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Persistence to antihypertensive drug treatment in Swedish primary care

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" The final forming of a person's character lies in their own hands."

Anne Frank

PROLOGUE

To Mom and Dad

It is cold outside. I am lying in bed trying to study, but the sleepiness after several days of high fever from having the flu, and the severe pain in my mouth from last week's dental surgery is hampering my willingness. I am picking up the book, and while attempting to read, the phone starts ringing. I answer, but have barely time finishing my name, before Mom is interrupting, telling me about how hard it is getting in touch with me now that I am not living in their house anymore. As I am listening, I am recognizing that something is different in her voice that is drawing my attention. Why does it sounds as if she is swallowing? Is she sad? Why is she sad? Is it because I have moved? She is telling me that I should have come visiting them next week instead, that I should not be coming when I am having the flue and that I had infected Dad. I answer her that I did not know that I was going to have the flu, but she is not listening to me, saying that Dad also have had the flu, and he has been sick all week, repeating that I shouldn't be coming when I might have the flu and that he should not been infected. I could not understand why Mom was sounding so upset, after all, it was just the flu. I started thinking about the fact that Mom might be upset since I recently moved away from their home, that she is coping with her and Dad's new life, and maybe Dad was sad for me having moved out.

All of a sudden, she is quiet. I hear that she is taking a deep breath. She tells me that she needs me to sit down, because she is going to tell me something important and does not want me to fall down. What is she saying? I am not capable of replying. Her different voice and talk is making me anxious and my whole body becomes tense. This is not good, is all I am thinking. She is quiet, probably trying to gain momentum, but then she is starts talking. Dad has been out shoveling snow last night, although she had kept telling him not to. She had been promising him to do it herself in the morning the next day before going to work, saying that she really wanted him staying in bed since he needed to rest after several days of fever. Dad had said that he needed to exercise, that staying in bed all week was boring, and a little shoveling would do him good. After shoveling snow for almost half an hour, he started feeling pain in his left shoulder. He was figuring it must be because of the shoveling, so he decided to go inside to get some rest. He goes to bed, but feels an intense pain that increases towards his left arm and left side of the upper body. He starts screaming in pain, waking Mom, who immediately asks him about what is happing, and as soon as he tells her about the location of the pain, Mom is calling the emergency. Five minutes later nurses from Karolinska University Hospital is knocking on the door. The doctors on the phone are telling the nurses that the ECG is showing that Dad is having a heart attack and that Dad needs to get to the emergency straightaway. My head is spinning around and my heart is beating fast. One question is screaming in my head, but I am not finding the courage in saying it out load should the answer be something terrible. Instead of asking if he is alive, I decide asking her about where

he is, and she tells me he is resting in bed and is going to have a surgery the next coming day.

The doctor had told him that he had had a high blood pressure for which he had none treatment for and they had acknowledge the fact that he also had diabetes. They initiated pharmacological treatment, talked about lifestyle changes. Dad decided that he would fully accept and embrace the doctor's recommendations, and start a new life, which was exactly what he did.

I am so grateful that Mom had done the right thing to call the emergency and that Dad had survived.

Dad, so proud of you that you were able to do all those lifestyle changes and that you take your medications every day.

Love you.

Miriam Qvarnström

ABSTRACT

Hypertension is The efficacy of antihypertensive drug therapy is undisputed, but large surveys report that one in four patients reach a target blood pressure of <140/90 mm Hg. Although there are several explanations to this problem, poor medication adherence and persistence to drug treatment suggests as important contributors.

We started with a cross-sectional study design, to describe drug prescription patterns and blood pressure control in 24 primary healthcare centers in southwestern part of Stockholm, Sweden. Electronic medical records of 21167 patients (≥30 years) with a diagnosis of hypertension and a consultation at one of the included primary health care centers in 2005-2006 were analyzed. A prescription of an antihypertensive drug were found in 89% of the patients, and the most common were the diuretics and beta blockers. One out of four primary care patients with hypertension had a target blood pressure <140/90 mm Hg with or without antihypertensive drug treatment.

Medication persistence is considered an important factor to poor blood pressure control. Therefore, in the subsequent project, we used a cohort study design to measure persistence after two years of follow-up and analyzed factors associated with low therapy persistence, i.e. persistence to any antihypertensive drug class treatment. Using electronic medical records for patients with hypertension in 48 Swedish primary healthcare centers and data linkage to national registers on dispensed drugs, hospitalizations, outpatient hospital consultations, deaths, migration, and socioeconomy, we were able to identify 5225 patients initiated on antihypertensive drug treatment during 2006- 2007. Among patients with a dispensed first prescription, 65 % were persistent after the two years of follow-up. Factors associated with low therapy persistence to antihypertensive drug treatment were male sex, younger age, mild-to-moderate systolic blood pressure elevation, and birth outside of Sweden.

After the assessment of therapy persistence, an important question remained, and that was to answer if there was a difference in persistence to the various antihypertensive drug classes? Again, we performed a cohort study with the same method described above, but analyzed each antihypertensive drug class in comparison to the diuretics. It appeared to be no difference in drug class persistence between diuretics and the other major antihypertensive drug classes. Predictors behind low class persistence were the same as for therapy persistence.

Although register studies are of interest and of great value, they lack certain information. To get a broader picture of the medication persistence, we decided to perform a cross-sectional study and use questionnaires to ask the patients about their beliefs about medicines and the hypertension diagnosis. The questionnaires were linked with data on the patient's filled prescription and the patients were categorized into persistent or non-persistent medication-users, to observe potential differences in the attitudes between the persistent and non-persistent patients. Out

of the 69 primary healthcare centers questioned, 25 agreed to participate in the study. In January 2016, patients with a diagnosis of hypertension and a consultation at one of the 25 primary health care centers received a questionnaire 3-12 months after initiation of drug treatment. Out of the 1197 patients newly initiated antihypertensive drug treatment, 711 patients (59%) responded. Patients were classified as persistent (609, 86%) or non-persistent (102, 14%) to antihypertensive drug treatment by analyses of their filled prescriptions. Compared to non-persistent medication users, patients persistent to medication believed to a higher degree that the diagnosis of hypertension was chronic, that it had less consequence on their life, that they can prevent cardiovascular disease by taking antihypertensive drug treatment and that there is something positive about taking the pharmacological treatment.

LIST OF SCIENTIFIC PAPERS

I. **Antihypertensive treatment and control in a large primary care population of 21167 patients. Results from the Swedish Primary Care Cardiovascular Database (SPCCD)**
Miriam Qvarnström, Björn Wettermark, Charlotta Ljungman, Ramin Zarrinkoub, Jan Hasselström, Karin Manhem, Anders Sundström, Thomas Kahan
Journal of Human Hypertension 2011;25:484-491

II. **Persistence to antihypertensive drug treatment in Swedish primary healthcare**
Miriam Qvarnström, Thomas Kahan, Helle Kieler, Lena Brandt, Jan Hasselström, Kristina Bengtsson Boström, Karin Manhem, Per Hjerpe, Björn Wettermark
European Journal of Clinical Pharmacology 2013;69:1955-1964

III. **Persistence to antihypertensive drug classes: A cohort study using the Swedish Primary Care Cardiovascular Database (SPCCD)**
Miriam Qvarnström, Thomas Kahan, Helle Kieler, Lena Brandt, Jan Hasselström, Kristina Bengtsson Boström, Karin Manhem, Per Hjerpe, Björn Wettermark
Medicine (Baltimore) 2016;95:e4908

IV. **Persistence to antihypertensive treatment – a cross-sectional study of patients' attitudes towards hypertension and medicines**
Miriam Qvarnström, Thomas Kahan, Helle Kieler, Lena Brandt, Jan Hasselström, Björn Wettermark
Submitted

CONTENTS

LIST OF ABBREVIATIONS

ACE-I	Angiotensin converting enzyme inhibitor
ARB	Angiotensin receptor blocker
ATC	Anatomical Therapeutic Chemical classification
BMQ	Beliefs about Medicines Questionnaire
CO	Cardiac output
CCB	Calcium channel blockers
CI	Confidence interval
DDD	Defined daily dose
DBP	Diastolic blood pressure
ESC	European Society of Cardiology
ESH	European Society of Hypertension
IPQ	Illness Perception Questionnaire
ICD	International Classification of Diseases
ICD-10	ICD, 10th version
ISH	Isolated systolic hypertension
PHC	Primary healthcare center
PVR	Peripheral vascular resistance
SBP	Systolic blood pressure
SBU	the Swedish Agency for Health Technology Assessment and Assessment of Social Services
SCB	Statistics Sweden
SPCCD	Swedish Primary Care Cardiovascular Database
TIA	Transient Ischemic Attack

INTRODUCTION

Hypertension or elevated blood pressure is a common condition, with high prevalences in many parts of the world.[1] For most patients, it is a condition with unknown aetiology and without symptoms. This silent illness can affect the arteries, veins, and inner organs for several years without a single notice. If the patient finds out about the blood pressure elevation, corresponding to a diagnosis of hypertension (≥140/90 mm Hg[2]), it is possibly during a visit to the pharmacy, primary healthcare center, hospital or at home (≥135/85 mm Hg)[2]. At this point, it can certainly be an unpleasant reminder or acknowledgement of the fragile, older body, and the higher risk of coronary heart disease, heart failure, stroke, peripheral arterial disease, renal failure, and dementia.[3-7] If the patient seeks healthcare professional, the patient will receive information about the necessary lifestyle changes, to lower the blood pressure elevation. There are patients that decide do these lifestyle changes. They lower their elevated blood pressures as they lose weight[8], reduce salt[9,10] and alcohol intake[11], do physical exercise regularly[12], and increase the intake of vegetables in their diet[2], but the majority of patients will need an antihypertensive drug prescription and more than one drug class to reach target blood pressure.[13] In most cases, the patient will fill the first prescription, but as it turns out, many patients will not continue to fill their prescriptions.[14-19]

Consistent and long-term antihypertensive drug therapy is crucial to maintain blood pressure control and benefit from treatment.[20] Discontinuation of antihypertensive drug treatment is associated with poor blood pressure control.[21] These facts are problematic, when results from a review report an average medication persistence of 63% after one year, with a variation from 35-92%.[22] This large variation is the proportion of patients persistent to drug treatment in later studies from Europe, Northern America, Australia and Asia.[15,23-27] However, it may be difficult to compare studies due to differences in patient populations, time of follow-up, definitions of persistence and data sources.

Although to measure the blood pressure itself is by far the most rational way to study if the patient takes the antihypertensive drug, is does not take into account the possibility that the patient might be adherent only before the consultation with the health care provider. Therefore, data on filled prescriptions from national registers are of great value to observe if patients continue on their antihypertensive drug treatment.[28] However, registries provide limited knowledge on patient behavior. Hence, to analyze the actual patient's attitudes, a questionnaire provide an opportunity to investigate the patient's own beliefs and ideas.

The studies in this thesis have the aim to: 1) describe blood pressure levels and antihypertensive drug treatment, 2) study which factors may be associated with patients' discontinuation of antihypertensive drug treatment and 3) describe differences in attitudes between persistent and non-persistent medication users.

