assessing drug exposure from dispensed prescription data there is a risk of drug exposure misclassification, classifying a patient as exposed when truly the patient was unexposed [81]. Although, by using dispensed prescription data, there is no risk of recall bias [109].

As primary outcome diagnoses for severe bleeding in study IV, we used the definitions (ICD-10 codes) validated by Friberg et al. [119], identified in the NPR as main or secondary diagnosis. 99.4% of intracranial bleedings events and 82.6% of gastrointestinal bleeding events were identified correctly in the registries. The sensitivity was 85.5% and the specificity 95.9% for major bleeding events in this validation study [119].

6.1.3.6 Generalizability

Warfarin treatment requires monitoring to maintain the International Normalized Ratio (INR) in plasma within the therapeutic range (2.0-3.0) [120], and a high time in therapeutic range (TTR) is associated with a lower risk of bleeding and thromboembolic events. There can be large differences in TTR between centers and countries. Among 44 countries, Sweden had the highest mean TTR in an efficacy and safety analysis of RE-LY trial data [121]. Therefore, the results found in study IV might not be reproducible in countries with warfarin treatment of a lower quality.

6.2 MAIN FINDINGS AND INTERPRETATION

6.2.1 ADRs in emergency medicine

The emergency ward is an ideal place to detect and assess the prevalence of ADRs with its high throughput of patients. In almost 20 percent of the study patients, ADRs had caused or contributed to hospital admission, in line with previous Swedish reports from a geriatric clinic and an internal medicine ward [44, 122]. In several meta-analyses, including not only emergency care data [48, 123-127], a lower incidence of ADR-related hospital admission was presented. In some of these studies, not only the patient population, but also the assessment of ADRs differed from our study. Patients admitted to hospital due to ADRs in our study were older and had a higher number of concomitant drugs than those admitted for other reasons, which is in line with other studies [46, 128]. The oldest patients (85+) in our study had the largest difference between women and men in ADR-admissions, which is also in line with other reports [34-38].

The most common drugs causing or contributing to hospital admission in our study were those with cardiovascular indications, followed by antineoplastic agents. The pattern of causative drugs may differ depending on the constitution of patient care at the studied hospital. The results in our study can in part be explained by the relatively high number of patients treated at the thoracic and oncology clinics.

Drug-safety issues differ depending on geography and the level of healthcare, and ways to address local safety problems have been presented in the literature [129]. In our study when assessing preventability, we focused on the ADRs with the largest impact on patient health and compared to other studies [130-132], and we found less preventable ADRs. Most preventable ADRs were caused by antihypertensives and antithrombotics and could have been avoided by better monitoring, e.g. BP, heart rate, therapeutic drug monitoring (TDM)/functional coagulation tests, of cardiovascular drugs given in combination and avoiding the combination of SSRIs and aspirin in patients with a high bleeding risk.

We found a substantial under-reporting of ADRs to national authority. The reasons for the under-reporting could be lack of implemented routines, lack of time while on duty and, unawareness. The reporting rate could perhaps be improved by making the healthcare professionals more aware of ADRs through built in routines and continuous education. Additionally, if there were to be financial incentives for reporting side effects, e.g. if the activity would be subsidized, together with facilitating the reporting process, would also possibly improve the rate of reporting.

The chart reviews in this study provided valuable ADR-data, but unfortunately the study population was not big enough to be able to sufficiently assess sex differences. One way to get a larger study population would have been to involve several hospitals in the Stockholm region, but that would require adequate resources and infrastructure.

6.2.2 Spontaneous reported ADEs from cardiovascular medicines

When studying spontaneous reporting, one should always know the data do not represent the real incidence rate but merely a proxy of it. Still data on sex differences within spontaneous reporting could give valuable information about differences in safety of drug treatment. In both studies on reported ADEs (study II and III), we adjusted for the number of individuals exposed, the number of dispensed prescriptions, and the number of DDDs. We believe the use of individualized data to be more accurate, reflecting the number of exposed individuals which is comparable to the safety population in a RCT. In pharmacoepidemiological studies it is common to use the number of dispensed prescriptions as a measure of exposed patients [133], due to the lack of nationwide patient identity drug databases which are only available in a few other countries [110]. The nationwide coverage of the database and the use of individualized data are two advantages compared to other pharmacovigilance studies found in the literature. Furthermore, we believe that the validation of the results with the secondary analyses of serious reports, is an advantage when analyzing differences between women and men. The number of total reports is significantly lower in SWEDIS compared to the international pharmacovigilance database, Vigibase, which is of course a noticeable limitation.

