Treatment of Hypertension in Women and Men

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ABSTRACT

Aims: The overall aim of the thesis was to investigate antihypertensive treatment in women and men. First, the aim was to analyze the scientific support for treatment recommendations in women and men. Second, the aims were to study achieved blood pressure levels and evaluate differences in antihypertensive treatment in women and men with new-onset and current hypertension and further to study if guidelines were pursued. Finally, the aims were to study the influence of comorbidities and psychosocial factors on antihypertensive treatment and achieved target blood pressure in women and men.

Methods: Paper I is a review based on "Moderately elevated blood pressure, a systematic literature review" by the Swedish Council on Technology Assessment in Health Care (SBU). Paper I analyses the proportion of women included and gender specific data on blood pressure reduction and outcome. Paper II is a retrospective study carried out in primary health care including patients with newly diagnosed hypertension, investigating blood pressure levels, antihypertensive treatment and time to satisfying blood pressure control in women and men. Paper III and IV are retrospective cohort studies carried out in the Swedish Primary Care Cardiovascular Database (SPCCD) including patients with ongoing hypertension. These studies investigate blood pressure levels, achieved target blood pressure, antihypertensive treatment, comorbidities and psychosocial factors in women and men with hypertension.

Results: In Paper I, two studies (VALUE and ALLHAT) showed a better blood pressure reduction with calcium channel blockers compared to angiotensin receptor blocker (ARB) and angiotensin converting enzyme inhibitor (ACEI) and this was more pronounced in women. In ALLHAT the calcium channel blocker was superior to both the diuretic and ACEI in reducing stroke incidence in women but not in men. In VALUE, calcium channel blocker-based therapy was superior to the ARB-based therapy in reducing the composite endpoint of cardiac morbidity and mortality in women but not in men ($p<0.05$). In Paper II, 332 male and 334 female patients were included. There was no gender difference in systolic blood pressure (SBP) before and after treatment. Women had a lower diastolic blood pressure (DBP) before and after intervention. There was no difference between the proportion of women and men reaching the predefined goal of treatment. In Paper III and IV, 40 825 patients with current hypertension were included. In patients older than 69 years, women had a higher SBP, except in patients of 90 years of age or older. Achieved DBP dropped with age in both genders and was lower in women in all age groups except in patients 90 years or older. Achieved SBP was higher in women in all subgroups of comorbidities except in patients with asthma. Fewer women than men reached target blood pressure ($p<0.0001$). Women were more often prescribed thiazide diuretics, loop diuretics and beta receptor blockers and men were more often prescribed ACEI, and this was consistent also after adjusting for age, comorbidities and smoking. The predominant use of ACEI and calcium channel blockers in men was not influenced by education, country of birth and psychiatric disorder. However, in well-educated patients women were not prescribed diuretics and beta receptor blockers more often than men. In women, education and psychiatric disorder was associated with reaching target blood pressure.

Conclusion: Women and men are treated with different antihypertensive drugs and this is not fully explained by differences in comorbidities. Women with diabetes mellitus are not treated with ACEI or ARB to the same extent as their male counterparts. Women with hypertension reach target blood pressure less often than men and women have a higher achieved SBP in all subgroups of concomitant cardiovascular disease. Higher educational level and psychiatric disorder are associated with reaching target blood pressure in women. Efforts should be made to emphasize the risk evaluation in women with hypertension and concomitant cardiovascular disease to improve blood pressure control.

Keywords: Hypertension, antihypertensive treatment, blood pressure, gender

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LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I   Ljungman C, Mortensen L, Kahan T, Manhem K. Treatment of mild to moderate hypertension by gender perspective: a systematic review.
J Womens Health 2009;18:1049-1062.

II   Ljungman C, Collén A-C, Manhem K. Swedish Hypertension Open care retrospective study in men and Women (SHOW).
J Hum Hypertens 2011;25:32-7.

III Ljungman C, Kahan T, Schiöler L, Hjerpe P, Hasselström J, Wettermark B, Boström K, Manhem K. Gender differences in antihypertensive drug treatment: Results from the Swedish primary care cardiovascular database (SPCCD).
Submitted

IV   Ljungman C, Kahan T, Schiöler L, Hjerpe P, Wettermark B, Boström K, Manhem K. Antihypertensive treatment and control according to gender and psychosocial factors: the Swedish primary care cardiovascular database (SPCCD).
Submitted

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CONTENTS

ABBREVIATIONS

ACEI	Angiotensin converting enzyme inhibitor
ARB	Angiotensin receptor blocker
BMI	Body mass index
DBP	Diastolic blood pressure
E2	17β-Estradiol
FSH	Follicle stimulating hormone
LH	Luteinizing hormone
LVH	Left ventricular hypertrophy
PP	Pulse pressure
SBP	Systolic blood pressure
SPCCD	Swedish primary care cardiovascular database

DEFINITIONS IN SHORT

Hypertension	≥140/90 mm Hg. At the time of the study patients with hypertension and diabetes mellitus and/or concomitant cardiovascular disease were recommended blood pressure levels <130/80 mm Hg

INTRODUCTION

*H*ypertension is the most important risk factor for global disease burden[1]. Blood pressure >115/75mm Hg is strongly and directly related to vascular and overall mortality in both women and men in middle and older age[2]. In current guidelines the definition of hypertension is repeated measurements of ≥140/90 mm Hg[3]. For hypertensive patients, the decrease in total life expectancy is 5.1 years in men and 4.9 years in women compared to normotensive subjects[4]. In a 30 year old subject with hypertension the lifetime risk of cardiovascular events is as much as 63.3% compared to 46.1% in a normotensive individual[5].

Hypertension is common. The risk of becoming hypertensive during a lifetime is estimated to be over 90% in developed countries[6]. Worldwide the prevalence of hypertension was 26.4% in 2000 and is predicted to increase so that approximately 29.2% of the population will have hypertension in 2025[7]. The prevalence of hypertension in Sweden is approximately 27% in the adult population[8]. Hypertension is more common in younger males but the prevalence in women is increasing with age, thus in the population hypertension is equally common in women as in men[9, 10].

Blood pressure levels

Blood pressure levels differ between women and men in different ages. Young men have a higher blood pressure, both SBP and DBP compared to young women[10]. SBP steadily increases with advancing age in both sexes. DBP rises until the fifth decade and then decreases in both women and men. Age-related rise in pulse pressure is more pronounced in women, Figure 1[11].
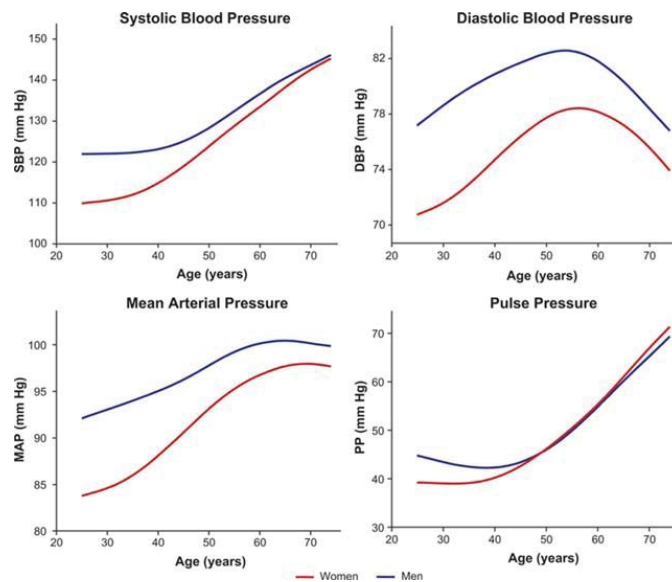
Figure 1. Unadjusted mean SBP, DBP, mean arterial pressure (MAP) and pulse pressure (PP) in women and men with increasing age. Data from the Framingham heart study. Cheng S et al. Published in Hypertension 2012:60;1393-1399.

In patients with hypertension there are contradictory results regarding blood pressure control and gender from observational and cross-sectional studies. Women are in some studies more likely to be treated but less likely to achieve blood pressure control[12, 13]. In a Swedish cross sectional survey women less likely reached target blood pressure[14]. However, in other investigations women are more likely than or just as likely as men to achieve blood pressure control[15, 16]. There seems to be an age-dependent relationship between blood pressure control and gender where younger men and older women have lower rates of blood pressure control[17].

There is evidence that the gender of the physician and the patients plays a role in reaching target blood pressure[18]. If there are differences in blood pressure levels in women and men with new-onset of hypertension treated in primary care is not fully known. How long it takes until blood pressure control is reached and if there are gender differences regarding this matter is not known.

Antihypertensive treatment

In early randomized trials regarding hypertension women were not included[19]. Over the years women were included to an increasing extent, however the lower absolute cardiovascular risk in women made the benefit of antihypertensive therapy on cardiovascular outcome difficult to show. This resulted in a debate whether or not women with moderately elevated blood pressure should be treated. Several reviews have concluded that gender differences in response to antihypertensive therapy have not been investigated completely and emphasize the need for more data to guide the management of women with hypertension[20].

The evidence for the benefit of antihypertensive treatment in both women and men has increased[21]. There are mainly five classes of antihypertensive drugs that have shown consistent evidence of reduced blood pressure and improved cardiovascular outcome; angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta receptor blockers, calcium channel blockers and thiazide diuretics (including thiazide-like diuretics for example chlortalidone). These antihypertensive drugs can be used in different combinations according to guidelines[3]. A large analysis could conclude that there was no evidence of a gender difference in response to different antihypertensive drugs in randomized controlled trials. However there was a borderline significant evidence ($P=0.05$) that women derived greater protection from stroke with regimens based on calcium channel blockers compared to regimens based on ACEI[22]. Nevertheless, it supports current guidelines which state that there should be no special considerations regarding antihypertensive drug class based on the patient´s sex. The only exception is pregnant women were ACEI and ARB should be avoided due to teratogenic effects. In patients with diabetes mellitus and chronic kidney disease antihypertensive treatment with ACEI or ARB is recommended[3]. There are other types of anihypertensive drugs that could be used but which have not shown evidence of reduced cardiovascular outcome in patients with hypertension. Spironolactone has blood pressure lowering effects and is commonly used in cases with primary hyperaldosteronism. Spironolactone reduced SBP in patients with resistent hypertension older than 62 years and results seemed to be similar in both genders[23, 24].