EPIDEMIOLOGY OF HYPERTENSION AND THE PATIENTS

In 2004, the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) published a report on the prevalence of hypertension with an estimate of 27%, which corresponded to 1.8 million of the adult population of Sweden over the age of 20 years old.[29] Eight years later, the Skaraborg project found that 20% of the adult population had hypertension and steep increase in older age.[30] These two estimates represented proportions of patients expected to have hypertension, whether or not diagnosed by a physician, i.e. *unknown* hypertension. The prevalence of hypertension is dependent on the number of blood pressures recordings on each occasion, and the number of visits to the health care provider. Therefore, results of hypertension prevalence between different populations and countries, may be compared with difficulty, and subsequently, it has been suggested to use surrogates for hypertension prevalence.[31]

The prevalence of hypertension was estimated to 10% in Östergötland County in 2004[32], 11% in southwestern part of Stockholm in 2005-2006[33] and 12% in Stockholm County in 2011[34] of the adult population. These estimates on prevalences of *known* hypertension are based on diagnoses recorded in primary health care as well as other caregivers. A study based on data from electronic medical records from the primary health care centers of Stockholm County in 2011, found that essential hypertension was one of the five most common diagnoses, recorded for almost 6% of all the inhabitants in the county during 2011.[35] However, although these represents different regions of Sweden, differences in prevalences of hypertension has been reported between rural and urban areas of Sweden[36,37].

A systematic review from 2004 found that the prevalence of hypertension varied widely between countries in the rest of the world, between 3.4% in rural Indian men and 72.5% in Polish women.[38] The authors estimated that 26.4% of the adult population in the world had hypertension in 2000, and 29.2% were predicted to have hypertension in 2025. However, a population-based review on the prevalence and control of hypertension in 90 countries was published recently in 2016, suggesting that 31% of the adult population of the world had hypertension in 2010.[1] This review defined the countries into low – and high-income countries according to the World bank classification system,[39] and found that the prevalence in 2010 was 25% in high-income countries such as Sweden.

BLOOD PRESSURE

In 2012, the World Health Organization stated that 17.5 million died from cardiovascular disease, which represented almost a third of all global deaths.[40] The same year the Global Burden of Disease project reported that an elevated systolic blood pressure above 115 mm Hg was the largest factor that contributed to the global burden of disease and mortality.[41] These findings gives us an overview of the significant problem we are facing with large populations of patients in need of lowering their blood pressure.

Older observational studies reported that few patients reached target blood pressures[42] and that there were differences in the level of blood pressure control between countries. The control rates in Europe were found to be worse than those of Canada and the United States.[43] More positive results come from longitudinal observational studies in the populations of Sweden[44], Germany[45], Czech Republic[46] and in the United States.[47] Those studies described a trend in increased proportion of patients with a controlled blood pressure over several decades. However, it is uncertain if this was due to better treatment or if patients with lower blood pressures were getting diagnosis and treatment earlier.

An overview of the ESH/ESC guidelines for initiation of antihypertensive drug treatment according to blood pressure, number of risk factors and disease history are provided in Table 1 with relevant year for the studies included in the thesis. The corresponding Swedish national guidelines comes from the Medical Product Agency, the Swedish national authority responsible for regulation and surveillance of the development, manufacturing and marketing of drugs and other medicinal products, and they are only slightly modified from the ESH/ESC guidelines.

Table 1. Modified summary of blood pressure thresholds for initiating antihypertensive drug treatment as stated by other risk factors and disease history according to the ESH/ESC guidelines from different years.

	Blood pressure (mm Hg) thresholds to initiate antihypertensive drug treatment		
	ESH/ESC guidelines (2003)[48]	**ESH/ESC guidelines (2007)[49]**	**ESH/ESC guidelines (2013)[2]**
No other risk factors	SBP ≥140 or DBP ≥90 (initiation of drug treatment should be *considered* after 3-12 months of monitoring of BP with an initial SBP between 140-179 or DBP 90-109)	SBP 140-159 or DBP 90-99	SBP 140-159 or DBP 90-99
1-2 risk factors	SBP ≥140 or DBP ≥90 (after at least 3 months of monitoring of BP with an initial SBP between 140-179 or DBP 90-109)	SBP 140-159 or DBP 90-99	SBP 140-159 or DBP 90-99
Diabetes	SBP 130-139 or DBP 85-89	SBP 130-139 or DBP 85-89	SBP 140-159 or DBP 90-99
Established cardiovascular or renal disease	SBP 130-139 or DBP 85-89	SBP 120-129 or DBP 80-84	SBP 140-159 or DBP 90-99

SBP – systolic blood pressure. DBP – diastolic blood pressure. The ESH/ESC guidelines from 2003 stated that the initiation of drug treatment should be <u>considered</u> in patients with no other risk factors. Patients with no other risk factors are those with low added risk. The ESH/ESC guidelines from 2007 and 2013 stated that the initiation of drug treatment should be considered in patients with no other risk factors if blood pressure is still uncontrolled after several months of lifestyle changes. The ESH/ESC guidelines from 2007 and 2013 stated that the initiation of drug treatment should be considered in patients with 1-2 risk factors if blood pressure is still uncontrolled after several weeks of lifestyle changes.

ANTIHYPERTENSIVE DRUG TREATMENT

In the four studies of this thesis, focus was primarily on the five major antihypertensive drug classes; angiotensin receptor blockers (ARBs), angiotensin converting enzyme inhibitors, beta blockers, calcium channel blockers and diuretics. These five antihypertensive drug classes were all first-line treatment according to the ESH/ESC guidelines from 2013, but the regional guidelines provided in Stockholm County, the Wise Drug List[50], did not recommend beta blockers in 2017. They were reduced to second line treatment in previous years. A Cochrane meta-analysis from 2012 reported that the beta blockers had a worse outcome than some of the other antihypertensive drug classes. [51,52]

The five main antihypertensive drugs classes studied in this thesis lower the blood pressure (BP) through the cardiac output (CO) and/or the peripheral vascular resistance (PVR):

$$BP = CO \times PVR$$

Beta blockers and diuretics were shown to lower the cardiac output, while the angiotensin converting enzyme inhibitors, the angiotensin receptor blockers and the calcium channel blockers reduced the peripheral vascular resistance.

Patients

Evidence suggested that women benefited from antihypertensive treatment similar to men.[53] Cross-sectional studies of antihypertensive drug treatment from various countries around the world reported that diuretics were the most commonly used by women, while ACE-I were more common among men.[54-58] It was suggested that these differences between sexes could not be explained by known factors that influenced the choice of initiation of antihypertensive drug treatment and that further investigations were needed. Studies of sex differences in indications not registered, such as the prescribing of diuretics in ankle edema and experiences of side effects, were proposed.[55]

In 2008, the Treatment of Hypertension in Patients 80 Years of Age or Older (HYVET) concluded that patients 80 years of age or older will benefit from antihypertensive treatment.[59] A meta-analysis of randomized trials published the same year concluded that the antihypertensive drugs are just as effective in patients 65 years of age or older as in younger patients.[60] Also, a recent publication investigated if there was an interaction in the antihypertensive treatment and the frailty in older patients, and concluded that there was none, but that more studies were needed to examine this possible interaction.[61] Despite the evidence in favor of treatment in patients 80 years or older, findings from a cross-sectional studies suggested that older were not treated as aggressive as younger patients.[62]

The prevalence of diabetes was found to be 6.8% with an incidence of 4.4 per 1000 patients in 2013.[63] A longitudinal study followed patients with hypertension for 28 years, and found that 20.4% of the patients developed diabetes.[64] These patients, as well the obese, had a higher insulin resistance. A problem would therefor arise if we

were to treat these patients with the old types of beta blockers or diuretics, since they could reduce the insulin sensitivity. Furthermore, beta blockers had shown results of increased risk of new-onset diabetes in patients with hypertension.[65] The ACE-I[66] would seem as a better option as they improved insulin sensitivity[67] and ARBs, or some of the relatively newer vasodilating beta blockers which doesn't seem to impair the insulin sensitivity to such as much as the older substances.[68,69]

MEASURES OF MEDICATION TAKING BEHAVIOUR

Numerous of names and definitions for the various measures of medication taking behavior have been used over the years. Although several decades of compliance and persistence research, there still has not been developed any uniform standard of definitions and measurements. This hampered the possibility to compare the different studies, and the complexity increases with the different healthcare policies of each country. The most common terms of medication taking behavior used today are described in the two sections following, with the definitions based upon the review published in 2008 by Joyce Cramer and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Work Group.[70] They developed definitions for the terms compliance and persistence during three years of review work and discussions with professionals from countries all over the world.

Four years after Cramer's review was published, a new review came. It was written by Vrijens et.al. with another definition of adherence and persistence.[71] Instead of defining adherence or compliance as a different measure compare to persistence[70], they proposed that persistence could be seen as a part of adherence.

Medication adherence, compliance and concordance

In 1990, Feinstein published an article about compliance[72] were he commented on the different terms, saying that : "Adherence seem to sticky; Fidelity has too many connotations; and Maintenance suggest a repair crew. Although adherence has its adherents, Compliance continues to be the most popular term." He was right at the time, but around 1993 the term Compliance was replaced by Adherence.[73-75] During this time there was a change in the way on how we see the relationship between the patient and health care provider. Compliance in the English language has a negative connotation and means that the patients are subservient to the prescriber [76,77] and that the patient is a passive and obedient to the prescriber's instruction.[78,79] The term concordance was introduced in 1995 by the Royal Pharmaceutical Society of Great Britain.[80] The meaning of term acknowledged the fact that patients and health care providers may have differing views and therefor need to cooperate.[80-83] However, around 2008 the term "Medication adherence" became a MeSH term, and according to Cramer's review are the terms medication compliance and adherence synonymous.[70]

Medication persistence

In the review by Cramer[70] medication persistence is defined as : "the duration of time from initiation to discontinuation of treatment". In this definition, a predefined gap should also be determined. The gap is the number of days between start and end of medication or observation, where the patient is allowed to be without drug treatment but is considered persistent. This definition has been used in all three studies on medication persistence included in this thesis.

A summary of selected publications on medication persistence on antihypertensive drug treatment are summarized in Table 2. The table is merely an overview of how different the published articles on medication persistence can appear. Medication persistence can further be divided into therapy or class persistence. There are no established definitions for these two terms, but in general, therapy persistence describes the studying of any antihypertensive drug class and if patients switch drug class, they are still considered therapy persistent.

Class persistence, on the other hand, is when you want to study medication persistence to a certain antihypertensive drug class, and if the patient switch to another antihypertensive drug class, the patient is considered non-persistent to the drug treatment. Systematic reviews on studies of medication persistence to antihypertensive drug treatment showed major differences in results.[22,84] They also reported large differences in used definitions of persistence to antihypertensive drug treatment and methods used. This results in severe difficulties in comparing the results between studies, and also leads to large variations in the findings. The source of information which has been suggested to be the golden standard for the assessment of persistence to drug treatment are the databases on filled prescriptions[85], primarily from national databases, since they provide unique source of complete follow-up of drug dispensing.

Several studies have analyzed persistence to antihypertensive drugs using data from various prescription- or dispensing databases, but without any linkage to diagnoses. These studies may be difficult to interpret in the context of hypertension since they also include antihypertensives prescribed for many other conditions. Some examples include beta blockers prescribed for migraine or atrial fibrillation, ACE-I/ARB prescribed for heart failure or diuretics prescribed for edema.