6.2.2.1 Sex differences in reported bleeding events from antithrombotic treatment

The prevalence of reported bleeding events in women compared to men, adjusted for the number of exposed patients, differed for the three studied substances; clopidogrel, low-dose aspirin and warfarin. For clopidogrel, when adjusting for patients exposed, women had a higher prevalence of reported bleeding events. Therefore, similar sex patterns for the even more potent antiplatelet drugs, like prasugrel and ticagrelor, could be interesting to follow. In contrast, for low-dose aspirin the reported bleeding risk was higher in men. The proportion of patients receiving 160 or 320 mg was higher in men as compared to women. Additionally, aspirin resistance, i.e., the inability of aspirin to protect patients from thrombotic complications, has been found to be more common in women in some studies [134-136], but not in others [137, 138], which also could play a role for the higher reported bleeding risk in men. Monitoring and individualized dosing could be reasonable explanations to the results for warfarin with no sex difference in reported bleeding events. In our attempt to estimate concomitant use of other antithrombotic treatment we found that co-prescription of more than one antithrombotic treatment was more common in men. An increased risk of bleeding is associated with dual antiplatelet therapy (DAT) [139], and for patients with oral anticoagulants the risk of developing bleeding complications is further enhanced [140-142]. The higher percentage of reports on CNS and GI bleeding in men for all three substances found in our study could possibly also reflect more intense antithrombotic combination treatments [143].

6.2.2.2 Sex differences in ADE-reports from common antihypertensives

Our findings with higher prevalence of reported ADEs for women in six of the ten subgroups of antihypertensives are in line with the greater risk of ADR-related admissions to hospital

found in women [37, 48, 144]. At the same time, there are data on sex and gender differences in the spontaneous reporting of ADEs pointing to women generally reporting more symptoms [75, 76]. Our findings are plausible from a mechanistic standpoint, with women frequently at higher risk for dose-dependent ADRs due to differences between women and men in pharmacokinetics and exposure [18]. For the antihypertensives with more reports in women, a higher dose exposure was found, which is also seen in the literature with a relatively higher exposure in women to a given dose [19]. The different effect of sex hormones on the RAAS could also be part of an explanation in the case of ACE-Is and ARBs, with estrogens downregulating and androgens upregulating the RAAS [27]. Although, it has not yet been established if the hormonal influences on the RAAS have an impact on efficacy and safety of the RAAS-agents [17].

The higher prevalence of ADE-reports found in women for thiazides and diuretics with potassium sparing agents could partially be explained by women being more susceptible to drug-induced hyponatremia and other electrolyte disturbances caused by drug treatment [145]. Female sex is one of the risk factors of thiazide-induced hyponatremia [146], and is found to be four times more common in women [147]. In our study, the only group of antihypertensives with a higher prevalence of ADE-reports in men was aldosterone antagonists, possibly due to the higher prevalence of co-prescription of ACE-Is or ARBs in men, with the risk of hyperkalemia. There are gender differences in prescription patterns and a study with Swedish primary care data found that men were more often treated with ACE-Is and women with diuretics, but no difference between women and men was found for the average number of antihypertensive drug classes. Furthermore, men interrupted their treatment to a higher extent and BP was less well controlled in women [148]. A gender difference in persistence to BP treatment was found in another Swedish primary care study [149], which of course could be a confounder to our finding with a higher prevalence of ADE-reports in women.