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Doxazosin is an alfa blocker that lowers blood pressure and which is also used for benign prostata hypertrophy. Doxazosin was evaluated in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) but the doxazosin arm was stopped prematurely due to a higher proportion of combined cardiovascular disease which was driven by worsening in heart failure compared to the chlortalidone group. However theses results have been questioned regarding how the diagnosis of heart failure was put. Results in the doxazosin arm seem to be eqvivalent in borth women and men[25].

Moxonidine is a centrally acting antihypertensive that decreases peripheral vascular resistance via inhibition of peripheral sympathetic activity and lowers blood pressure. Most studies regaring this antihypertensive drug are small with short duration and there is no information regarding differences between women and men[26].

Despite guidelines, observational trials in both Europe and the United States have shown that women and men are treated with different antihypertensive drugs[12, 13, 27]. In general, women are more often treated with diuretics or beta receptor blockers and men with ACEI or calcium channel blockers. The reasons for this are not clear. The gender differences in antihypertensive treatment in patients with concomitant cardiovascular disease seem to be smaller suggesting that comorbidities could explain the differences[28]. Another possible explanation could be gender differences in side-effects. Women more often get cough when treated with ACEI compared to men[29]. However, women could then be treated with an ARB instead according to guidelines[3]. Women also seem to be more susceptible to vasodilation-related adverse symptoms by dihydropyridine which is a class of calcium channel blockers[30]. If there are gender differences regarding first line antihypertensive treatment in primary health care in Sweden is not known. If differences in antihypertensive treatment in women and men can be explained by comorbidities is similarly not known.

Antihypertensive treatment in relation to cardiovascular disease

Even if the choice of antihypertensive treatment is based on the patient´s anamnesis some important aspects must be considered. Thiazide diuretics and beta receptor blockers have known negative metabolic effects which are enhanced if the two drugs are combined, and they may induce diabetes mellitus[31]. Women with diabetes have been shown to have a higher risk of cardiovascular morbidity and mortality compared to their male counterparts[32]. Beta receptor blockers have about half the effect on reducing stroke risk compared to other antihypertensive drugs[33]. Stroke is more common in men, however it is increasing in younger women. Further women get more disabled following a stroke compared to men[34].

In contrast, calcium channel blockers have neutral effects on glucose metabolism. ACEI and ARB may even delay the development of diabetes mellitus[35, 36]. Diabetes mellitus is often concomitant with hypertension. In the Swedish Primary Care Cardiovascular Database (SPCCD) the prevalence of diabetes mellitus in hypertensive patients is almost 22%[37]. According to guidelines from the European Society of Hypertension patients with hypertension and diabetes mellitus are recommended treatment with ACEI or ARB especially in the presence of proteinuria and micro-albuminuria[3].

The Joint British Societies´ Consensus Recommendations for the Prevention of Cardiovascular Disease (JBS3) recommends first line antihypertensive treatment with an ACEI or an ARB in patients <55 years and a calcium channel blocker in patients >55 years. Further these recommendations emphasize the risk evaluation in patients with a low ten year risk but a high life time risk of cardiovascular disease, which is common in younger patients and in women[38]. ACEI and ARB may reduce the risk of the development of atrial fibrillation among hypertensive patients[39, 40]. Women with atrial fibrillation have an increased risk of stroke compared to men and women who suffer from stroke more often have atrial fibrillation and hypertension as risk factors compared to men[41].

Left ventricular hypertrophy (LVH) is an independent risk factor for cardiovascular disease in both women and men[42]. LVH is present in approximately 30% of patients with hypertension. There is evidence that LVH is a stronger risk factor for cardiovascular disease in women than in men[43]. In different investigations it has been suggested that ACEI, ARB and calcium channel blockers may be better in reducing LVH compared to beta receptor blocker in hypertensive patients[44, 45].

Socioeconomic factors

Socioeconomic factors cover a variety of aspects, including ethnicity, immigration status, education, occupation, income, and living conditions. There is a strong association regarding low socioeconomic status, higher blood pressure levels and hypertension[46, 47].

High educational level is associated with healthy behavior and low educational level increases both cardiovascular mortality and all-cause mortality[48]. Low educational level is associated with a higher blood pressure and a higher prevalence of hypertension and this seem to be more pronounced in women[46, 49]. The mediator by which education affects the development of hypertension has been suggested to be through an increased body mass index/waist circumference and higher heart rate in subjects with low educational level[50]. Alcohol consumption and smoking probably also contribute to this association but the relationship is complex[51].

Blood pressure levels vary between different countries[15, 52]. In Sweden approximately 16% of the inhabitants are born outside Sweden (Statistics Sweden). Finnish immigrants seem to have a higher prevalence of hypertension and non-European immigrants seem to have lower prevalence of hypertension compared to native Swedes[53]. The reasons for these differences are most likely multifactorial and could be attributed to both genetic differences and differences in life style factors. It has also been shown that patients born outside of Sweden have a lower persistence to antihypertensive therapy[54].

Mental health and socioeconomic factors are associated. Patients with schizophrenia and bipolar disease have a higher prevalence of hypertension and a higher mortality in cardiovascular disease, compared to subjects without psychiatric disorders[55-57]. Patients with severe mental illness (schizophrenia, bipolar disease and depression) are more likely to smoke, be overweight and psychiatric disorders are associated with a
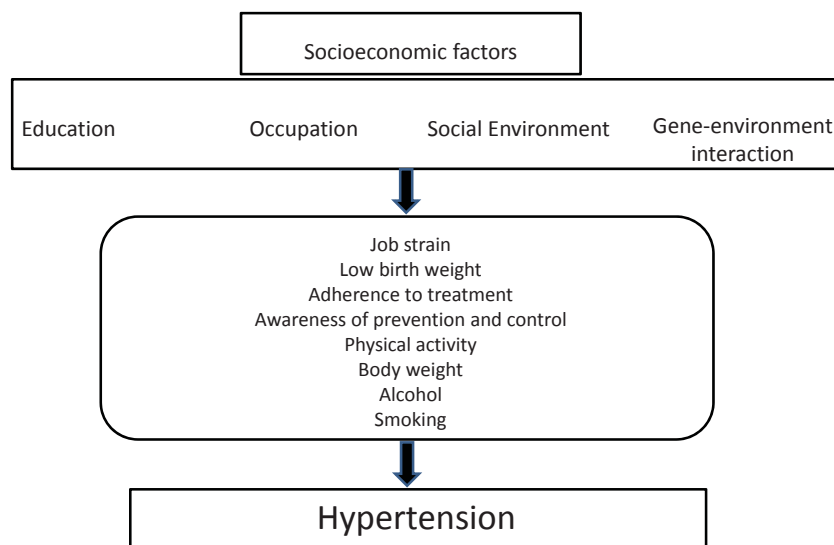
Figure 2. Socioeconomic determinants and possible mechanism for their effect on hypertension. Adopted after Grotto et al. Curr Opin. Cardiol. 2008;23:335-339

chronic elevation of stress hormones[55]. Furthermore, depression has been suggested an independent risk factor of hypertension[58]. Studies have shown that depressive disorders are linked to lower adherence to antihypertensive therapy and an increased mortality in hypertensive patients with concomitant depression[59, 60]. If there are differences in blood pressure control and prescription pattern of antihypertensive treatment in relation to gender and education, country of birth and psychiatric disorders are not known (Figure 2).

Sex differences

The differences between women and men regarding blood pressure levels are consistent in different populations and is also found in animals[61]. The fact that younger men have higher blood pressure and that women´s blood pressure begins to rise after the fifth decade of life have suggested that gonadal hormones and/or sex chromosomes complement can be involved in the development of hypertension[62]. However the connection is complex which is indicated by the fact that hormone replacement therapy in postmenopausal women did not reduce the risk of cardiovascular disease[63].

Studies have shown that menopause is associated with higher blood pressure even after adjustments for age and body mass index[64]. 17β-Estradiol (E2) prevents blood pressure from rising after ovary-ectomy in several different mice models supporting the conclusion that menopause increases blood pressure[62]. Further, women who have undergone hysterectomy have a higher incidence of hypertension[65]. At menopause E2 levels drop but several other changes occur that cannot be separated from the decline in E2. Testosterone declines and FSH and LH increases just after menopause. Hypertensive men have lower testosterone levels. If a man is treated for testis cancer and testis is removed this results in a higher blood pressure suggesting that testosterone

may also play a role in the regulation of blood pressure[66]. Testosterone is converted to E2, hence lower testosterone levels results in lower E2 levels. Women with polycystic ovarian syndrome have higher testosterone levels and also higher blood pressure compared to healthy women. Salt sensitivity correlates inversely with circulating ovarian hormones[67]. It has been suggested that salt sensitivity after menopause contribute to a higher blood pressure in postmenopausal women[68]. Further it has been implied that estrogen might influence blood pressure in women trough a stimulation of nitric oxides and that the salt sensitivity in postmenopausal women is related to abnormal vascular reactivity which is mediated through nitric oxide[69]. In summary, it is clear that blood pressure increases with age and also with ovarian dysfunction, but it is not known to what extent the different pathways may overlap.