Persistence may be influenced by many patient-, provider or health system characteristics. A majority of studies include age, sex and comorbidity in the analyses. Others have analyzed adherence and persistence in relation to patient characteristics such as number of drugs, concomitant medication, level of insurance, income, living area, ethnicity, social insurance, health status, education and marital status or provider characteristics such as organization of the clinic or physician education specialty and qualifications. An overview of the determinants included in the studies from Table 2 are presented in Table 3.

Table 2. Overview of different studies on persistence to antihypertensive treatment.

Name of publication (year)	Allowed gap (days)	Number of patients	Therapy or class persistence (T/C)	Proportion persistent (%)	Time of follow-up (years)	Studies based on medical records	Studies based on filled prescriptions	
						Time period between pre-scriptions issued	Time between filled pre-scriptions	Time between end of supply and new filled pre-scription
Bourgault et.al. (2005)[18]	60	21 326	T	29-53	3		X	
Elliott et.al. (2007)[86]		60 685	C	56-69	1			X
Ishisaka et.al. (2012)[16] Ah et.al. (2015)[17]		51 772	C	58-69	3.5			X
Friedman et al. (2010)[23]		207473	T/C	66	2			X
Patel et al. (2007)[87]		242 882	C	30-52	1			X
Burke et al. (2006)[88]	90	109 454	T	7	9			
Tamblyn et al. (2010)[89]		13 205	T	78	0.5			X
Vinker et al. (2008)[90]		3 799	C	41	3		X	
Corrao et.al. (2008)[19]		445 356	T/C	50	5			X
Simons et.al. (2008)[26]		48 690	T	44	<3		X	
Briesacher et.al. (2007)I[91]		23 047	C	52-73	1		X	
Nicotra et.al. (2009)[25]		49 805	C	76	3/4			X
Saleh et.al. (2008)[92]		22 821	C	43	1			X
Hasford et.al. (2007)[24]	180	13 763	T/C	15	3	X		
Wong et.al. (2009)[93]		93 286	T	87	0.5	X		
van Wijk et.al. (2005)[27]		2 325	T	61	10			X
Lachaine et.al. (2008)[94]	n/a	4 561	T	53-69	2		X	
Mancia et.al. (2014)[95]	n/a	493 623	T	57	1			X
Grimmsmann et.al. (2014)[14]	n/a	9 513	T	44-82	4	X		
Selmer et.al. (2012)[15]	n/a	78 453	T	65-96	5		X	
Trimarco et.al. (2012)[96]	n/a	2 409	C	n/a	>2		X	

Allowed gap is the number of predefined days in which the patient is allowed to be without treatment, but is still considered persistent. End of supply can be estimated from the actual dosage text or the less precise measure DDD (Defined Daily Dose); the assumed average maintenance dose per day for a drug used for its main indication in adults (problem here is that all of the antihypertensive drug classes do not have DDD's for the indication of hypertension).

Table 3. Number of studies assessing the various variables in association to persistence to antihypertensive drug treatment.

Assessed variable	Number of studies
Sex	18
Age	18
Comorbidity	12
Income	5
Country of birth/immigrant	1
Initial blood pressure	1
Education	0

An overview of the determinants included in the studies from Table 2 are presented here.

SPCCD – THE SWEDISH PRIMARY CARE CARDIOVASCULAR DATABASE

In December 2007, a collaboration started with of a group of ten highly devoted researchers, including cardiologists, general practitioners, pharmacists, PhD students and data managers from Stockholm, Gothenburg and Skövde, with the goal of creating a research database consisting of patients with diagnosis of hypertension in the primary health care. After five years of devotion into work and meetings, the Swedish Primary Care Cardiovascular Database was created. The database has provided data for the involved researches since 2012, and other researches interested in the data may send a request to the board to ask permission on using the data for scientific use only. A list of all publications from the SPCCD by publication year is provided in Table 4.

Table 4. List of publications from the Swedish Primary Care Cardiovascular Database

Study	Diagnoses	Main finding
Qvarnström M, et al. 2011[33]	Essential hypertension	Antihypertensive drug treatment and control according to sex, age and comorbidity
Qvarnström M. et al. 2013[97]	Essential hypertension	Therapy persistence to antihypertensive drug treatment
Hasselström J. et al. 2014[98]	Essential hypertension	Descriptive data of the SPCCD
Ljungman C. et al. 2014[56]	Essential hypertension	Gender differences in antihypertensive drug treatment
Ljungman C. et al. 2015[99]	Essential hypertension	Antihypertensive treatment and control according to gender, education, country of birth and psychiatric disorder
Qvarnström M. et al. 2016[100]	Essential hypertension	Class persistence to antihypertensive drug treatment
Holmqvist L. et al. 2016[101]	Treatment resistant hypertension	Prevalence of treatment resistant hypertension
Bokrantz.T. et al. 2017[102]	Essential hypertension and osteoporotic fractures	Thiazide diuretics and the risk of osteoporotic fractures in hypertensive patients

SPCCD – Swedish Primary Care Cardiovascular Database.

AIMS

The overall aim of this thesis was to add knowledge about antihypertensive drug treatment and medication persistence in primary health care patients.

The main objectives of the studies of this thesis:

1. To describe the antihypertensive pharmacological treatment prescribed and blood pressures levels.

2. To assess therapy persistence for antihypertensives and to assess factors associated with poor therapy persistence.

3. To assess differences in class persistence between the various antihypertensive drug classes.

4. To assess differences in attitudes towards hypertension, drugs in general and the antihypertensive drug treatment in persistent and non-persistent patients.

MATERIALS AND METHODS

This thesis consists of four observational studies on patients with diagnosis of hypertension in primary health care. An overview of the materials and methods used in this thesis are presented in Table 5.

STUDY DESIGNS

The thesis comprises two different study designs, the cross-sectional and the cohort (Figure 1 and 2). In a cross-sectional study design, all information obtained for the study is gathered at the same time point. It means that the information that the results can rely upon in this type of study design, is limited to this specific time, and gives only a snapshot of the population under study. Conclusions possible to draw from such study designs are limited to the prevalence of the population and potential associations between various factors and variables. It is useful when there is a need to give a general description of a population, but cannot be used for studying casual relationships, where patients need to be followed over time and data on what happened before and after is needed.

Figure 1. The two study designs of the thesis; the cross-sectional and the cohort.
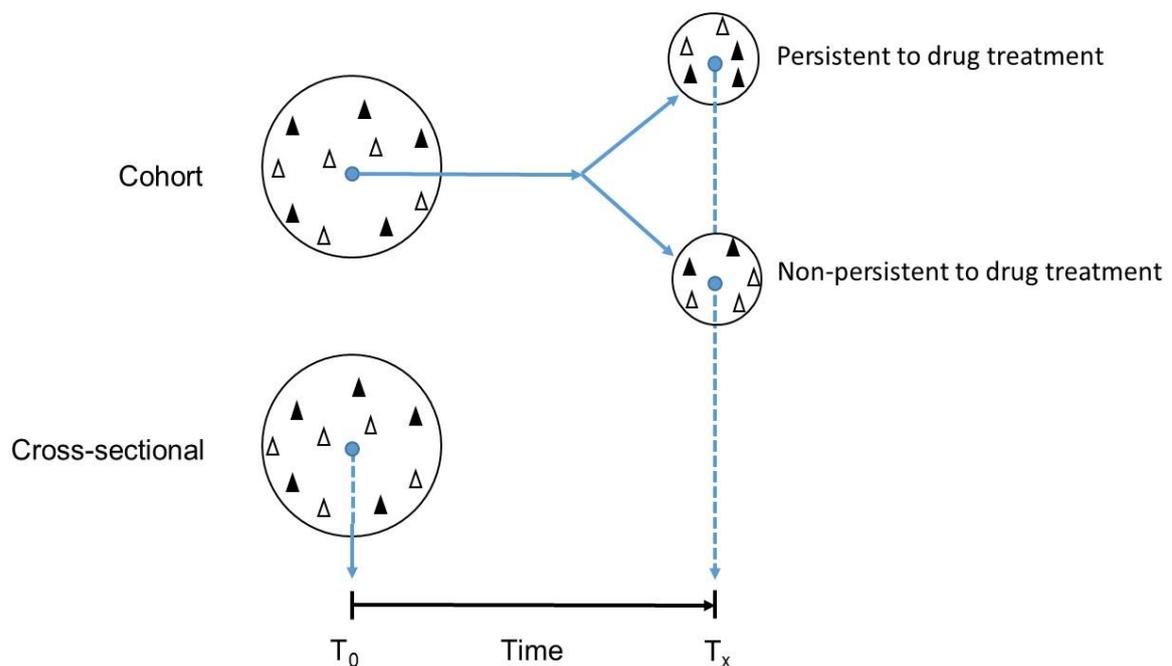
Black and white triangles represents two different exposures examined in this thesis, for example men and women. In the cross-sectional study design from Study I, a prevalence of hypertension was estimated, and in Study IV, attitudes towards hypertension at time T_0. The cohort studies in this thesis investigated persistent versus non-persistence to drug treatment as the outcomes of interest, measured from T_0 until time T_x, and corresponds to two years in the studies of this thesis.

Table 5. Overview of the studies included in the thesis.

Study	I	II	III	IV
Design	Cross-sectional	Cohort	Cohort	Cross-sectional
Setting	24 primary health care centers in south-western part of Stockholm	24 primary health care centers in south-western part of Stockholm and 24 primary health care centers in Skövde district in Western Sweden	24 primary health care centers in south-western part of Stockholm and 24 primary health care centers in Skövde district in Western Sweden	25 primary health care centers in the north-eastern and south-western part of Stockholm
Hypertension diagnosis	2005-2006	2001-2007	2001-2007	2013-2015
Number	21167	5225	4997	711
Data source(s)	Electronic medical records from primary	The Swedish Primary Care Cardiovascular Database	The Swedish Primary Care Cardiovascular Database	Questionnaires merged with the national register on dispensed drugs
Study period	2005-2006	2006-2010	2006-2010	2013-2016
Main factors analyzed	Blood pressure in all hypertensive patients and patients with diabetes. Prescribed antihypertensive drug treatment	Persistence to any antihypertensive drug treatment	Persistence to antihypertensive drug classes (diuretics compared to beta blockers, CCBs, ACE-Is or ARBs)	The patients' attitudes towards diagnosis of hypertension and drugs in relation to their persistence to antihypertensive drug treatment
Data analysis	Student's t-test	Cox model	Cox model	Mann-Whitney U-test and Cox model

CCB – calcium channel blockers. ACE-I – angiotensin converting enzyme inhibitor. ARB – angiotensin receptor blocker. Study period includes the years of inclusion period and the time of follow-up.

An example of such study design is the cohort study design. In a cohort study, a defined group of people without the outcome of interest is being analyzed and

followed forward in time, starting at the date when the exposures were defined. The outcome of interest in these cohort designs of this thesis (Study II-IV) is the date when the patient is defined as non-persistent to antihypertensive drug treatment. Patients are *censored* (further discussed under "Methods"/"Cox regression") when they die or when the end of study period, corresponding to a maximum of two years (Study II-III).