6.2.3 Sex differences in bleeding events during warfarin treatment

In study IV, we found that the risk of severe bleeding was lower in women, with the lower risk even more pronounced after adjustments, and with the CNS bleeding risk following the same pattern. A similar finding, with a lower bleeding risk in women, has been found in the literature [62]. In our study, sex differences in age, comorbidities and co-medication could not explain a lower total incidence of severe bleeding in women. In certain subgroups, e.g. in patients with renal failure and in the age groups of 40-49 and 50-59, the overall pattern was reversed with a higher bleeding risk in women. We did find sex differences in comorbidities and co-medication, with hypertension and ischemic stroke or TIA more frequent among women while MI and ischemic heart disease were more frequent in men, and more men were treated with other antiplatelet agents compared to women, consistent with findings in the literature [67, 150-154]. Furthermore, the combination of warfarin with other antiplatelet

agents was associated with a higher severe bleeding risk in our study, was also in line with other findings [155].

When interpreting our results with the lower bleeding risk in women, the differences in stroke epidemiology between women and men must be considered, which affect the risk benefit balance for stroke prevention in women with AF on warfarin. Studies have found a higher risk of stroke in women [59, 156], and with a suggestion of a possible higher net clinical benefit of VKA treatment in women [61]. The results in our study could partially be explained by differences in prescription patterns with the physicians not prescribing anticoagulation treatment to women with a high bleeding risk to the same extent as in high risk men, especially in the elderly. A more direct evaluation of benefit-risk could be obtained by studying the possible sex differences in the incidence of stroke and recurrence of VTE during warfarin treatment, either as separate or as co-primary outcomes.

Additionally, we lacked data on BP control in the NPR and the lower severe bleeding risk in women could potentially partially be explained by sex/gender differences in hypertension control. We also lacked data on INR (international normalized ratio) and TTR, which also could be part of an explanation of the results. Thus, including information about sex and/or gender differences in factors influencing treatment choices and intensity, BP and INR, in additional studies could possibly clarify our findings.

Although NOACs are currently stepwise replacing VKA as first-line therapy in e.g. stroke prevention in atrial fibrillation (SPAF) our results are of interest. VKAs are still prescribed in many countries/regions, indications, and situations and therefore possible sex and gender differences, as highlighted here, merit further studies.

7 CONCLUSIONS

In this thesis, I have investigated sex differences in ADEs from cardiovascular medicines in routine care. The overall conclusion is that there are sex differences in reported ADEs from clopidogrel, low-dose aspirin and common antihypertensive treatment and bleeding events from warfarin. From the analyses we concluded that:

- ADRs were common in Emergency medicine in tertiary care in Sweden, and the under-reporting of ADRs to national authority was substantial. The ADRs were significantly associated with age and number of drugs. The ADRs were most frequently caused by cardiovascular medicines.

- For clopidogrel, there was a signal towards a higher prevalence of reported bleeding events in women, with standard dosing as a possible explanation. For low-dose aspirin, a lower prevalence of bleeding event reports was found in women, possibly explained by higher dosing in men.

- A higher prevalence of ADE-reports was found in women using ACE-Is, ACE-I-combinations, ARB-combinations, thiazides, diuretics and potassium-sparing agents and DHPs, with a potential linkage to dose exposure. The only group with a higher prevalence of reports in men was aldosterone antagonists, with a similar dose exposure in women and men.

- In the population-based cohort study with patients treated with warfarin, we found a lower incidence of severe bleeding in women, corresponding to a lower overall bleeding risk even after adjusting for age, comorbidities, and co-medications. We also found a lower risk of CNS and urogenital bleeding in women. However, women had a higher risk of severe bleeding compared to men among the middle-aged and in patients with renal failure.

8 FUTURE PERSPECTIVES

As a take-home-message from this thesis, there is a need of more and more reliable data on sex and gender differences concerning the safety aspect of cardiovascular treatment. To be able to answer the question of who has a higher risk of experiencing a side effect, data on sex differences in ADEs is one of the prerequisites for individualized drug treatment. Already in the development of new drugs, data on sex differences in ADEs should be presented in the pivotal RCTs preceding registration of the drug on the market. Sex and gender analyses should also be included in the post-marketing surveillance of ADEs.