Estrogen influences the renin-angiotensin system in different ways. In normotensive postmenopausal women plasma angiotensin II levels nearly double with oral administration of estrogen and medroxyprogesterone[70] Estrogen effects the angiotensinogen gene expression and synthesis through modulation of regulatory elements in the gene promotor[71]. This increases the concentrations of circulating angiotensinogen in women[72]. Further, females have a lower expression of the angiotensin II type 1 receptor, angiotensin converting enzyme and plasma renin compared to males[73] (Figure 3). The gene for the angiotensin II receptor is located on the X chromosome making it plausible that there can also be gene interactions that can explain the differences in women and men[74]. Men with an extra sex chromosome (XYY) have normal blood pressure suggesting that the Y chromosome do not adversely affect blood pressure. However women with Turner´s syndrome (XO) have a higher incidence of hypertension suggesting that the X chromosome might be involved[62].
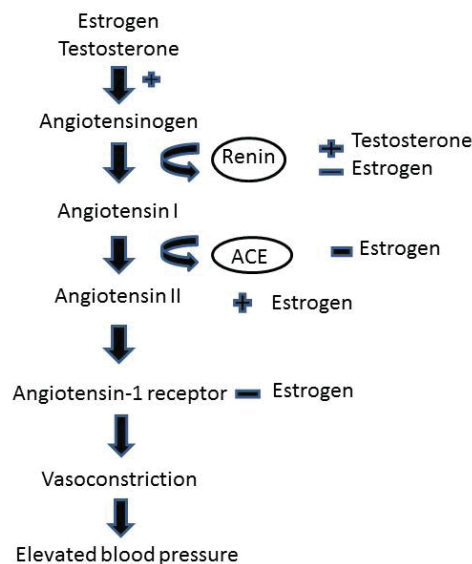
Figure 3. Schematic figure showing estrogen and testosterone´s role in the reninangiotensin system.

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Pharmacodynamics and kinetics in short

There are some basic differences between women and men that can affect pharmacodynamics and kinetics. Women are smaller with a lower body weight and smaller organs. Men have larger distribution volumes[75]. Women have higher proportion of body fat which may increase the distribution volume for lipophilic drugs[76]. Moreover, women have a 50-70% increased risk of suffering from adverse drugs reactions compared to men[75].

Beta receptor blockers

In experimental models sex hormones can modulate the regulation of β-adrenergic receptors in heart and vessels. Further, β1-receptors are up-regulated in estrogen deficiency[77]. There are gender differences regarding both cardio selective and non-selective beta receptor blockers. Both metoprolol and propranolol have higher plasma concentrations in women and women demonstrate a more pronounced decrease in heart rate and SBP, when treated with beta receptor blockers[75].

ACEI

Estrogen influences the renin angiotensin system with a net inhibition. It has been proposed that the cardio protective effect of endogenous estrogen may in part result from the inhibition of this system. However it has not been established if this modulates the effects of ACEI in women. Gender specific differences between different ACEI have not been described other than higher plasma levels can be found in women due to women´s lower body weight. Blood pressure reduction with different ACEI is comparable in women and men. Women exhibit side effects i.e. cough more often than men[29].

ARB

Gender specific pharmacokinetic differences have not been observed for ARBs except for the fact that women have twice as high plasma concentrations compared to men[75].

Calcium channel blockers

Women have faster clearance and lower serum levels of some calcium channel blockers that are subject to metabolism in the liver by the CYP3A4. Possibly women have a more pronounced blood pressure reduction on calcium channel blockers compared to men[78].

Thiazide diuretics

There are no gender differences in the antihypertensive effect on thiazide diuretics. Hyponatremia is a well-known side effect which women more often are hospitalized for. This is most likely due to the more frequent use in women and not to the fact that women are more susceptible to hyponatremia on thiazide diuretics[79]. Thiazide diuretics can probably reduce the risk of osteoporotic fractures which can be an advantage especially in older women[80].

AIMS

Against this background, the aims of the thesis were:

- To analyze antihypertensive treatment in women and men and investigate the scientific support for treatment recommendations and further to evaluate if treatment recommendations are pursued.

- To study achieved blood pressure levels and evaluate differences in antihypertensive treatment in women and men with new-onset and current hypertension.

- To study the influence of comorbidities and socioeconomic factors on antihypertensive treatment in women and men.

PATIENTS AND METHODS

Paper I

The review is based on The Swedish Council on Technology Assessment in Health Care (SBU) systematic review of treatment of mild to moderate hypertension and the effects on outcome. The review by SBU did not include patients with impaired renal function associated with diabetes, hypertension in children, or hypertension during pregnancy.

The SBU performed a systematic, step-by-step perusal of the literature for all published randomized controlled trials that studied the effect of blood pressure-lowering treatment of at least six months' duration and where stroke, acute myocardial infarction, total cardiovascular morbidity, or death were reported. Pre-specified criteria for eligible studies for the systematic review and definitions of outcome have been described in detail[8]. The literature search was performed in MEDLINE.

From the initial approximately 930 publications retrieved, two independent reviewers read and selected 80 individual studies. Following a structured review (based on a protocol by Fowkes and Fulton) by the working group within the Swedish Council on Technology Assessment in Health Care, the working group finally included 67 studies, as described previously[8, 81]. All included trials and their abbreviations are presented in Appendix.

Method

For the present study (I), we performed an additional literature search of the 67 studies in MEDLINE, and checked reference lists in available systematic and other reviews and meta-analyses to not overlook results regarding gender. For the 67 selected studies, two independent investigators examined selected and extracted data on the following subjects:

  - Proportion and number of women included
  - If gender-specific data were reported
  - Differences and/or similarities between women and men regarding BP response to treatment
  - Choice of therapy and additional therapy in respect to gender
  - Lost to follow-up in women and men
  - Outcome in women and men

If it was described that the statistical analyses were adjusted for gender this was noted In case of disagreement, consensus was sought by consulting with another two experts.

Paper II

Swedish hypertension open care retrospective study in men and women was a retrospective study in patients in Sweden, carried out in patients visiting primary health

care centers from January to December 2003, followed up from November 2004 to April 2006. The trial was performed in 89 sites, of which 61 were private practitioners and 28 were primary health care centers. The sites were mainly located in the regions of Stockholm, Göteborg and Malmö, which are urban areas.

Patients

Women and men aged ≥50 years and <80 years at baseline, with new onset of hypertension and where pharmacological treatment was considered necessary, were included in the study. The treating physician at each site recruited the patients to the study. The first female patient and the first male patient being diagnosed with hypertension in one of the pre-specified months were included, with an upper limit of 12 patients per site, six women and six men. Only one female and one male patient per month were included. Patients were included every second month from January to December 2003. If no patient could be found in the pre-determined month, the first patient in the next month could be included.

Method

Antihypertensive treatment was to be started not later than December 2003. Blood pressure after intervention was measured following a minimum of 8 weeks and a maximum of 6 months after treatment start or after the last change in medication. The site determined when they had reached satisfying blood pressure control. Patients where non pharmacological treatment was sufficient to reach blood pressure goals or patients who did not attend follow-up visits were not included in the study.

Baseline characteristics were sex, age, weight, height, and body mass index. Risk factors were considered to be diabetes mellitus, family history of cardiovascular disease (male relatives <55 years and female relatives <65 years), smoking, known coronary disease, cholesterol levels considered clinical significantly elevated by the physician, and proteinuria. The incidence of hormone replacement therapy in women was registered. Blood pressure at baseline was a mean value of three measurements measured before the start of treatment according to the normal standard in each site. Blood pressure could be measured by either a nurse or a physician. Achieved target blood pressure was defined as ≤140/90 mm Hg. Weight was also measured at follow up. Medication was recorded with trade name and dose in milligrams. Blood samples were collected when treatment was started. The exclusion criteria were concomitant heart failure, myocardial infarction within the last 6 months or unstable angina pectoris, serum creatinine >130 mmol/l, atrial fibrillation, ALT (alanine aminotransferase) or AST (aspartate aminotransferase) >3 times upper limit of normal, pregnancy, body mass index >35 or secondary hypertension. Patient data from the investigator files was logged. All data were anonymous once logged.

Ethics

The study was approved by the Regional Ethical Review Board in Göteborg. The sponsor of the study, Solvay Pharma AB, had no role in the data analyses, data interpretation or writing of the report.

Paper III and IV

The studies were performed within the Swedish Primary Care Cardiovascular Database (SPCCD). The SPCCD is a database which includes 74 751 patients 30 years or older, with hypertension who were treated in primary health care centers in the south-western part of Stockholm County, and the area of Skaraborg in south western Sweden. Patients with a recorded diagnosis of hypertension in any of the primary healthcare centers between 1 January 2001 and 31 December 2008 were included. Twenty-four public primary healthcare centers (out of 25) in Skaraborg and 24 primary healthcare centers in south-western Stockholm were included. A validation of the diagnoses in Skaraborg 2010 showed that the diagnosis of hypertension had a sensitivity of 83%[82]. Hypertension was diagnosed according to the prevailing recommendations of ≥140 and/or ≥90 mmHg in the seated or supine position after 5 min of rest on at least three occasions, or ongoing antihypertensive treatment, and was based on the clinical decision of the physician. The SPCCD holds information from the medical records regarding demographic information, part of the free text (e.g. blood pressure), lifestyle information (height, weight, smoking), comorbidity (by ICD-10 codes: diabetes mellitus, ischemic heart disease, heart failure, atrial fibrillation/flutter, cerebrovascular disease, and asthma), laboratory results (creatinine, fasting glucose, total cholesterol, HDL and LDL cholesterol, and triglycerides), and all prescribed drugs[37, 83].

SPCCD uses the unique personal identity number assigned to each Swedish resident, linking medical records to five population based registers: the Prescribed Drug Register, which covers all dispensed prescriptions in Sweden since June 1, 2005, the National Patient Register including all hospitalizations and outpatient consultations in hospitals, the Cause of Death Register, the Census Registers, and the Swedish Register of Education. The details around the SPCCD has previously been described[37].