SETTINGS

The thesis includes patients from three settings, marked out on the map of Sweden in Figure 3. The setting in Study I included 24 primary healthcare centers of southwestern Stockholm, Sweden, all of which are part of a collaboration since 1992[103]. The group EK-gruppen, consisting of five general practitioners interested in improving the quality of drug prescription started the collaboration. They agreed on how diagnoses and quality parameters should be registered in the medical records and data from the medical records were used in feedback to the primary healthcare centers to discuss potential areas of quality improvement. The second setting was used in Study II and III, comprising of patients from the southwestern part of Stockholm and the Skövde district, representing an urban and a rural area, with a total of 48 primary health care centers, equally distributed between the areas. These patients were all collected from the Swedish Primary Care Cardiovascular Database (SPCCD), including a combination of electronic medical records data and national registers for the 48 primary health care centers. The third setting comprised of patients consulting primary health care centers from the southwestern and northeastern part of Stockholm, representing two different socioeconomic areas.

EPIDEMIOLOGY AND PATIENTS

The patients were 30 years or older and had consulted and received a diagnosis of essential hypertension (ICD-10 code I10) at one of the primary health care centers included in the studies of this thesis (Study I-IV). The patients' were newly initiated on antihypertensive drug treatment from one of the primary health care centers involved in the studies (Study II-IV), or included all patients diagnosed with hypertension irrespective of patients being prevalent or incident antihypertensive drug users, or not prescribed an antihypertensive drug at all (Study I). The prevalence of hypertension was calculated. The number of patients with diagnosed hypertension was divided with the number of people in the catchment area during the study period of 2006 (Study I).

VARIABLES

Variables assessed or described in the studies of this thesis are summarized in Table 6.

**Table 6. Variables described or assessed in the studies of this thesis.**

	Study I	Study II	Study III	Study IV
Age	X	X	X	X
Sex	X	X	X	X
Blood pressures (mean recorded)	X			
Blood pressures (last recorded)	X	X	X	X
ACE-inhibitors	X	X	X	X
Angiotensin receptor blockers	X	X	X	X
Beta blockers	X	X	X	X
Calcium channel blockers	X	X	X	X
Diuretics	X	X	X	X
Fixed combination therapy	X		X	
More than one drug class prescribed	X		X	
Cardiovascular comorbidity	X	X	X	X
Atrial fibrillation	X	X	X	
Congestive heart failure	X	X	X	
Diabetes mellitus	X	X	X	X
Ischemic heart disease	X	X	X	
Stroke/TIA	X	X	X	
Number of other drugs		X	X	
Educational level		X	X	
Country of birth	X	X	X	X
Income		X	X	
Attitudes towards hypertension				X
Attitudes towards drugs in general				X
Attitudes towards antihypertensive drug treatment				X

Cardiovascular comorbidity – a diagnosis of atrial fibrillation, congestive heart failure, diabetes mellitus, ischemic heart disease or stroke/TIA. We analyzed prescribed drug classes (Study I) and filled prescriptions (Study II-IV).

DATA SOURCES

The data sources of this theses comprised of national registers held by the National Board of Health and Welfare and Statistics Sweden, the electronic medical records provided by the primary health care centers and the Swedish Primary Care Cardiovascular Database (SPCCD).

Figure 2. Map of Sweden highlighted with the three settings of this thesis and data on primary health care centers.
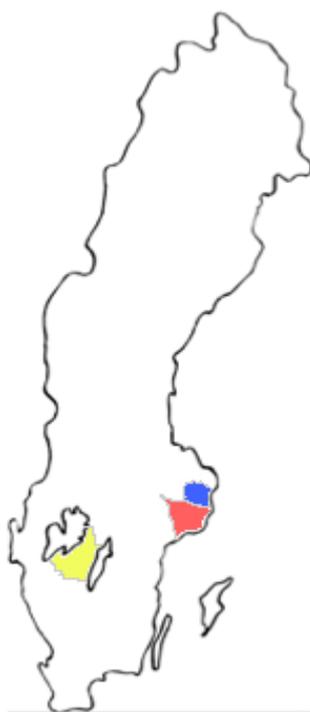
Red area – representing Study I. Yellow and red areas – representing Study II-III (the settings of the Swedish Primary Care Cardiovascular Database). Blue area – representing Study IV.

Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register contains information about filled prescriptions from primary and specialized care, including data from all pharmacies in Sweden since July 2005[104]. The data on each prescription is ordered by the drugs Anatomic Therapeutic Classification code and date of filled prescription. The information is updated monthly and comes from the E-health authority, to which the pharmacies are obliged to inform about sell statistics and prescribed drugs according to law (2009:366, 1996:1156)[105,106]. The Swedish Prescribed Drug Register is a unique source of information, since it also includes the patients ID-number, making it possible to link patient information from this register with other registers and databases[107]. The register provided information on age, sex, filled prescription, and date of filled prescription, dosage text, number of tablets dispensed and strength of the dispensed drug (Study II-IV). Problems faced when using the register for

analyzing chronic medication is the way the Swedish reimbursement system work for these types of drugs. It encourage patients to fill their prescriptions when they have reached top payment for the drugs, and receives the drugs for free. This may lead to hoarding of drugs and moreover, patients may fill their prescriptions irregular due to this system. It is also important to acknowledge that some elderly residents in nursing homes may receive prescriptions from stock orders and, consequently, their medications may not be included in the register. Other difficulties with this register is the lack of information about the indication for which the drug has been prescribed and the fact that the dosage text is unstructured or may be missing for many prescriptions.

National Patient Register

The register includes data on main and supplemental diagnoses according to ICD codes and surgical treatments for each patient visit to hospitals in Sweden. The register is held by the National Board of Health and Welfare, which started in the 1960's to collect data on patients in the public hospitals. Since 1984 it is mandatory for all county councils in Sweden to participate, and data on all in-patient care in the country is provided since 1987, while out-patient care consultations has been provided since 2001[108]. Today all of the 21 county councils in Sweden report the data monthly to the National Board of Health and Welfare. The in-patient data is estimated to have almost 100% coverage. The out-patient data has much lower coverage and estimated to around 80%, which has been suggested to be explained by the lower reporting of diagnoses by the private health care[108]. In this thesis, information from the National Patient Register was used in Study II and III, where the SPCCD was the data source, to include the main and supplemental diagnoses from hospitals. The register lack information about visits to primary health care centers, and therefore underestimates diagnoses such as hypertension which is managed and detected primarily by general practitioners.

Cause of Death Register

The register is held by the National board of Health and Welfare and provides information about the cause of death. The register includes data on the cause of death for patients registered in Sweden, with corresponding international ICD code. The data is updated yearly.

Statistics Sweden

Data on country of birth, educational level, income of the Swedish citizens and population living in the municipals of Sweden are held by Statistics Sweden since 1985, and is updated yearly.

Electronic Medical Records

Electronic medical records contain information about the medical history of the patient from one practice and is stored digitally. Information about diagnoses, blood pressures, and prescriptions was used for the four studies in this thesis. Heads of

the primary health care centers gave written approval for data extraction from the medical records.

SPCCD (Swedish Primary Care Cardiovascular Database)

The research database SPCCD contains information on 74751 patients with diagnosis of hypertension from 48 primary health care centers in southwestern part of Stockholm and Skövde-district in region Västra Götaland.[98] The two geographical areas represents an urban and a rural area of Sweden, respectively. They have used the same methods for extracting data on consultations, clinical and laboratory data, diagnoses and prescribed medications, making it possible to link the data together. The data is stored on a virtual server at the University of Gothenburg (Windows server 2008 R2, Microsoft Corp., Redmond, WA, USA).[98] The database also contains information from the national registers of Sweden and the patients' identification number, facilitating the linkage of data between the data sources. The casserole of SPCCD data is illustrated in Figure 3.

Figure 3. The Swedish Primary Care Cardiovascular Database
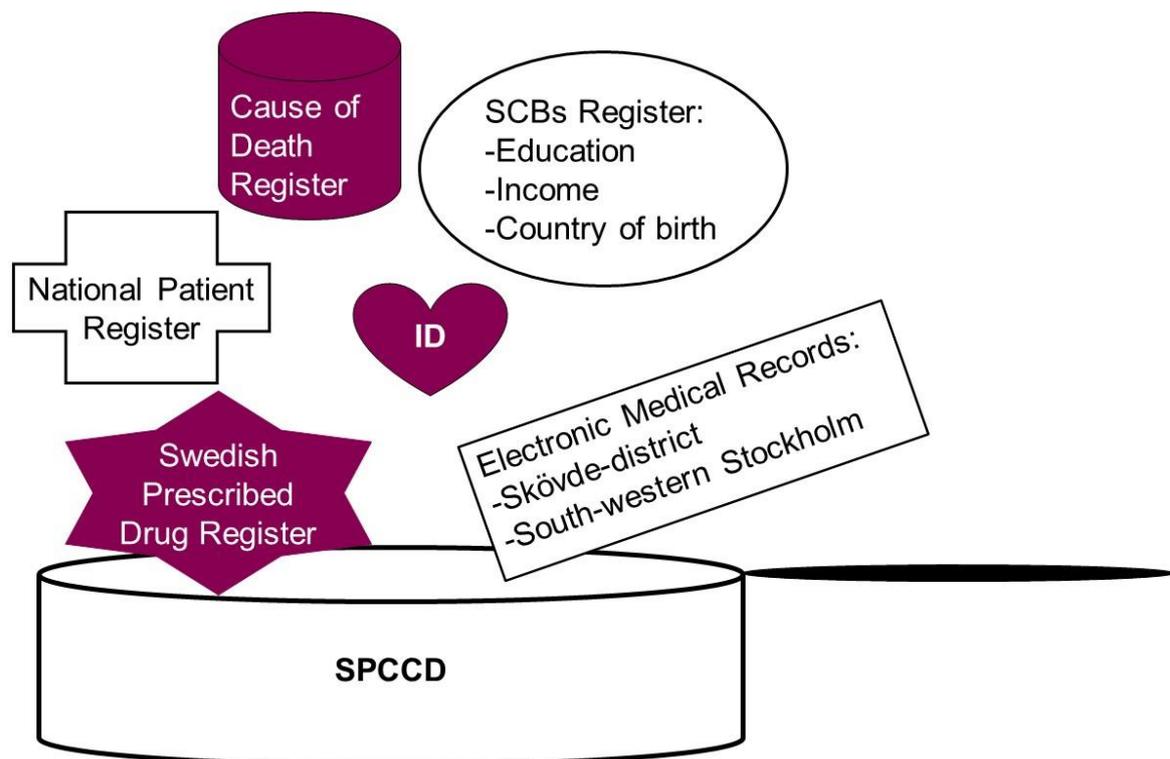
ID – identification number of the patient. All Swedish citizens have their own unique identification number, and it is recorded in the national registers and medical records. The ID number facilitates linkage of data between the registers and electronic medical records   SCB – Statistics Sweden. SPCCD – Swedish Primary Care Cardiovascular Database.

Questionnaires

In Study IV, questionnaires filled by patients newly initiated on antihypertensive drug treatment was used as data source. The questionnaire contained a total of 30 questions and space for general comments by the patients (see Appendix). There were six general questions about sex, antihypertensive treatment and blood pressure measuring, if born in Sweden and side effects, eight questions from the Brief-Illness Perception Questionnaire (IPQ)[109] and twenty-two questions from the Belief about Medicines Questionnaire (BMQ)[110].