To facilitate researching and obtaining sex-specific data, the accessibility and usage of the electronic patient record and pharmacovigilance databases should be improved. Having access to nationwide patient data through a common and user-friendly electronic patient record with the possibility of directly e-reporting should improve both the quantity and the quality of clinically related drug safety data. This of course comes with several ethical and legal aspects to consider, but the potential of improved drug safety should be considered.

The pharmacovigilance databases should be designed and adapted to research containing structured and easily accessible data. The data in SWEDIS consisted of solid but less accessible safety data, and with the disadvantage of fewer reports compared to the international database Vigibase. The new legislation from 2012 broadening the inclusion of reports into the national pharmacovigilance database BiSi changed the quality and accessibility of data for the clinical researcher. However, the ADE-reports in BiSi are included in the European pharmacovigilance database, EudraVigilance, and adapting this database to research would most certainly widen the horizon for drug safety research. Therefore, by using this database in future pharmacovigilance studies, a larger study population would bring more and better information on the sex differences of reported ADEs from cardiovascular medicines in routine care.

Considering the results here presented, it would be of special interest to study sex and gender differences concerning ADEs from the more recently introduced antiplatelet drugs prasugrel and ticagrelor. Furthermore, it would be highly important to study NOACs, given that these are prescribed in standard doses and usually still without monitoring.

9 SVENSK SAMMANFATTNING

Läkemedelsbehandling av hjärtkärlsjukdom består till stor del av förebyggande behandling, och framförallt när det gäller preventiva läkemedelsbehandlingar så är risken stor att patienten inte fortsätter sin behandling vid uppkomst av läkemedelsbiverkningar, vilket i sin tur kan leda till en ökad risk för stort lidande, funktionella handikapp och för tidig död. Ökad kunskap om eventuella skillnader i läkemedelsbiverkningar hos kvinnor och män kan i sin tur leda till att läkemedelsbehandlingen bättre anpassas efter individen. Detta kan öka chanserna för att patienten fortsätter med sin preventiva behandling. Det övergripande syftet med avhandlingen är att få ökad kunskap om och förståelse för könsskillnader i läkemedelsbehandling av hjärtkärlsjukdom, med särskilt fokus på blödningar som orsakats av läkemedel för att förebygga blodproppar, specifikt warfarin.

Den första delstudien i avhandlingen beskriver förekomsten av och möjligheten att förebygga läkemedelsbiverkningar samt och spontan biverkningsrapportering på en akutvårdsavdelning på Karolinska Universitetssjukhuset Solna. Studien visar att fyrtio procent av patienterna hade minst en möjlig läkemedelsbiverkan, och närmare en femtedel av patienterna hade biverkningar som orsakat eller bidragit till sjukhusinläggning, varav cirka en fjärdedel bedömdes som förebyggbara. De vanligaste förekommande biverkningarna var orsakade av läkemedelsbehandlingar mot hjärtkärlsjukdom, och spontan biverkningsrapportering förekom i mycket liten utsträckning.

Den andra delstudien beskriver könsskillnader i rapporterade blödningar orsakade av tre olika läkemedel mot blodpropp: klopidogrel, lågdos acetylsalicylsyra (ASA) samt warfarin. Studien visar att fler män behandlades med klopidogrel men att rapporterade blödningar orsakade av klopidogrel var vanligare hos kvinnor. Rapporterade blödningar orsakade av lågdos-ASA var däremot vanligare hos män samtidigt som det inte fanns någon könsskillnad i blödningsrapporter orsakade av warfarin.

Den tredje delstudien undersökte könsskillnader i samtliga biverkningsrapporter för vanligt förekommande läkemedel mot högt blodtryck. I sex av tio av de läkemedelsgrupper som undersöktes så fanns det totalt fler biverkningsrapporter för kvinnor, med tecken till att dosen i dessa fall kunde haft betydelse.

Den fjärde delstudien undersökte könsskillnader i allvarliga blödningar orsakade av warfarin och den visade att dessa förekom i mindre utsträckning hos kvinnor, vilket även gällde risken för bland annat hjärnblödningar, specifikt. Risken för allvarliga blödningar var lägre hos kvinnor även efter det att man tagit hänsyn till ålder, andra sjukdomstillstånd och övrig läkemedelsbehandling.

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