Patients

In Paper III and IV patients from the SPCCD who made at least one blood pressure measurement from the first of January 2007 until the 31th of December 2008 were included. The cohort consisted of 40825 individuals, 23458 women and 17367 men. They were all diagnosed with hypertension before January 1, 2007, to exclude patients with newly diagnosed hypertension. Patients who deceased during the period (n=1746) were excluded from the analysis due to incomplete prescription data. Two patients did not have a registered country of birth and 1713 patients did not have a recorded level of education and were excluded from the analysis in Paper IV.

Method

Patient characteristics included age, gender, height, weight, smoking, blood pressure, comorbidity, and laboratory results. Data were analyzed by the most recent value available in the SPCCD. The most recent blood pressure recorded has been analyzed and shown a valid marker for an average of the last three measurements[37]. Cardiovascular comorbidity was defined as a diagnosis of (with corresponding ICD-10 codes) atrial fibrillation/flutter, heart failure, diabetes mellitus, ischemic heart disease

or cerebrovascular disease documented in the medical records of the primary health care and/or the National Patient Register from January 1, 2001, to January 1, 2007. Antihypertensive drug classes assessed (with corresponding anatomic therapeutic chemical classification system (ATC) codes) were ACEI, ARBs, beta receptor blockers, calcium channel blockers, thiazide diuretics including amiloride, loop diuretics, aldosterone antagonists, and other (which include clonidine, moxonidine, doxazosin, and hydralazine). Fixed drug combinations (e.g. combinations of a diuretic and an ACEI or ARB, and the combination of a beta receptor blocker and a calcium channel blocker) were counted twice, in their respective groups. No patient was prescribed a renin inhibitor. All prescribed antihypertensive drugs from the Prescribed Drug Register from January 1, 2007, until December 31, 2008 were registered and used for analysis. If the patients did not receive treatment with an ACEI or ARB the history of earlier prescriptions from June 1, 2005, were analyzed in the Prescribed Drug Register (Paper III). There were made no analysis for possible changes in antihypertensive therapy during the study period. Paper III was as a retrospective cohort study.

In Paper IV data from the Swedish Register of Education was collected in 2005. Educational level was divided in three categories; nine years or less corresponding to primary educational level, ten to twelve years corresponding to secondary school, and more than twelve years of education corresponding to college or university. Country of birth was obtained from the Census Register in 2005. Country of birth was grouped as follows; Sweden, Europe (excluding Sweden) and World (including Africa, North America, South America, Asia, Oceania, and former Soviet Union, excluding Europe and Sweden). If data was missing in 2005 additional data from the Swedish Register of Education and from the Census Register was collected in 2008 and 2010. A proxy for psychiatric disorder was defined by more than one prescription of an antidepressant (N06A) and/or neuroleptic drugs including lithium (N05A) during one year prior to inclusion in the study cohort. No time interval was required between the two prescriptions and there was no compulsory requisite for the same drug class in both prescriptions. Paper IV was a cross sectional cohort study.

Ethics

The study was approved by the Regional Ethical Review Board in Göteborg. Written consent to data extraction from all directors of the primary healthcare centers was obtained.

Statistics

Paper I

Descriptive data are presented as mean values. The percentage of women included in the studies was calculated. To explore whether the proportion of women included in trials studying the outcome of antihypertensive therapy had changed over time, a linear regression analysis was performed including the year of publication of the study and the proportion of women included.

Paper II

The sample size was calculated from data in the SCOPE trial, in which a difference of 3.2 mmHg in SBP was associated with a reduction of stroke. Thus a sample size of 1190 patients, 595 in each group (women/men) would have a 90% power to detect a difference of 3.2 mmHg between groups for the SBP. Comparability of the groups was assessed using Student´s t-test for independent samples, or Wilcoxon's ranksum test if the normal assumption did not hold for continuous variables and Chi²-test for categorical variables. All statistical tests were two-sided and considered significant at $P<0.05$. All confidence intervals were 95%. The proportion of women and men reaching the predefined goal of treatment ($\leq$140/90 mmHg) were calculated using a dichotomous variable. Only subjects reaching both systolic and diastolic blood pressure goal were defined as reaching the target. Patients were not excluded from the analysis for reasons other than missing values. Patients who did not fulfill all of the inclusion criteria and patients who fulfilled at least one of the exclusion criteria were described and summarized.

Paper III and IV

Data are presented as mean values ±SD or with 95% confidence intervals (CI), as appropriate. Comparisons of groups were made using Fisher's exact test or Chi²-test for categorical variables, and Student's t-test for continuous variables. Comparisons between groups were made with logistic regression and age was adjusted for with ANCOVA. Relative risks were calculated using a Poisson regression model. A two-tailed probability value (P)<0.05 was considered significant. Covariates adjusted for in the Poisson models (age, comorbidities, smoking, antihypertensive drug class, education, country of birth, psychiatric disorder assessed by prescribed antidepressant or neuroleptic drug) were tested and found significant ($P<0.05$) in univariabel regression analyses. All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Paper I

Women were represented in 59 of the 67 reviewed studies. A total number of 357365 patients were included, and 147560 were women. Studies of hypertension and concomitant disorders often included a smaller number of women. The proportion of women included in studies has increased over time (Figure 4). None of the studies was designed to primarily examine the outcome for women and men separately. However, in 28 studies (42%) the analysis for outcome was adjusted for gender by regression analysis or for interaction by gender with multivariate analysis.
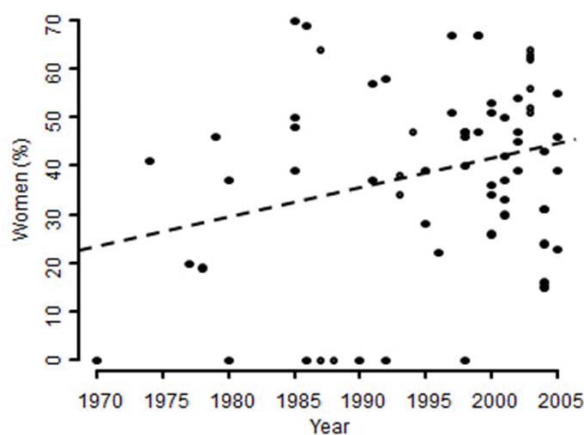
Figure 4. The proportion of women included in the 67 studies according to the year of publication. There was an increase in the proportion of women over time (r=0.27, *P*<0.05).

Blood pressure

In 15 of the studies blood pressure reduction was reported separately in women and men. The majority of the studies showed a similar blood pressure reduction in women and men but in LIFE and ANBPS women had a higher SBP at inclusion and at follow-up. In VALUE calcium channel blocker-based therapy lowered BP more than ARB-based therapy (*P*<0.001). The average SBP reduction in favor of calcium channel blocker-based therapy was 2.8 mmHg in women and 1.8 mmHg in men. A similar result was seen in ALLHAT where calcium channel blocker based therapy lowered systolic and diastolic BP more than ACEI-based therapy. Thus, SBP and DBP were 1.3 and 0.9 mmHg lower, respectively, in women on a calcium channel blocker. In men, a 0.5 mmHg reduction in favor of the calcium channel blocker was seen only for DBP.

Outcome

Outcome results were presented separately for women and men in 33 studies (49%). In five studies the number of women included and the number of events was insufficient to consider gender differences in outcome. In studies regarding active drug ther-

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apy versus a control group; HEP, SHEP, MRC Older, Syst-Eur and SCOPE all showed outcome results that were independent of gender. In studies regarding comparison of different therapies; results from NORDIL, LIFE, CONVINCE, INVEST, JMIC-B and ASCOT were independent of gender. In ALLHAT the calcium channel blocker was superior to both the diuretic and the ACEI in reducing stroke incidence in women but not in men. In VALUE, calcium channel blocker-based therapy was superior to ARB-based therapy in reducing the composite end point of cardiac morbidity and mortality in women but not in men ($P<0.05$). ANBP2 demonstrated that in men and women combined, the ACEI reduced all cardiovascular events better than diuretics. When women were analyzed separately, both treatment regimens were equal, implying that the ACEI was favorable in men.

Paper II

A total of 666 patients, 332 male and 334 female patients, were included in the study. There were some differences between women and men at baseline. Women were older with a lower BMI and with a lesser concomitant prevalence of diabetes mellitus compared to the men.

Blood pressure

There was no difference in mean SBP between men and women before or after intervention, Table 1. The decrease in the SBP in response to treatment was equal in women and men.

**Table 1.** SBP and DBP presented as mean value with 95% CI. Ns=non-significant

Blood pressure	Men (mm Hg)	Women (mm Hg)	*P-value* for difference between women and men
SBP baseline	169.8 (168.1-171.5)	171.9 (170.1-173.8)	ns
SBP follow-up	141.3 (139.8-142.8)	141.5 (139.8-143.1)	ns
DBP baseline	98.6 (97.6-99.5)	97.1 (96.1-98.1)	*p<0.05*
DBP follow-up	83.3 (82.4-84.2)	81.4 (80.5-82.4)	*p<0.05*

However, women had a lower mean DBP both before and after intervention compared with men. There was no difference in the change of DBP from before to after intervention between women or men. As a result mean pulse pressure before and after intervention was higher in females ($P<0.05$). There was no difference between the proportion of women and men reaching the predefined goal of treatment. Fifty-three percent of the women and fifty-two percent of the men reached target blood pressure. Patients older than 65 years of age reached target blood pressure in 38%, whereas patients younger than 65 reached target blood pressure in 59% of the cases.

Antihypertensive treatment

Beta receptor blocker was the most commonly prescribed treatment in both women and men; more than 50% of the patients were treated with beta receptor blockers.