The Brief-IPQ is a validated questionnaire used for assessing attitudes towards diagnoses, and stems from the Illness Perception Questionnaire – Revised, which contains 80 questions. [111] The Brief-IPQ contains nine questions, including eight single-item questions that are answered on a continuous linear scale from 0-10, and one last ninth question that asks about the most likely causes of the disease. The ninth question was not included in the questionnaire, since the purpose was to analyze quantitative research.

To assess attitudes towards drugs in general and the specific prescribed antihypertensive drug treatment, the BMQ was used as source of information. It contains two parts with one section asking twelve questions about general beliefs about drugs and the other section contains ten questions that examines attitudes towards the actual specific treatment of interest, which here corresponds to the antihypertensive drug that has been prescribed.

MEASUREMENT OF PERSISTENCE

In all studies of this thesis, except for Study I, persistence was measured and the same method of calculating was used. To determine the persistence, the dosage texts from the Swedish Prescribed Drug Register was read, either by detection of prespecified algorithms or manually. As the dosage texts were read, they were translated into variables of number of tablets prescribed and days of treatment. The patients were followed for a maximum of two years. A gap of 30 days between end of supply of the drug dispensing and the next filled prescription was applied for all persistence calculations. For a patient to be classified as non-persistent, the patient had not filled the next prescription with less than 30 days of non-treatment, eg. gap. In addition, if patients filled a prescription before end of the tablets of the former filled prescription, the tablets remaining were accumulated to the next prescription.

STATISTICS

All calculations were performed in SAS version 9.2 and 9.4 (SAS Institute Inc., Cary, NC, USA), except for Study I, where Microsoft Office Excel and Stata version 10.1 (College Station, TX, USA) was used. Statistical significance was assumed when p <0.05.

Descriptive statistics

The results from Study 1 and the descriptive analysis of Study II-IV were presented as percentages, means, medians, standard deviations and interquartile ranges. We used the Chi-square test and the Students t-test for comparisons of two groups.

Survival analysis

To estimate the time in days when the patient became non-persistent to the initiated antihypertensive treatment, we used survival analysis, also called time-to-event analysis (Study II-IV). Often, especially when longer time of follow-up (Study II-III), it is important to take into account censoring. It is an analytical problem and occurs in our studies when the lack of information about when the exact time when the patient became non-persistent and occurs when the study ends before the patient becomes non-persistent, the patient dies, is hospitalized more than 21 days or is put on individual dosing dispensed services. To illustrate survival analysis, it is common to use the Kaplan-Meier curves. It is a method where each patient gets three variables; their serial time, if they have become non-persistent or censored and which exposure group they are in. Here, study group refers to the studied exposures, for example women and men. The patients are followed over time, and two things can happen to them, either they become non-persistent or they are censored. Survival analyses offers many advantages over standard logistic regression for studying persistence, such as adjustments for right-censoring and varied duration of follow-up.[112]

Cox (Proportional Hazards) regression

We used Cox regression to assess associations between persistence and different patient characteristics, blood pressures and socioeconomical factors (Study II-III). It is expressed in hazard ratios (HR) when we are comparing two exposure groups and assumes that the ratio of the hazards remains constant over time.

Mann-Whitney U-test

To test for differences in attitudes of hypertension diagnosis and drugs between persistent and non-persistent medication users, the non-parametric Mann-Whitney U-test was used on the Likert-type scales. It tests if it is equally likely that a randomly selected value from one of the Likert type scales in the persistent group will be less than or greater than a randomly selected value from one of the Likert type-scales in the non-persistent medication-taking group.

ETHICS

The studies of this thesis was approved by the Regional Ethical Review Board in Gothenburg (dnr 569 – 08) and the Regional Ethical Review Board at Karolinska Institutet (dnr 2015/589-31/4). Written consent was obtained for all primary health care centers.

In all studies of this thesis, data from electronic medical records were used. These data are only available to the consulted general practitioner and the head of the primary health care center according to Swedish law. Therefore, all the heads of the involved primary health care centers gave their written consent for us to use the data for our study.

The data for all studies in this thesis were anonymous in the delivered file.

All patients received written information about the aim and utility of the study (Study IV). They were also informed that no information would be traceable to a single individual, that the study was voluntary and would not affect the health care that they would receive in the future and that they could withdraw consent at any time by the phone number given in the questionnaire.

The patients were sent a questionnaire from the consulted primary health care center. The patients might feel that the questions regarding their attitudes towards the diagnosis of hypertension, medicines in general and their antihypertensive drug treatment to be sensitive (Study IV). Analyzes of register based data may also be sensitive for the patient, although the data is anonymous (Study I-IV). To minimize this risk, we informed the patients that their participation was voluntary. We believed that the risk of personal encroachment was small and that the benefits of new knowledge about how to improve pharmacological treatment of hypertension is large.

RESULTS

EPIDEMIOLOGY OF HYPERTENSION AND PATIENTS

The prevalence of hypertension in 2005-2006 was estimated to 11% in the catchment area of the primary health care centers in the southwestern part of Stockholm. The catchment area represented populations of 197 000, aged 30 years or older.

An overview of the patient characteristics of the study populations included in this thesis are presented in Table 7.

Table 7. Overview of the patient characteristics included in the studies of this thesis.

Study	I	II-III[a]	IV
Women, %	58	55	50
Mean age, years	66±15	61±13	62±12
Diabetes mellitus, %	21	9	7
Cardiovascular comorbidity, %	40	16	5
Born in Sweden, %	n/a	76	69

[a]*Study II-III – same population of patients. The diagnosis of diabetes mellitus and cardiovascular comorbidity came from electronic medical records from the primary health care centers and the National Patient Register, while Study IV only had data from the electronic medical records from the primary health care centers. Cardiovascular comorbidity – diagnosis of atrial fibrillation, diabetes, heart failure, ischemic heart disease, or stroke/transient ischemic attack*

The mean age and the proportion having a diagnosis of diabetes or cardiovascular comorbidity was highest when both incident and prevalent medication users with hypertension were included (Study I). This is in contrast to the studies only including patients newly initiated on antihypertensive drug treatment (Study II-IV). The proportion of patients born outside Sweden was higher in the register studies (Study II-III) compare to the questionnaire-based study (Study IV).

BLOOD PRESSURES

Attainment of target blood pressure

In 2005-2006, a total of 27% of the patients in south-western part of Stockholm reached a target blood pressure of <140/90 mm Hg. The proportion of patients with a normal or grade 1-3, according to the ESH/ESC guidelines[49], of the mean diastolic or systolic blood pressures taken during the study period, are illustrated in Figure 4. The last recorded diastolic and systolic blood pressures in the study according to severity of hypertension are shown In Table 8.

Figure 4. The mean recorded diastolic and systolic blood pressures according to severity of hypertension in 2005-2006 (Study I).
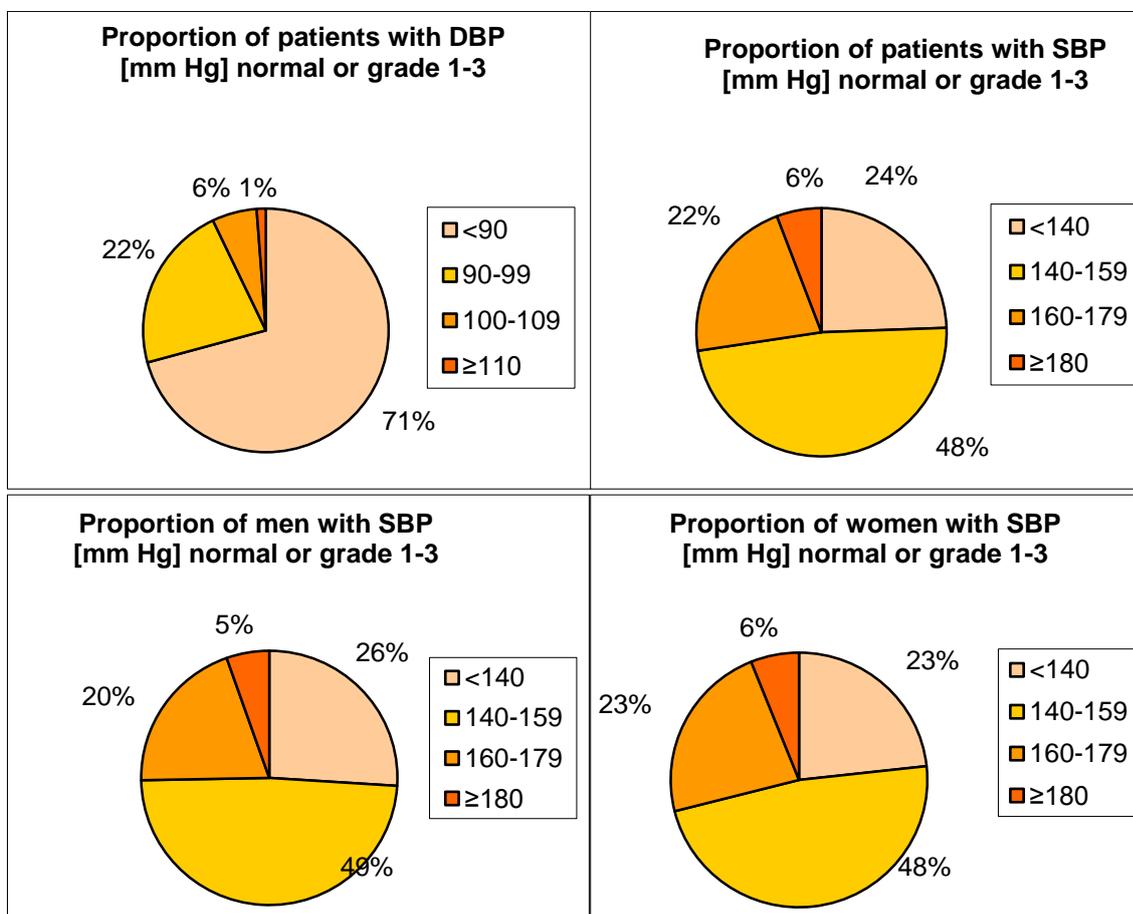
DBP – Diastolic blood pressures. SBP – Systolic blood pressures. SBP normal – a systolic blood pressure below 140 mm Hg. Grade 1-3 -

For patients with diabetes mellitus with a target blood pressure of <130/85 mm Hg at the time, an overall 7% achieved this goal.

Table 8. Severity of hypertension in women and men (Study I) from 2005-2006 according to ESH/ESC guidelines from 2007.[49]

Blood pressures (mm Hg)	Women		Men		Total	
	N/value	%	N/value	%	N/value	%
Mean SBP mm Hg	150.6		149		149.9	
Mean DBP mm Hg	83.8		85.3		84.4	
High normal - normal (DBP <90)	7797	73.5	5295	67.1	13092	70.8
Grade 1 (DBP 90-99)	2188	20.6	1909	24.2	4097	22.1
Grade 2 (DBP 100-109)	543	5.1	548	6.9	1091	5.9
Grade 3 (DBP ≥110)	86	0.8	136	1.7	222	1.2
High normal - normal (SBP<140)	2470	23.3	2051	26	4521	24.4
Grade 1 (SBP 140-159)	5071	47.8	3842	48.7	8913	48.2
Grade 2 (SBP 160-179)	2427	22.9	1569	19.9	3996	21.6
Grade 3 (SBP ≥180)	646	6.1	426	5.4	1072	5.8
ISH (SBP ≥140 DBP <90)	5512	51.9	3419	43.3	8931	48.3
Normal (SBP<140 DBP <90)	2286	21.5	1876	23.8	4162	22.5
Grade 1 (SBP 140-159 DBP 90-99)	1050	9.9	1024	13	2074	11.2
Grade 2 (SBP 160-179 DBP 100-109)	248	2.3	268	3.4	516	2.8
Grade 3 (SBP ≥180 DBP ≥110)	50	0.5	71	0.9	121	0.7

Mean recorded blood pressure values for 18 502 patients, 10614 women and 7888 men corresponding to 87% of the total study population of 21167 patients in Study I. DBP – Diastolic blood pressure. SBP – Systolic blood pressure. ISH – Isolated systolic hypertension.