Diuretics were the second most common antihypertensive drug; 47.6% of the women were treated with diuretics but only 39.2% of the men. Calcium channel blockers and ACEI were numerically more common in men. ARB was equally common in both women and men (Figure 5). About 39% of the patients were treated with only one antihypertensive drug and among these patients 49% reached blood pressure. In patients treated with two antihypertensive drugs (28%), 55% reached target blood pressure and patients with three different antihypertensive drugs (18%) reached treatment goals in 59%.
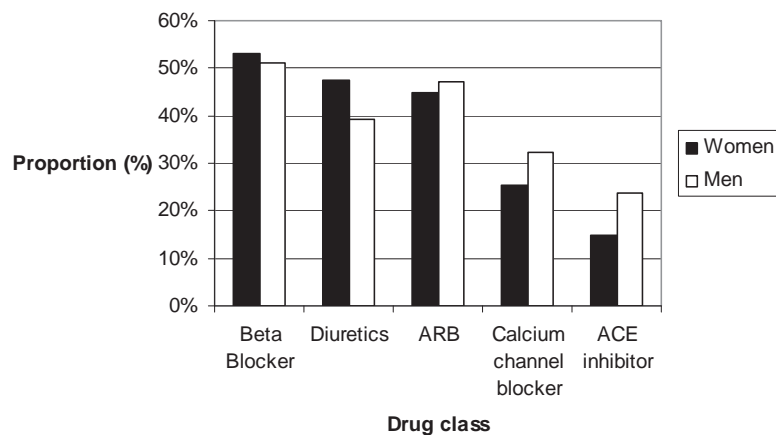
Figure 5. Proportion of subjects per drug class and gender. ARB=angiotensin receptor blocker, ACE inhibitor=angiotensin converting enzyme inhibitor.

Paper III

A total of 40825 patients with hypertension were included. Women were older and had higher SBP and lower DBP, compared to men. Diabetes mellitus, ischemic heart disease, cerebrovascular disease, and atrial fibrillation/flutter were more common in men, whereas heart failure was equally common in women and men.

Blood pressure

Achieved blood pressure levels according to age and gender are presented in Figure 6. Men had a higher achieved SBP than women up to the age of 49. In patients older than 69 years, women had a higher SBP, except in patients of 90 years of age or older. Achieved DBP dropped with age in both genders and DBP was lower in women in all age groups except in of 90 years or older. This pattern was consistent in all subgroups of comorbidities. However, achieved SBP was higher in women in all subgroups of comorbidities except in patients with asthma. Fewer women (38%) than men (41%; $P<0.0001$) reached target blood pressure.

Anithypertensive treatment

There were gender differences concerning antihypertensive treatment with all drug classes except ARB. Women were more often prescribed thiazide diuretics, loop di-
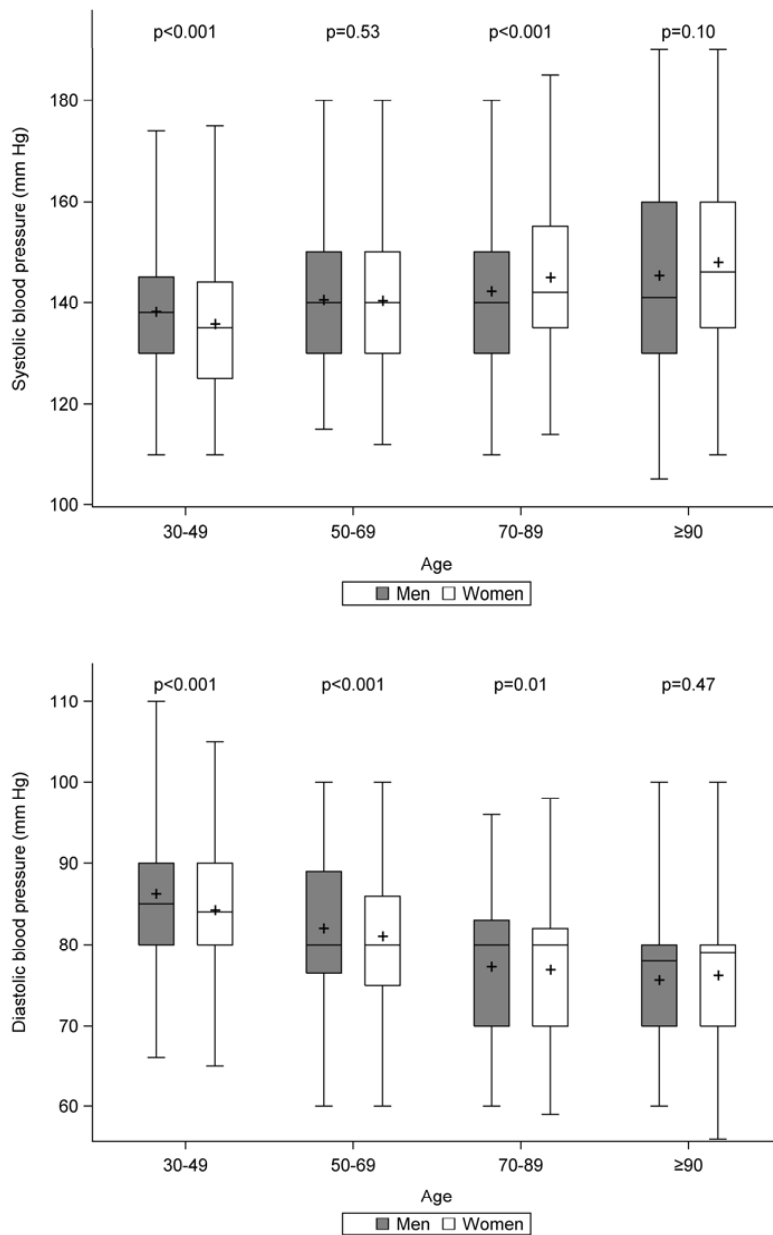
Figure 6. Systolic and diastolic blood pressure according to age and gender presented in box-and-whiskers plot with the top and bottom boundaries of the box representing third and first quartile and the line and the plus in the box represents the median and the mean, respectively. The whiskers show the upper and lower extreme, excluding outliers. *P*-values for differences in blood pressure between women and men in different age groups.

uretics and beta receptor blockers than men, and this was consistent also after adjusting for age, comorbidities, and smoking, Figure 7. Men were more often prescribed ACEI and calcium channel blockers. Similar results were seen in patients with diabetes mellitus, ischemic heart disease, and cerebrovascular disease. Women had on average 2.3±1.2 antihypertensive drug classes and men 2.4±1.2. Monotherapy was present in 24% of the women and 22% of the men. The combination of two different drug classes was most frequent (in women 33% and in men 32% of the patients), followed by the combination of three antihypertensive drugs which was present in 24% of both women and men. The combination of four or more antihypertensives was found in 17% of the women and 19% of the men.

For patients not on current treatment with an ACEI or ARB we assessed if they had previously been on such treatment and for some reason had stopped treatment. In all, 6.0% of the women and 7.5% of the men had previously been prescribed an ACEI or an ARB. Corresponding figures in the diabetic patients were 9.3% and 13.2%, respectively. Compared to men, women not treated with an ACEI or an ARB, were older and had a decreased renal function.
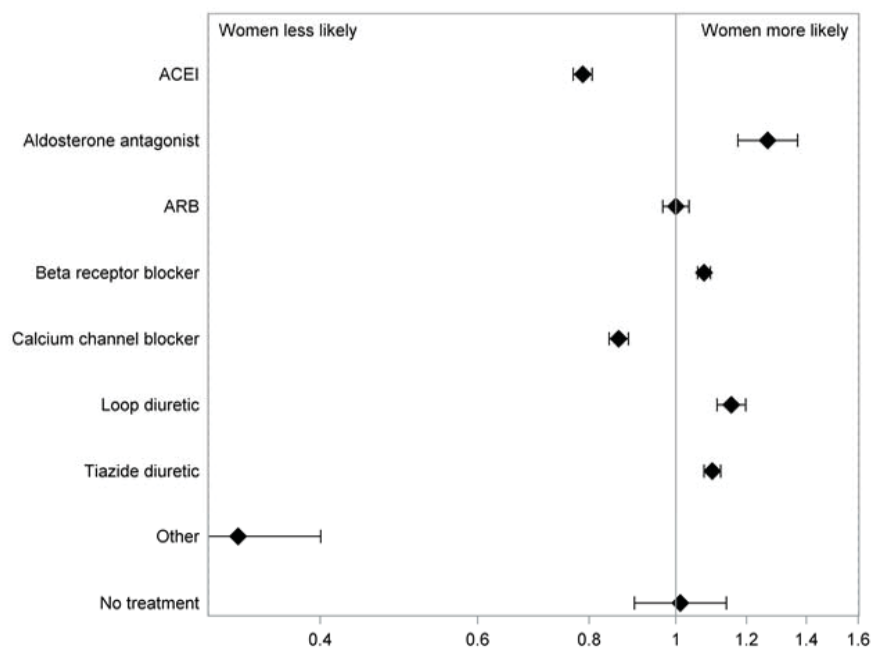
Figure 7. Different antihypertensive drug treatment according to gender in all patients. Relative risk with 95% confidence intervals of receiving different antihypertensive treatment. Poisson regression model adjusted for age, comorbidities (diabetes mellitus, ischemic heart disease, cerebrovascular disease, heart failure, atrial fibrillation/flutter, and asthma), and smoking. ACEI angiotensin converting enzyme inhibitor, ARB angiotensin receptor blocker.

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Paper IV

The majority of patients were women, native Swedish, without psychiatric disorder, and with a low educational level. Patients with lower educational level were older. In an age-adjusted model patients with lower educational level had higher glucose levels, higher SBP and lower DBP, as compared to patients with the highest educational level. Native Swedish patients were older, had lower glucose levels, and lower SBP, as compared to patients born in Europe. Patients born in Europe had the highest SBP and DBP values. Patients with psychiatric disorder were predominantly female with lower SBP and DBP, and higher cholesterol and triglyceride levels, as compared to patients without psychiatric disorder.

Diabetes mellitus, ischemic heart disease and a history of cerebrovascular disease were more common among men than women in all groups (except for cerebrovascular disease in patients born outside Europe). Educational level was inversely related to the prevalence of all comorbidities (except asthma) and this was more pronounced in women. Patients born outside Europe had the highest prevalence of diabetes mellitus, followed by patients born in Europe, in comparison with native Swedes.
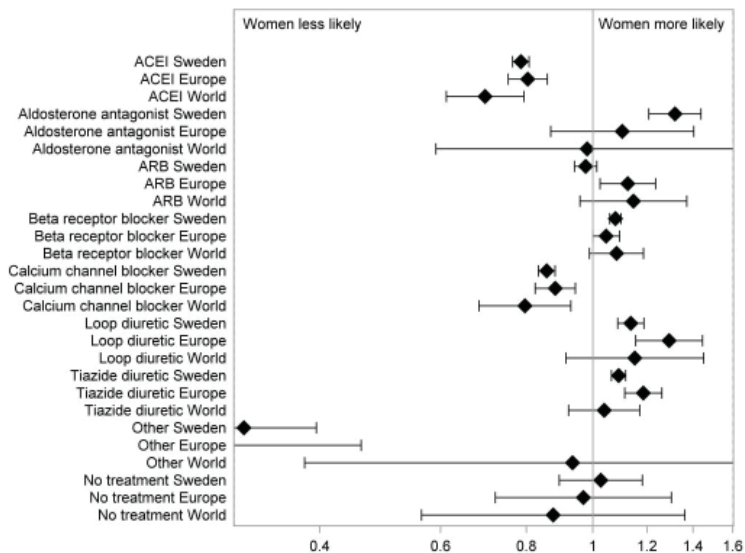
Antihypertensive treatment

Women were more often treated with diuretics, beta receptor blockers and aldosterone antagonists, whereas men more often were treated with calcium channel blocker and ACEI. ARB was equally often prescribed in women and men. Loop diuretics, aldosterone antagonists and beta receptor blockers were more common in women with lower educational level, while calcium channel blocker and ACEI were more common among men with lower educational level. No treatment was more common among the best educated irrespective of gender. Women not born in Sweden were more often prescribed ARB compared to their male counterparts. In patients with psychiatric disorder there was no interaction between drug class and gender. Similar results for education and country of birth were obtained in analyses adjusted for age, smoking and all other variables, Figure 8 and 9.

Blood pressure

In a Poisson model (adjusted for age, smoking, comorbidities, antihypertensive drug class, education, country of birth and psychiatric disorder) cardiovascular comorbidity, educational level of ten to twelve years, being native Swedish, and the comorbidity of psychiatric disorder, were associated with better achievement of target blood pressure in women. In men, however educational level and psychiatric disorder did not influence achieved target blood pressure, while being born in Sweden and having a history of cardiovascular comorbidity was associated with achieving target blood pressure.
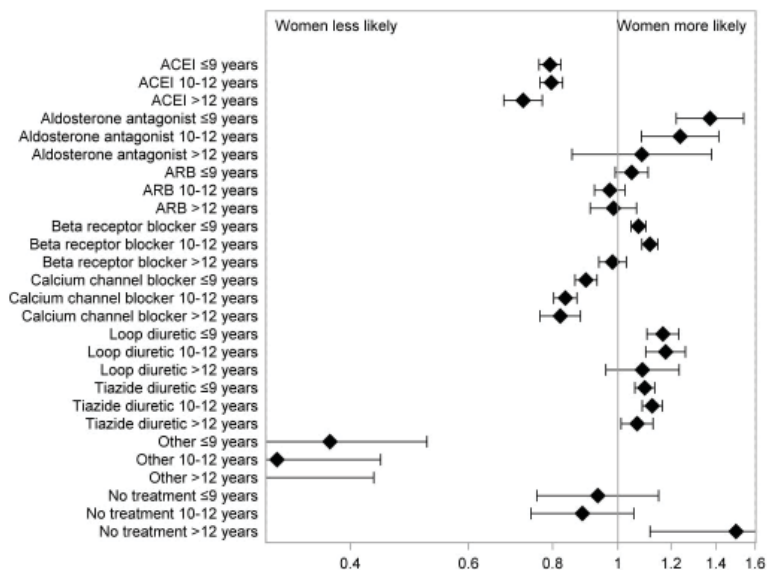
Figure 8. Antihypertensive treatment according to education and gender. Relative risk with 95% confidence intervals of receiving different antihypertensive treatment. Poisson regression model adjusted for age, comorbidities (diabetes mellitus, ischemic heart disease, cerebrovascular disease, heart failure, atrial fibrillation/flutter, and asthma), country of birth, psychiatric disorder and smoking. ACEI angiotensin converting enzyme inhibitor, ARB angiotensin receptor blocker.

Figure 9. Antihypertensive treatment according to country of birth and gender. Poisson regression model adjusted for age, comorbidities (diabetes mellitus, ischemic heart disease, cerebrovascular disease, heart failure, atrial fibrillation/flutter, and asthma), educational level, psychiatric disease and smoking. For details see legend Figure 8.

DISCUSSION

Main findings

Women have been included to a lesser extent in large randomized controlled trials. Despite this women seem to benefit as much as men from antihypertensive therapy which may indicate that the hypertensive disease carries at least the same risk in women as in men. Women and men are treated with different antihypertensive drugs. Women are more often treated with diuretics and beta receptor blockers and men are treated with ACEI and calcium channel blockers. The differences cannot fully be explained by differences in comorbidities, education, country of birth or psychiatric disorders. In a selected patient group in primary care women and men with hypertension have equal blood pressure levels before and after treatment. However in a larger cohort in primary care hypertensive women have a higher achieved blood pressure in all subgroups with cardiovascular comorbidities and fewer women achieve target blood pressure compared to men.

Antihypertensive treatment in randomized controlled trials (I)

In none of the 67 studies that contributed to the results of the SBU report "Treatment of mild to moderately elevated blood pressure", the main objective was to compare treatment effect size between women and men. Barely half of the studies reported outcome separately for women and men and only 15 studies reported blood pressure reduction separately for women and men. In one third of the studies the statistical analysis for outcome was adjusted for sex and results appear to be similar regarding blood pressure reduction and reduction in cardiovascular outcome which is supported by current guidelines[3]. However, two large studies, VALUE and ALLHAT showed an increased blood pressure reduction on calcium channel blockers compared to an ARB or ACEI, and this was most evident in women. This contributed to the borderline significance in reduced incidence of stroke in women with calcium channel blocker compared to ACEI seen in a large meta-analysis[22]. Further, in ANBP2 results favoring ACEI compared to diuretics in reducing cardiovascular events was not significant when analyzing women alone. There is some experimental support for the fact that women might have an inferior effect on ACEI on blood pressure reduction compared to men[72]. However this is only circumstantial evidence and it needs to be examined more thoroughly. Interestingly a large observational trial showed inferior results for ACEI in women with heart failure compared to ARB[84]. This is interesting because in women, hypertension more often contributes to the development of heart failure compared to men. Satisfying, the amount of women in studies regarding hypertension seems to increase over time. However, to conclude with certainty that there are no gender differences regarding reduction in blood pressure and outcome in different antihypertensive therapies is bold.

Antihypertensive treatment in primary health care (II-IV)

The differences in antihypertensive treatment in women and men was similar when studying patients in primary health care with both new-onset and current hypertension. Differences in comorbidities with a higher prevalence of diabetes mellitus and

ischemic heart disease in men has been suggested to explain this finding but in Paper III we could conclude that this do not fully explain the differences. Women with hypertension and diabetes mellitus were less often treated with ACEI or ARB compared to men despite current treatment recommendations[3]. Further, women were less often prescribed an ACEI or ARB and subsequently interrupted treatment compared to men. This implies that women perhaps are not even giving the opportunity to try an ACEI or ARB. Possibly this could be explained by expected side effects with ACEI, which women are more susceptible to. Another speculation could be that the lower absolute risk of cardiovascular disease in women influences the physician's inertia in treating women with hypertension who by tradition are at low risk. It has been shown that when giving physicians case studies they are more prone to reassign women of intermediate risk to a lower risk group and reassign men of intermediate risk to a higher risk group[85].

However, women with diabetes mellitus have erased the lower risk of cardiovascular disease in being a woman and have a risk of cardiovascular disease comparable to or higher than that of a man with diabetes mellitus[32]. Further, women with the metabolic syndrome, which hypertension is a part of, also has an increased risk of cardiovascular disease compared to their male counterparts[86]. In other cardiovascular diseases women less often seem to be treated according to guidelines and it is possible that the differences in antihypertensive treatment partly could explain the higher risk in women with diabetes mellitus[87].

Further the more frequent prescription of ACEI and calcium channel blockers in men was not influenced by education, country of birth and psychiatric disorders. Other factors could influence the choice of antihypertensive treatment, such as side-effects on ACEI or calcium channel blockers which women seem more susceptible to. Moreover, women might more often suffer from ankle edema due to venous insufficiency which could motivate the use of thiazide diuretics instead of calcium channel blockers[29, 30]. However the prescription pattern was to some extent influenced by socioeconomic factors. Well-educated women were not prescribed aldosterone antagonists, beta receptor blocker or loop diuretics more often than men. A hypothesis could be that more well-educated patients, both women and men, influence the choice of prescribed drugs which results in a more gender neutral prescription pattern. In women born in Europe there was a higher frequency of ARB which could possibly be explained by a higher frequency of diabetes mellitus in this group, despite the fact that the model was adjusted for comorbidities[3].