Mean systolic and diastolic blood pressure

The mean systolic blood pressure was 148±20 mm Hg in women and 147±18 mm Hg in men (Study I), including patients newly initiated on antihypertensive treatment and prevalent users. When only the patients newly initiated on antihypertensive treatment were included, the mean systolic and diastolic blood pressures were 167±20 mm Hg and 92±11 mm Hg in women and 166±20 mm Hg and 95±12 mm Hg in men (Study II-IV). Corresponding values for the mean systolic and diastolic blood pressures in Study IV were 160±18 mm Hg and 93±11 mm Hg in women and 160±18 mm Hg and 94±12 mm Hg in men, respectively. The overall mean systolic and diastolic blood pressures with standard deviations are illustrated in Figure 5.

Figure 5. Mean systolic and diastolic blood pressures in the four studies of this thesis.
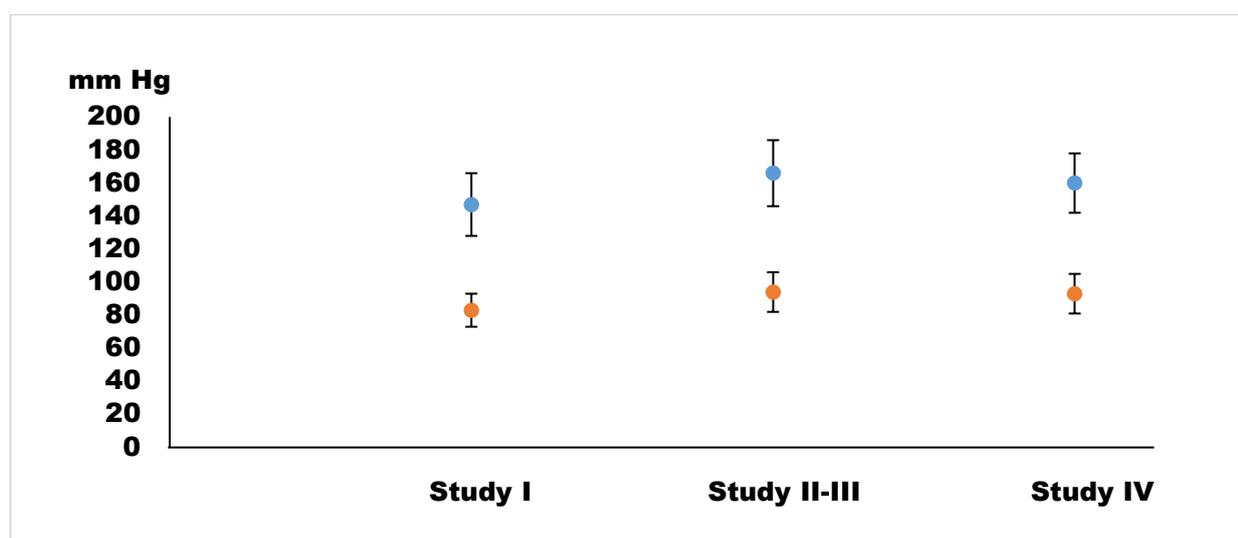
Blue dots – mean systolic blood pressure with error bars representing standard deviation. Red dots – mean diastolic blood pressure with error bars representing standard deviations.

ANTIHYPERTENSIVE DRUGS

The prevalence of prescribed antihypertensive drug treatment was 89% of the patients (89% women, 88% men) diagnosed with hypertension in the south-western part of Stockholm in 2005-2006 (Study I). The antihypertensive drug classes prescribed according to number of classes are presented in Table 9. In Study I, the patients included were both incident and prevalent antihypertensive drug users. More than half of the patients were prescribed two or more antihypertensive drugs. The most common antihypertensive drug class prescribed at the time of the study (2005-2006) were the beta blockers and diuretics.

An overview of the drug classes prescribed to the patients newly initiated on antihypertensive drug treatment are shown in Table 10 and is illustrated in Figure 6 according to sex (Study II-IV).

26

Table 9. Proportions of women and men newly or previously initiated on antihypertensive drug therapy or without pharmacological treatment in 2005-2006 according to number of drug classes (Study I).

| Prescribed antihypertensive drug therapy		Women	Men	Total
	N	12 189	8 978	21 167
None		10.8	11.7	11.2
Monotherapy		34.9	32.7	34
Beta blocker		11.2	10.7	11
Diuretic		10.8	5.2	8.4
ACE-I		4.6	8.8	6.4
CCB		4.3	4.1	4.2
ARB		3.9	3.9	3.9
Combinations of two drug classes		34.4	32.1	33.4
Beta blocker + diuretic		10.8	5.8	8.7
Beta blocker + CCB		5.1	6	5.5
Diuretic + ACE-I		4.8	5	4.9
Diuretic + ARB		4.5	3.9	4.2
Beta blocker + ACE-I		2.6	4.5	3.4
Diuretics + CCB		3.2	1.8	2.6
Other antihypertensive drug combinations		3.5	5.1	4.2
Combinations of three drug classes		16	17.4	16.6
Beta blocker + diuretic + ACE-I		3.7	4.5	4.1
Beta blocker + diuretics + ARB		3.7	2.9	3.4
Beta blocker + diuretics + CCB		3.6	2.6	3.2
Diuretic + ACE-I + CCB		1.4	2	1.7
Diuretic + ARB + CCB		1.7	2.2	1.9
Other antihypertensive drug combinations		1.9	3.2	2.4
Combinations of four-five drug classes		**3.9**	**6.1**	**4.8**
Beta blocker + Diuretic + ACE-I + CCB		1.7	3.1	2.3
Beta blocker + Diuretic + ARB + CCB		1.7	2.1	1.9
Other antihypertensive drug combinations		0.5	0.9	0.7

ACE-I – Angiotensin converting enzyme inhibitor. CCB – Calcium channel blocker. ARB – Angiotensin receptor blocker.

Table 10. Overview of the drug classes prescribed to the patients newly initiated on therapy (Study II-IV).

Study	II-III	IV
Year of prescription	2006-2007	2015
Antihypertensive drug therapy		
Angiotensin converting enzyme inhibitor	39	44
Angiotensin receptor blocker	5	16
Beta blocker	23	7
Calcium channel blocker	8	23
Diuretics	31	2
Fixed combinations	2	3
More than one drug prescribed	3	6

Fixed combinations – two various antihypertensive drug classes combined in one tablet, e.g. diuretics and angiotensin converting enzyme inhibitors.

Figure 6. Drug classes prescribed to women and men newly initiated on therapy (Study II-IV).
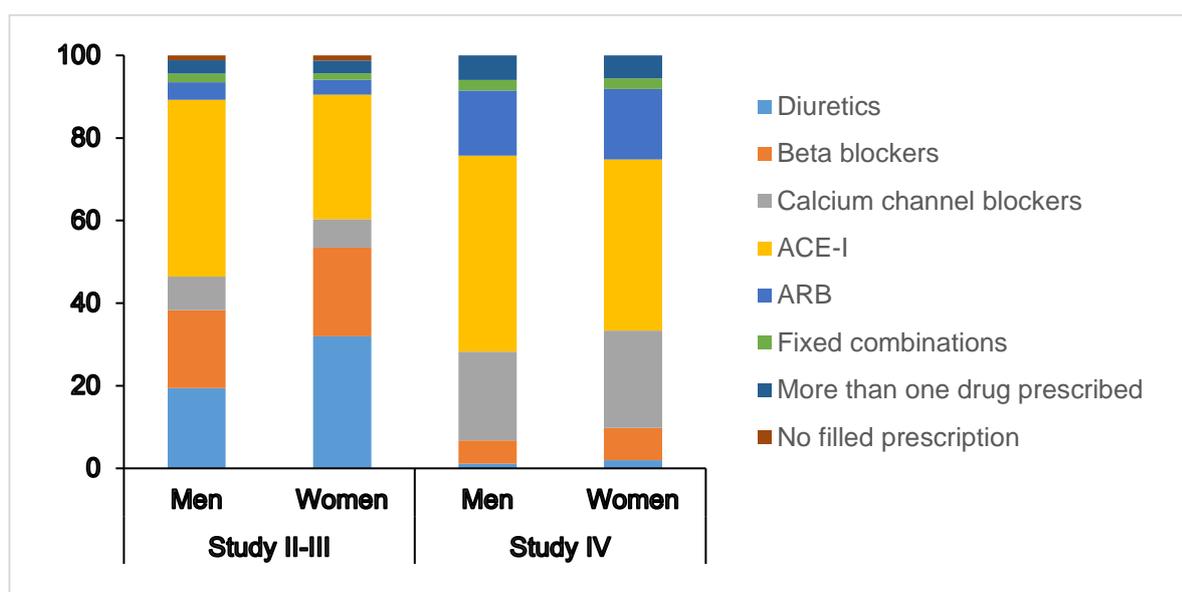
ACE-I - Angiotensin converting enzyme inhibitors. ARB – Angiotensin receptor blockers.

PERSISTENCE TO ANTHYPERTENSIVE MEDICATION

Therapy and class persistence to antihypertensive medication

The overall therapy persistence after two years of follow-up was estimated to 63% (Study II) and class persistence to 44% (Study III). This gave us an approximation of the proportion of patients switching, corresponding to 19%. This is illustrated in Figure 7. Our other calculated estimate of switching was 25 % (Study III).