Blood pressure levels and achieved blood pressure in primary health care (II-IV)

In Paper II which was a retrospective study in primary health care where patients were recruited by the physician at each site although in a random manor, SBP levels did not differ between women and men before or after treatment while DBP was lower in women resulting in a higher pulse pressure. Likewise there was no difference between women and men in the time to satisfactory blood pressure control. However, the study was underpowered to show differences in systolic blood pressure between women and men. Further it is possible that the sites recruited were particularly interested in

hypertension. This is also reflected by the fact that 50% of the patients reached target blood pressure which is unusually high. In most studies approximately 25% of the patients with hypertension reach target blood pressure[88]. On the contrary, in a large non-selected hypertensive population with ongoing hypertension in primary health care (Paper III) women reached blood pressure goals less often than men. Men up to the age of 49 years had a higher achieved SBP, but in patients older than 69 years women had a higher achieved SBP (except in patients ≥90 years where the differences were not significant). Moreover, women had a higher SBP in all groups of cardiovascular comorbidities even after adjusting for age. This is remarkable. There is strong evidence that lowering SBP to <140 mmHg is beneficial in patients with hypertension and concomitant diabetes mellitus, ischemic heart disease and/or cerebrovascular disease[3]. The choice of antihypertensive treatment should not remove focus from the importance of reaching target blood pressure irrespective of gender. If women reached target blood pressure to a similar extent as the men one could argue that the choice of antihypertensive treatment is irrelevant, since the most important aspect in treatment of hypertension is to achieve target blood pressure. However, as this is not the case it is difficult to understand why women are not treated with ACEI, ARB and calcium channel blockers as often as the men. Nevertheless the difference in treatment is somewhat smaller, when comparing patients with cardiovascular comorbidities, which is gratifying.

The benefit of lowering blood pressure in the elderly is strengthened after the publication of the HYVET trial were patients 80 years or older were included. The SBP was lowered to in mean 144 mmHg which was beneficial in reducing stroke, heart failure and all-cause death[89]. However, there is still a debate whether or not to recommend SBP <140 mmHg in all patients older than 80 years. But in patients younger than 80 years treatment goals can be SBP <140 mmHg if the patient is fit and treatment is well-tolerated, thus for a majority of the elderly patients in Paper II and III the target SBP should be <140 mmHg[3].

In Paper IV the presence of cardiovascular comorbidity was associated with reaching target blood pressure (<140/90 mmHg) in both women and men in a Poisson model. This could be expected since the target blood pressure at the time of the study was <130/80 mmHg in this group. Further patients with cardiovascular comorbidities are known to have better persistence to antihypertensive therapy[90]. What is more alarming is the fact that diabetes mellitus was not associated with reaching target blood pressure in neither women nor men. At the time of the study the target blood pressure was <130/80 mmHg in patients with diabetes mellitus. It is well known that patients with hypertension and diabetes mellitus have a high risk of both macrovascular and microvascular disease with an increased SBP and that there is a benefit in reducing SBP to <140 mmHg[91, 92].

In women an educational level of 10-12 years was associated with achieving target blood pressure. In the group with an education level of more than 12 years the results were not significant but compared to men women seem to benefit more from a higher educational level. This is in line with previous investigations in Sweden and abroad[49, 93]. The reason for this is not clear. The impact of education on blood pressure is probably mediated through different pathways involving lifestyle factors, such as

exercise, alcohol consumption and body mass index[94]. Why this seems more important in women is not completely understood.

In both women and men being born in Europe was inversely associated with reaching target blood pressure. It is known that a large proportion of the immigrants from Europe come from Finland where hypertension is more common compared to Sweden[53]. Many immigrant groups have been shown to have an increased risk of cardiovascular disease compared to native Swedes and as blood pressure is an important risk factor this must be considered highly unsatisfactory[95, 96]. The high frequency of diabetes mellitus in the same group can also contribute to this finding but does not make it less alarming. This calls for national actions in cardiovascular prevention in the group of immigrants.

In women psychiatric disorder was associated with reaching target blood pressure. This was not expected rather the opposite could be expected due the fact that patients with psychiatric disorders have an increased sympathetic activity and there is also an association between depression and mortality in hypertensive patients[55, 59]. The majority of patients with psychiatric disorder in our study suffered from depression and even though hypertension is more common among patients with depression to the best of our knowledge there is no data reporting worse blood pressure control among these patients which is commented in the review by de Hert and coworkers[55]. However, it is possible that our definition of psychiatric disorder which was not based on the diagnosis but rather the dispensed prescription of an antidepressant and/or neuroleptic drug leaves us with a compliant group of patients who are not representative for all patients with psychiatric disorders. Also, concomitant psychiatric disorder may increase contacts with care givers and increase the number of blood pressure measurements, hence blood pressure control might increase.

Limitations

There are some important limitations that need to be addressed. Paper I is a review that did not include unpublished results, thus there may be publication bias. We did not have access to individual data from the studies. Paper II was calculated to include 595 women and 595 men to show difference in SBP but this could not be met due to difficulties in recruiting patients. This results in an underpowered study. The sites were not recruited by random rather by interest which could influence the results. The patients were identified from investigator´s files retrospectively in a random manor ever second month but the process cannot be considered completely random. Paper III and IV did not include patients who did not attend primary health care in the two regions. In Paper IV the proxy for psychiatric disorder was based on more than one prescription of an antidepressant or neuroleptic drug. This could include patients treated temporarily for pre-menstrual dysphoric disorder or chronic neuropathic pain, which should not be classified as a psychiatric disorder. However, the number of affected patients should be low. Patients who deceased during the study period were excluded from analysis. It is not unlikely that these patients had lower socioeconomic status and this could have influenced our results. In the SPCCD there is no information on alcohol consumption and physical activity which is a limitation as this can influence blood pressure.

CONCLUSION

- Women seem to benefit from antihypertensive treatment to the same extent as men.

- Differences in antihypertensive treatment in women and in men are not explained by gender differences in comorbidities.

- Women with hypertension and diabetes mellitus are not treated with ACEI and ARB to the same extent as their male counterparts.

- Psychosocial factors influence prescription pattern to some extent but do not influence the predominant use of ACEI and calcium channel blockers in men.

- Women with hypertension reach target blood pressure less often than men and have a higher achieved SBP in all subgroups of concomitant cardiovascular disease.

- Efforts should be made to emphasize and improve the risk evaluation in women with hypertension and concomitant cardiovascular disease to further increase treatment results regarding blood pressure levels.

- Other explanations for the gender differences in antihypertensive treatment should be sought such as gender differences in side effects or treatment traditions.

- The choice of antihypertensive drug class should not remove focus from the importance of achieving target blood pressure, irrespective of gender.

- Future studies regarding hypertension should have the power to show treatment results on cardiovascular outcome in both women and men.

FUTURE PERSPECTIVES

The fact that women and men are treated differently both regarding antihypertensive treatment and achieved blood pressure levels is important and warrant further investigation. However, it is not clear to what extent this can influence outcome in cardiovascular morbidity and mortality. It is well known that blood pressure levels correlates with outcome but to what extent gender differences in antihypertensive treatment can have an impact on morbidity and survival is not known. In a future study we will examine cardiovascular morbidity; cardiovascular mortality and all-cause death in the cohort from the SPCCD used in Paper III and IV and hopefully bring clarity regarding this matter. To further study the reasons for the gender differences in antihypertensive treatment a multilevel study in primary health care including interviews with primary health care physicians could be performed. Mainly to elucidate if differences could be attributed to side effects in the patients or treatment traditions in different primary health care centers and/or physicians.

The impact of socioeconomic factors also deserves attention. The fact that patients who were born in Europe had a decreased level of achieved blood pressure control compared to native Swedes is unsatisfying. The high frequency of diabetes mellitus in patients born in Europe in combination with a higher achieved blood pressure most certainly affects cardiovascular outcome, which will also be investigated in the SPCCD. National information campaigns and efforts to improve risk factor control and cardiovascular prevention among immigrants are important for the future.

Studies within the SPCCD can reveal differences and inequalities, but changes in treatment traditions and risk evaluations must be made in the primary health care system.

Finally, the hypertensive disease differs in many aspects in women and men and the reasons and impact of this is not fully understood. Future randomized controlled trials regarding hypertension and cardiovascular disease should be powered to show treatment effects in both women and men, taken into account the lower absolute risk in women.

SAMMANFATTNING PÅ SVENSKA

Bakgrund

Högt blodtryck är vanligt förekommande, cirka 27% av den vuxna befolkningen i Sverige har högt blodtryck, ungefär lika många kvinnor som män. Hos kvinnor stiger det systoliska blodtrycket efter klimakteriet så att äldre kvinnor har ett högre systolisk blodtryck jämfört med män i samma ålder. Högt blodtryck är en av de starkaste riskfaktorerna för hjärt-kärlsjukdom hos både kvinnor och män. Kvinnor och män verkar ha lika stor nytta av blodtryckssänkande behandling och enligt rådande riktlinjer ska behandlingen ske utan att hänsyn tas till kön. Trots detta behandlas kvinnor och män med olika blodtryckssänkande läkemedel enligt observationella studier. Orsaken till detta är inte klarlagd, men samsjuklighet med hjärt-kärlsjukdom som män oftare har skulle kunna vara en förklaring. Kvinnor får oftare läkemedelsbiverkningar jämfört med män och detta skulle också kunna vara en bidragande orsak. Andra faktorer som skulle kunna påverka förskrivning är psykosociala faktorer som utbildning, födelseland eller psykisk sjukdom men detta är inte studerat. I olika studier har kvinnor med behandling för högt blodtryck antingen högre eller lika högt blodtryck som män. Hur det ser ut i Sverige idag med uppnådda blodtrycknivåer och målblodtryck i relation till kön är inte helt klarlagt och inte heller vet vi hur det ser ut hos patienter med hjärt-kärlsjukdom eller om psykosociala faktorer påverkar detta.

Syfte

Syftet med avhandlingen var att undersöka det vetenskapliga underlaget för dagens svenska riktlinjer för behandling av måttligt förhöjt blodtryck hos kvinnor och män. Vidare var syftet att studera uppnådda blodtrycksnivåer och skillnader i läkemedelsbehandling mellan kvinnor och män både med nyinsatt och pågående behandling. Slutligen var syftet att studera vilket inflytande samsjuklighet med hjärt-kärlsjukdom och psykosociala faktorer (utbildning, födelseland och psykisk sjukdom) har på blodtrycksbehandling hos kvinnor och män.

Resultat

Kvinnors deltagande i studier som gäller högt blodtryck har ökat med åren. I delarbete I fann vi två stora studier där blodtryckssänkande behandling med kalciumflödeshämmare sänker blodtrycket bättre än med ACE-hämmare och angiotensinreceptorblockerare. Detta var tydligast hos kvinnor. Likaså verkar kalciumflödeshämmare minska risken för stroke och större hjärt-kärlhändelse mer än ACE-hämmare och angiotensinreceptor-blockerare och detta var tydligast hos kvinnor. I delarbete II studerades 332 män och 334 kvinnor i en studie i primärvården på patienter med nyinsatt behandling för högt blodtryck. Det fanns inga skillnader mellan kvinnor och män i systoliskt blodtryck före och efter behandling, däremot hade kvinnor ett lägre diastolisk blodtryck innan och efter behandling. Det skiljde inte heller i tid till uppnått målblodtryck mellan kvinnor och män. I delarbete III och IV inkluderades 40 825 patienter i primärvården med pågående blodtrycksbehandling. Hos patienter över 69 år hade kvinnorna ett högre systolisk blodtryck överhuvudtaget och i samtliga grupper

med samsjuklighet i hjärt-kärlsjukdom. Kvinnor uppnådde målblodtryck (<140/90 mm Hg) mer sällan än männen. Kvinnor behandlades oftare med vätskedrivande läkemedel och betablockerare medan männen oftare behandlades med ACE-hämmare och kalciumflödeshämmare. Även hos patienter med diabetes, ischemisk hjärtsjukdom och tidigare stroke behandlades männen oftare med ACE-hämmare. Män hade oftare provat ACE-hämmare eller angiotensinreceptor-blockerare men slutat, jämfört med kvinnorna. Utbildningsnivå, födelseland eller psykisk sjukdom påverkade inte förskrivningen av ACE-hämmare och kalciumflödeshämmare till männen. I gruppen med högst utbildningsnivå förskrevs inte vätskedrivande läkemedel och betablockerare oftare till kvinnorna vilket talar för att förskrivningsmönstret till viss del påverkas av utbildningsnivån hos patienten. Faktorer som påverkar uppnått målblodtryck skiljer till viss del mellan kvinnor och män. Hos kvinnor var högre utbildningsnivå och psykisk sjukdom associerat med uppnått målblodtryck.

Slutsats

Kvinnor och män behandlas med olika blodtryckssänkande läkemedel och detta förklaras inte helt av skillnader i samsjuklighet med hjärt-kärlssjukdom. Kvinnor med högt blodtryck och diabetes behandlas inte lika ofta med ACE-hämmare eller angiotensinreceptor-blockerare som män med högt blodtryck och diabetes. Kvinnor når målblodtryck mer sällan än männen och har ett högre systoliskt blodtryck i samtliga grupper med hjärt-kärlsjukdom jämfört med männen. Högre utbildningsnivå och psykisk sjukdom är associerat med uppnått målblodtryck hos kvinnor. Riskbedömning och behandling av kvinnor med högt blodtryck och hjärt-kärlsjukdom behöver förbättras.

ACKNOWLEDGEMENT

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APPENDIX

Paper I Included trials, acronym, abbreviation, year of publication and location

| AASK 2002 | African American Study of Kidney Disease and Hypertension United States |

AASK
2002

African American Study of Kidney Disease and Hypertension
United States

ABCD
2000

Appropriate Blood Pressure Control in Diabetes
United States

ACTION

2004

A Coronary disease Trial Investigating Outcome with Nifedipine GITS
Australia, Canada, Europe, Israel, New Zealand

ALLHAT

2002

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
Canada, Puerto Rico, United States, Virgin Islands

ANBPS
1980

The Australian National Blood Pressure Study
Australia

ANBP2

2003

Australian Comparative Outcome Trial of Angiotensin-Converting Enzyme Inhibitor- and Diuretic-Based Treatment of Hypertension in the Elderly
Australia

ASCOT
2005

Anglo-Scandinavian Cardiac Outcomes Trial
Scandinavia, United Kingdom

BBB
1994

Behandla Blodtryck Bättre (Treat Blood Pressure Better)
Sweden

CAPPP
1999

Captopril Prevention Project
Finland, Sweden

CONVINCE

2003

Controlled Onset Verapamil Investigation of Cardiovascular End points
Brazil, Canada, Europe, Israel, Mexico, United States

DIABHYCAR

2004

Non-Insulin-Dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events and Ramipril
Europe, Morocco, Tunisia

Dutch TIA
1993

Dutch TIA Trial
Netherlands

E-COST 2005	The Efficacy of Candesartan on Outcome in Saitama Trial Group Japan	
ELSA 2002	European Lacidipine Study on Atherosclerosis Europe	
ESPIRAL	Efecto del Tratamiento Antihypertensivo Sobre la Progresion de la Insuficienca Renal en Paricentes no Diabeticos (Effect of Anti-hypertensive Treatment on the Progression of Renal Failure in Non-Diabetic Patients)	
2001	Spain	
EUROPA	European Trial on Reduction of Cardiac Events with Perindopril in Patients with Stable Coronary Artery Disease	
2004	Europe	
EWPHE	The European Working Party on High Blood Pressure in the Elderly Trial	
1985	Europe	
FACET	Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial	
1998	Italy	
FEVER 2005	The Felodipine Event Reduction Trial China	
GPPT 1986	Gothenburg Primary Preventive Trial Sweden	
HAPPHY 1987	Heart Attack Primary Prevention in Hypertension Canada, Europe, United States	
HDFP 1979	Hypertension Detection and Follow-up Program United States	
HEP 1986	Hypertension in Elderly Patients United Kingdom	
HOPE 2000	Heart Outcome Prevention Evaluation Study Argentina, Brazil, Canada, Europe, Mexico, United States	
HOT 1998	Hypertension Optimal Treatment Asia, Europe, North America, South America	
HSCSG 1974	Hypertension-Stroke Cooperative Study group United States	

HYVET pilot   Hypertension in Very Elderly Trial
2003   Europe

IDNT   Irbesartan Diabetic Nephropathy Trial
2001   Asia, Argentina, Australia, Brazil, Canada, Europe, Mexico, New
                 Zealand, Puerto Rico, United States

INSIGHT   International Nifedipine GITS Study Intervention as a Goal in
                 Hypertension Treatment
2000   Europe, Israel

INVEST   International Verapamil-Trandolapril Study
2003   Australia, Canada, Europe, Israel, Mexico, New Zealand, South
                 Africa, United States

IPPPSH   The International Prospective Primary Prevention Study in
                 Hypertension
1985   Canada, Europe, Israel

JMIC-B   The Japan Multicenter Investigation for Cardiovascular Disease-B
2004   Japan

J-MIND   The Japan Multicenter Investigation of Antihypertensive Treatment
                 for Nephropathy in Diabetes
2001   Japan

LIFE   Losartan Intervention For Endpoint Reduction in Hypertension
2002   Europe, United States

MAPHY   Metoprolol Atherosclerosis Prevention in Hypertension
1988   Canada, Europe

MIDAS   Multicenter Isradipine Diuretic Atherosclerosis Study
1996   United States

MOSES   Morbidity and Mortality After Stroke, Eprosartan Compared With
                 Nitrendipine for Secondary Prevention
2005   Austria, Germany

MRC   A British study by the Medical Research Council
1985   United Kingdom

MRC Older   Medical Research Council Trial of Treatment of Hypertension in
                 Older Adults
1992   United Kingdom

MRFIT 1990	Multiple Risk Factor Intervention Trial United States
NICS-EH 1999	National Intervention Cooperative Study in Elderly Hypertensive Japan
NORDIL 2000	Nordic Diltiazem Study Norway, Sweden
OSLO 1980	The Oslo Study Norway
Patel 1985	Trial of relaxation in reducing coronary risk: four year follow up United Kingdom
PATS 1995	Post- Stroke Antihypertensive Treatment Study China
PEACE 2004	Angiotensin Converting Enzyme Inhibition in Stable Coronary Artery Disease Canada, Italy, United States
PROGRESS 2001	Perindopril Protection Against Recurrent Stroke Study Asia, Australia, Europe, New Zeeland
RENAAL 2001	Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan Study Asia, Central America, Europe, North America, South America
RIS 1998	Risk Factor Intervention Trial Sweden
SCOPE 2003	Study on Cognition and Prognosis in Elderly Canada, Europe, Israel, United States
SHELL 2003	Treatment of Isolated Systolic Hypertension Italy
SHEP 1991	Systolic Hypertension in Elderly Program United States
Stamler 1987	Nutritional therapy for high blood pressure United States
STOP 1991	The Swedish Trial in Old Patients with Hypertension Sweden

STOP-2   The Swedish Trial in Old Patients with Hypertension-2
1999   Sweden

Syst-China   Systolic Hypertension in China
2000   China

Syst-Eur   Systolic Hypertension in Europe
1997   Europe

TEST   Tenormin after Stroke and TIA
1995   Sweden

TOMHS   Treatment of Mild Hypertension Study
1993   United States

TONE   Trial of Nonpharmacological Intervention in the Elderly
1998   United States

UKPDS   United Kingdom Prospective Diabetes Study
1998   United Kingdom

USPHS   US Public Health Service Study
1977   United States

VA II   Veterans Administration Study II
1970   United States

VALUE   Valsartan Antihypertensive Long-term Use Evaluation
2004   Argentina, Asia, Australia, Brazil, Canada, Europe, Mexico, Russia,
                South Africa, United States

VA-NHLBI   Veterans Administration-National Heart, Lung and Blood Institute
                Feasibility Trial
1978   United States

VHAS   Verapamil in Hypertension and Atherosclerosis
1997   Italy

Yurenev   Management of essential hypertension in patients with different
                degrees of left ventricular hypertrophy
1992   USSR