Figure 7. Proportion of patients' therapy or class persistence to antihypertensive drug treatment according to sex (Study II and III).
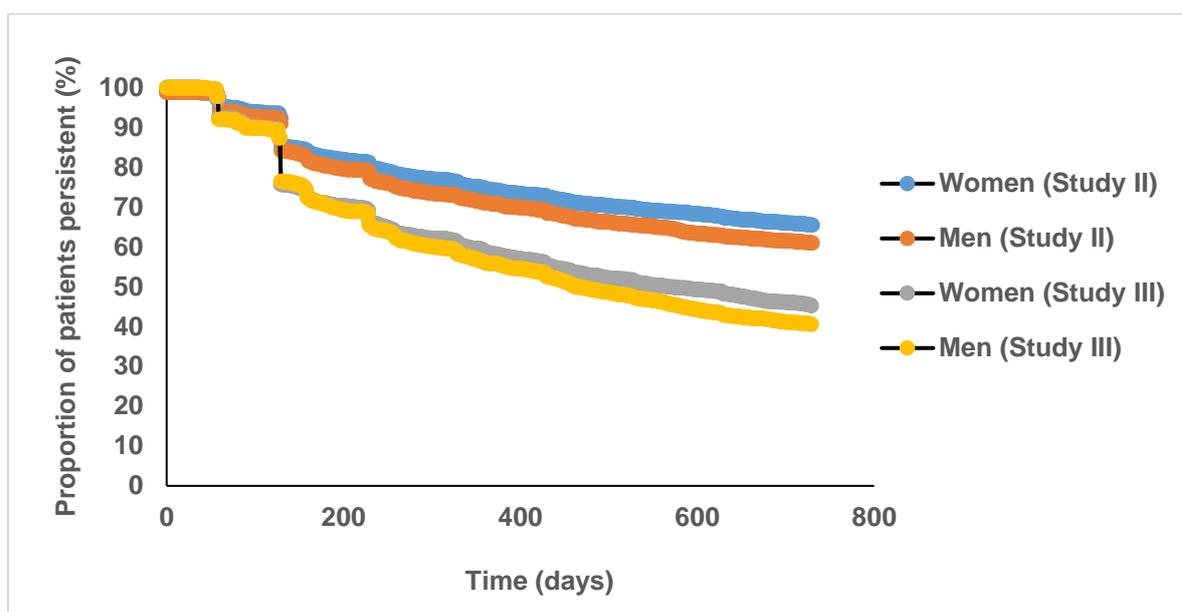
Kaplan - Meier curves of the measured discontinuation of any antihypertensive drug treatment (therapy persistence) and drug class (class persistence) in Study II and III according to sex. The "fall" after 60 days and 130 days is explained by patients not filling their second prescription after a prescription of tablets for 30 or 90 days, respectively.

Factors associated with low therapy and class persistence

The patient characteristics and socioeconomical factors that may influence persistence to antihypertensive drug treatment were observed to better understand reasons for why patients stop filling their prescriptions (Study II and III). Also, the differences in attitudes between persistent and non-persistent patients were examined. These variables are listed in Table 11. Male sex, young age, born outside Sweden and mild-to-moderate elevated blood pressure were associated with a lower therapy persistence. The same factors were also important predictors for low class persistence. No major difference in class persistence between diuretics and the other antihypertensive drug classes were found.

Table 11. Various factors examined in association to persistence in three of the studies of this thesis (Study II-IV)

Study	II	III	IV
Sex	X	X	X
Age	X	X	X
Diastolic blood pressure	X	X	X
Systolic blood pressure	X	X	X
Diabetes mellitus	X	X	X
Cardiovascular comorbidity	X	X	X
Number of other drugs	X	X	
Education	X	X	
Income	X	X	
Country of birth	X	X	X
Patients attitudes towards their hypertension diagnosis			X
Patients attitudes towards medicines in general			X
Patients attitudes towards their antihypertensive drug treatment			X

Number of other drugs – filled prescriptions of other drugs than antihypertensives.

Attitudes towards hypertension and pharmacological treatment

All the results on attitudes towards the hypertension diagnosis, pharmacological treatment in general and the specific prescribed antihypertensive drug treatment are presented in Manuscript (Study IV).

METHODOLOGICAL CONSIDERATIONS

STUDY DESIGN AND GENERALIZABILITY

Observational studies using registries provide the opportunity to investigate the quality of prescribing and dispensing of medicines in large complete populations. The studies in this thesis included all patients diagnosed with hypertension in a large number of primary care practices representing both urban and rural settings with different socioeconomic compositions. The first study included data collected from medical records, while the other studies included individual level data from the Swedish Prescribed Drug register on all prescription drugs dispensed to the patients included in the studies. Such a complete coverage of patients and their medication use increases the external validity and the generalizability of the findings. It is important, though, to emphasize that there may be differences in patient characteristics, healthcare organization, and guidelines that might limit the generalizability of studies to other settings.

Study I and IV had cross-sectional study designs, while Study II and III had a cohort design. Cross-sectional studies describe the utilization of drugs in populations at a certain point in time. It is important to acknowledge that since these studies lack information on whether the factor of interest precedes or follows the effect they may not be used to draw any conclusions on cause and effect.

In a cohort study, subjects are included based on their exposure to a factor, and followed over time. This study design is a preferred choice in persistence research to assess discontinuation rates and identify factors associated with discontinuation, switching or combination of therapy. Still there are many methodological challenges around the definition of these outcomes (see further below).

VALIDITY IN DATABASES

There is no perfect way to measure patient persistence. Methods that rely on patients' self-reporting are biased by the fact that patients do not remember or want to give the most "correct" answer, thinking that their answers will influence their future consultations with their doctor. Further, methods based on measurements taken during a consultation are subject to "white-coat persistence" i.e. improved persistence before a scheduled visit to the clinic or laboratory.   Consequently, databases offer unique opportunities with their large samples of patients with hypertension, followed over long time with minimal risk for bias.

There are many advantages of using databases in observational research on medication use.[113] One feature is the possibility to study rare events, since they contain a lot of information. Another advantage is their data on routine clinical care, which makes it possible to study the drugs effectiveness in real practice, and also the utilization of the prescribed pharmacological treatment. Further, they are relatively inexpensive and mostly accessible without long delays.[113] Data collected from medical records contain complete populations representative for routine care, thus minimizing the risk for selection bias. Furthermore, they may provide the

opportunity of linking prescribing data to clinical parameters, such as diagnosis, vital signs, laboratory data and more or less structured clinical notes. However, there are some important limitations of using medical records in observational research. Diagnoses may be missing or inaccurate, and the validity may vary substantially between different primary healthcare centers. While many validation studies have been conducted on hospital based diagnoses in the Swedish National Patient Register106, validation studies from primary care are to a large extent missing. In our studies, inappropriate diagnostic information on hypertension and the included comorbidities could potentially lead to selection or information bias.

MEASURE OF PERSISTENCE

There are several methodological challenges in assessing persistence with register based data.[22,70,84,114] We performed sensitivity analyzes and found that persistence increased from 65% to 83% when we changed the allowed gap defining discontinuation from 15 to 120 days. Similar variations have also been found in other studies.[115] However, changing the gap did not influence the major determinants of discontinuation.

Although persistence is best calculated from the national prescription databases on dispensed drugs, compare to the self-assessment of persistence, the methods have to be adapted to the context in each country. There is also a potential bias of non-responders, and recall bias related to survey. In addition, it is possible that attitudes in the patients responding to the questionnaire are different to those not responding. Furthermore, all instruments to assess attitudes have their inherent limitations, , IPQ and BMQ have previously been used in studies on adherence to antihypertensive medication but, to the best of our knowledge, have not previously been used early after medication initiation to assess differences in attitudes in patient discontinuing treatment, compared to those being persistent.

STATISTICAL METHODS

Pharmacoepidemiological studies are generally subject to three sources of bias; information bias, selection bias and confounding. A particular problem in pharmacoepidemiological studies is the potential for confounding, i.e. a systematic error resulting from the fact that a secondary variable is linked to both the exposure and the event of interest. Such a confounder could have been an important factor associated with non-persistence, potentially taken into account when prescribing. Potential factors influencing the decision to prescribe, thus potentially leading to confounding, may vary by physician and over time and involve a mix of clinical, functional and behavioral patient characteristics.[116] Channeling of prescribing to specific patients may also occur as a result of guidelines or reimbursement restrictions favoring certain drugs. In the in this theses (Study II-IV), we have addressed confounding through the Cox regression, but still, it is possible that there may be some residual confounding on factors not included in the model.

FINDINGS AND IMPLICATIONS

EPIDEMIOLOGY AND PATIENTS (STUDY I – IV)

We estimated that the prevalence of known hypertension in the adult population to 11% in the southwestern part of Stockholm in 2005-2006. Similar proportions were found in two other studies in rural Sweden and Stockholm County, also reporting diagnosed patients with hypertension in the health care system.[32,34,35] The SBU estimated the prevalence of high blood pressure in the adult population to be 27%. Thus, the proportion of patients unaware of their elevated blood pressure would correspond to around 16% of the population in Sweden, and almost exactly one million people of the Swedish adult population in 2006.[117] . The prevalence of hypertension decreases in high-income countries today, while it increases in low- and middle-income countries.[1] This result refutes the hypertension paradox, that the prevalence of hypertension increases although improvement in the pharmacological treatment and other therapies.[118] Lifestyle modification, including high salt intake[119] and high body weight[120], excessive alcohol intake, low socioeconomic status, genetic predisposition or family history, sleep apnea, use of illegal drugs and tobacco, increasing age, genetic predisposition, diagnosis of prehypertension, are all affecting the risk of developing hypertension.[121] All these factors need to be taken into account in each individual patient, to reduce the risk of developing hypertension, and to keep in mind that untreated hypertension can shorten life expectancy by approximately five years.[122]

The patients newly initiated on antihypertensive drug treatment in three of the studies of this thesis (Study II-IV) had similar patient characteristics, including mean age, proportion of women and men and comorbidities as studies conducted in primary care populations in other countries.[23,86,88] Since these patients were newly initiated on therapy, they had a lower mean age and less comorbidities than the patients with hypertension and either no antihypertensive drug prescribed, newly initiated on treatment or prevalent medication users (Study I).

BLOOD PRESSURE (STUDY I)

We found that few had a recorded blood pressure below target of 140/90 mm Hg (Study I). There are of course several potential explanations to why, including the health care provider organization, organizational issues in primary healthcare and insufficient systematic follow up. Physicians may prescribe an inappropriate dosing, or inadequate drug combinations and may consider side effects with antihypertensive drugs a problem, or that available evidence to treat the very old insufficient. Furthermore, patient adherence or persistence to prescribed therapy may be low due to lack of motivation among prescribers or patients. In addition, some patients may have resistant or secondary hypertension. We also found that the proportion reaching blood pressure targets remained low, independent of the number of antihypertensive drugs prescribed (Study I). These results may indicate that poor persistence or adherence to drug treatment is an important factor to achieve target blood pressure goals.

However, these results are not so surprising since the guidelines at that time were less rigorous in the enforcement to lower the blood pressures by antihypertensive drug treatment. It is merely important to acknowledge the fact that *this* is one out of many reasons to why we today face a great problem with patients developing cardiovascular disease.

Half of the patients had mild elevated blood pressure. Most patients have an elevated systolic blood pressure of 140-159 mm Hg and/or diastolic blood pressure of 90 to 99 mm Hg.[123] Due to the high prevalence of patients with mild hypertension, the burden of cardiovascular disease caused by hypertension in the general population comes from those with relatively mild hypertension. Up until recently it has been unclear whether antihypertensive drug treatment prevents cardiovascular events and deaths in patients with mild hypertension, but a recent review reported that a blood pressure reduction likely prevents stroke and death in these patients.[124] Thus, it is important to treat these patients with mild hypertension, which is also supported by the current guidelines that target blood pressure should be below 140/90 mm Hg, and even lower targets for high-risk patients.

ANTIHYPERTENSIVE DRUG TREATMENT (STUDY I - IV)

All our studies presented data on the proportion of patients with a diagnosis of hypertension that were treated with antihypertensives and to what extent the different drug classes were used. We analyzed prescribing were patients were prevalent on antihypertensive drug treatment (Study I) and filled prescriptions in patient newly initiating antihypertensive treatment (Study II-IV). Study I and Study II-III have similar study periods for the inclusion of patients (2005-2007), while Study IV was performed almost ten years later (2015-2016).

We found beta blockers and diuretics to be the most commonly prescribed drugs among prevalent medication users, although some included were newly initiated on antihypertensive treatment (Study I). In patients newly initiated on antihypertensive treatment, the most common filled prescriptions during the mid-2000 were the ACE-Is, diuretics and beta blockers (Study II-III).

The finding that a majority of patients were most commonly prescribed beta blockers and diuretics (Study I), probably reflected the old guidelines in Sweden prior to the time of the study, specifically recommending beta blockers and diuretics as first-line choices for elderly patients. Utilization of antihypertensives can vary between countries in prescribing patterns. Suggested factors behind this variation include cross-country differences in reimbursement policies, therapeutic traditions, impact of opinion leaders, domestic pharmaceutical production, and clinical guidelines. However, the patterns of use have changed over the past 20 years, and there has been a consistent increase in the use of ACEIs, ARBs and CCBs in all countries.

In study I, we also analyzed gender differences in drug treatment as well as prescribing patterns in different age groups and for patients with different cardiovascular comorbidities. This is further discussed in the paper, and gender differences is also thoroughly assessed in another study from the SPCCD.[56]

When we assessed only those patients newly initiated on treatment, we found that ACE-I were the most commonly prescribed drug treatment, followed by diuretics and beta blockers (Study II-III). Thus, there is a difference in initiation of treatment and patients prevalent on antihypertensive medication. Doctors and patients not wanting to change a drug class that "works", into another, although guidelines tell differently, can explain this phenomenon. It is possible that the new guidelines are implemented faster today than ten years ago when the study was conducted. This would be explained by the more advanced decision-support systems and computerized access to medical records we have today.[125] However, although some drug classes have shown to be favorable in some patients more than others are, the most important for the doctor is to lower the blood pressure itself.

We found choice of initiated antihypertensive drug treatment changed between 2006-2007 (Study II-III) and 2015 (Study IV). ACE-I was still the most prescribed, but on second and third place came the calcium channel blockers and angiotensin receptor blockers, respectively. The diuretics and beta blockers were not common at all. This is more in line with the current guidelines of the initiation of drug treatment in patients with hypertension, and the findings are also found in other countries. Thus, doctors do follow the guidelines, but it might take some time before they are implemented.

THERAPY PERSISTENCE (STUDY II)

An important finding was that one sixth of all patients only purchased their first prescription, one out of four patients discontinued the treatment within the first year, and a further one tenth discontinued during the second year of follow-up. This early discontinuation is in accordance with findings from other settings, although the proportion being classfiied as persistent varies substantially between studies.[15,22-27,126] This large variation between studies is most likely attributable both to the patient populations included and to the large variation in methodologies.[22,70,84] The importance of the method was illustrated in the sensitivity analyses conducted in which the proportion persistent varied substantially depending on the allowed gap.

CLASS PERSISTENCE (STUDY III)

One fourth of all patients filled one prescription only, and approximately 40% of all patients discontinued their initial drug class during the first year. This high proportion of patients discontinuing treatment early after initiation confirms findings from other studies.[14,23,88]

In studies where antihypertensive drug classes were compared with one another, diuretics and beta blockers most often have been reported with the lowest class persistence[23,24,87], whereas ACE-I or ARBs have the highest class persistence. Accordingly, our crude results found a lower persistence for ACE-inhibitors than for diuretics. More important, however, this difference did not remain after adjustment for confounding factors shown to be important for drug class persistence. Thus, we found no differences in persistence between diuretics and the other drug classes. Our observations thus support recent findings on persistence from Germany also

using primary healthcare population data, adjusting for many possible confounders.[14] These results suggest that there are no important differences in persistence between the most common antihypertensive drug classes. Prior studies may have been biased by not adjusting for important factors associated with persistence to antihypertensive drug treatment.

FACTORS INFLUENCING PERSISTENCE TO TREATMENT (STUDY II – III)

In the study on therapy persistence (Study II), we found that factors associated with low therapy persistence to the drug treatment were male sex, lower age, mild-to-moderately elevated systolic blood pressure, and birth outside Sweden.

These factors found to be associated with therapy persistence, were also associated with poor class persistence (Study III). Similar patterns were also observed in a study from Canada.[23]

A broad generalized assumption would be to translate the difference between therapy and class persistence into a proportion of patients switching treatment, eg. those patients who are not persistent to the class, but to some antihypertensive treatment, could be considered switchers. We estimated that 25% were switchers by counting the proportion of patients who had switch in the Cox regression analysis (Study III) and to 19% by subtracting the proportion of patients who were therapy persistent to the proportion of patients who were class persistence (results shown in this thesis). These results can considered being quite similar, although the methods used for estimating switching is different between the studies. Overall, it seems as many patients do switch treatment, which should be considered a better option than a final discontinuation of treatment.

THE PATIENTS' ATTITUDES TOWARDS HYPERTENSION AND DRUGS (STUDY IV)

We found that persistent and non-persistent medication users have slightly different attitudes towards the diagnosis of hypertension, drugs in general and the antihypertensive drug treatment prescribed. Persistent medication users believe, compare to non-persistent, that hypertensive disease has fewer consequences to their life, that the hypertension is a chronic disease and consider to a greater extent that the antihypertensive medication protect from future cardiovascular disease, and have a more positive attitude towards medication, in particular for specific antihypertensive medications, as compare to non-persistent patients. They are also less concerned about the effects of antihypertensive drugs.

These findings suggest that the health care providers in primary health care, but also pharmacists at the pharmacy, should inform the patients about the importance of antihypertensive drug treatment, that hypertension is a chronic disease and that there are a lot to benefit from antihypertensive drug treatment.

CONCLUSIONS

- Only one in four hypertensive patients reach a target blood pressure below 140/90 mm Hg in the primary health care. During the time of the study, patients were mostly prescribed beta blockers and diuretics. Patients not reaching target blood pressure may be explained by poor adherence or persistence, since the increase in the number of prescribed drugs did not correspond to an increased proportion of patients with target blood pressure.

- Major determinants of therapy persistence to antihypertensive drug treatment are male sex, young age, mild-to-moderate systolic blood pressure elevation, and birth outside of Sweden.

- There appears to be no difference in drug class persistence between diuretics and other major antihypertensive drug classes, when factors known to be associated with poor persistence are taken into account.

- There are some differences in attitudes towards hypertension diagnosis and drugs in overall between persistent and non-persistent patients. Patients persistent to drug treatment, compare to non-persistent, believed that their diagnosis of hypertension were chronic, and that they need and benefit from antihypertensive medication in preventing future cardiovascular disease.

FUTURE PERSPECTIVES

A few questions have arisen during the course of studies of this thesis, including:

- How does the degree of therapy persistence effect the patient's ability to reach target blood pressure?

- How does the risk of cardiovascular disease and death change depending on the patient's degree of medication persistence and medication adherence, given that we have 10-year follow-up of patients in the SPCCD?

- Have the proportion of medication persistent patients increased in different part of the world over the years? A new review with the same method used by Cramer et.al.[22] from 2008, would provide new knowledge and insight.

- What is the cost for the society to pay for patients being non-persistent tp treatment and compare those figures with cost of adequate monitoring of patients after initiation of antihypertensive treatment (lifestyle or medication)?

SAMMANFATTNING PÅ SVENSKA

Hypertoni är en av de främsta orsakerna till förtida sjuklighet och död. I Sverige uppskattas omkring 2 miljoner personer av den vuxna befolkningen ha hypertoni som kräver medicinsk behandling. Mildare former är ofta symptomfria, men obehandlad hypertoni ökar risken att insjukna i kranskärlssjukdom, hjärtsvikt, slaganfall, njursvikt och andra hjärt-kärlsjukdomar. Högt blodtryck ökar dessutom risken för utveckling av demens. Genom att kombinera olika blodtryckssänkande medel går det att nå målblodtryck <140/90 mm Hg hos de flesta personer. Undersökningar visar dock att andelen som når behandlingsmålet sällan uppgår till mer än 20–30 % av dem som ordinerats blodtryckssänkande läkemedel. En viktig bidragande faktor tros vara bristande långtidsföljsamhet till behandlingen, då många studier visar på att patienterna avslutar behandlingen redan inom ett år efter behandlingsstart.

Vi började med att kartlägga läkemedelsbehandlingen och måluppfyllelse av blodtryck hos patienter med högt blodtryck. I studien tog vi med 24 vårdcentraler från sydvästra Stockholm med totalt 21 167 patienter som besökt någon av de inkluderade vårdcentralerna under 2005-2006. Vi fann att endast en utav fyra patienter når målblodtryck under 140/90 mm Hg.

Nästa steg var att studera persistens till blodtryckssänkande läkemedel och vilka faktorer som är kopplade till att patienterna fortsätter ta sina läkemedel. Vi använde oss av hypertonipatienters elektroniska journaler från de 48 vårdcentralerna som var med i studien. Vi sammankopplade data från nationella register med läkemedelsuthämtningar, diagnoser från sjukhus, död, födelseland, inkomst och utbildningsnivå. Vi fann 5225 patienter som var nyinsatta på blodtryckssänkande behandling under 2006- 2007. Över en tredjedel av patienterna slutade helt att ta blodtryckssänkande behandling inom två års tid. Vi fann att de faktorer som verkar vara sammankopplade med en sämre långtidsföljsamhet till blodtryckssänkande behandling är manligt kön, ung ålder, mild till måttlig systoliskt blodtryckshöjning och födelseland utanför Sverige.

En fråga kvarstod från den tidigare studien, och det var att se om långtidsföljsamheten skiljer sig åt mellan de olika blodtryckssänkande läkemedelsklasserna? Vi använde liknande metod som beskrivits i studien ovan, men analyserade specifikt varje läkemedelsklass. Vi fann att det inte var några skillnader i långtidsföljsamhet till de olika läkemedelsklasserna i jämförelse med vätskedrivande läkemedelsbehandling.

Även om registerstudier är viktiga och kan ge mycket värdefull information, så kan de inte ge all information. De saknar information om patienters åsikter och attityder. För att utöka kunskaperna om långtidsföljsamhet till blodtryckssänkande behandling, bestämde vi oss för att studera patienternas attityder till högt blodtryck och läkemedelsbehandling, och se om det finns skillnader mellan en som är långtidsföljsam och en som inte är det. Vi skickade ut enkäter till patienter som var nyinsatta på blodtryckssänkande behandling och fann genom analys av

läkemedelsuttag från Läkemedelsregistret att 609 (86%) var långtidsföljsamma och 102 (14%) icke-långtidsföljsamma till den blodtryckssänkande behandlingen. Vi fann att i jämförelse med icke-långtidsföljsamma så uppfattade långtidsföljsamma patienter i högre grad att hypertonidiagnosen var kronisk De uppfattade att den hade mindre konsekvenser för deras liv och att de kan förhindra hjärt-kärlsjukdom genom att ta blodtryckssänkande behandling samt att det är positivt med läkemedelsbehandling vid sjukdom.

Studierna syftade till att identifiera orsaker till bristande behandlingseffekter vid hypertoni och studera hur behandlingen kan förbättrats. Att skapa förståelse kring varför så få patienter når sitt målblodtryck och identifiera lösningar som kan förbättra deras behandling. Detta kan bidra till kampen för att minska risken för följdsjukdomar och för tidig död hos patienter med hypertoni.

My dear friends, for which I am so grateful. I do not dear to mention your name, since I am too afraid of forgetting someone. To all of you, you are in my heart.

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