

Clinical hypertension

From early prediction to prevalence, treatment adherence and outcome of resistant hypertension

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ABSTRACT

Aims The four studies in this thesis highlight both undetected hypertension and hypertension in patients receiving extensive blood pressure treatment. The aim of the first study was to investigate whether, and by which blood pressure measurements, one can predict the probability of future hypertension by analyzing the blood pressure response during exercise testing. The second study aimed to investigate the prevalence of treatment resistant hypertension (TRH) i.e. patients who do not reach target blood pressure despite treatment with three or more antihypertensive drugs. The aim was further in the third study to describe cardiovascular outcomes in a TRH population. The fourth study compared the two-year medication adherence to antihypertensive treatment in patients with controlled and uncontrolled hypertension. The overall aim of this thesis was to give rise to increased knowledge regarding hypertension in clinical practice.

Methods In study I, a cohort of patients without known hypertension or cardiovascular disease who performed exercise testing for various reasons during 1996-1997 was investigated. Blood pressure data from the exercise test were used to predict hypertension. Ten years after the exercise test, a questionnaire evaluating development of hypertension was carried out. In study II-IV, data from the Swedish Primary Care Cardiovascular Database (SPCCD) were used. In the SPCCD, data from medical records of hypertensive patients aged ≥ 30 from 48 primary health care centres in two regions in Sweden, collected between 2001 and 2008, are linked to five Swedish population based registers. In study II the prevalence of TRH according to the different prevailing TRH-definitions from the treated hypertensive population was evaluated. Study III analysed the association between TRH and cardiovascular events with adjustment for important confounders in the SPCCD from 2006 and with follow-up in the population based registers until 2012. Patients with known cardiovascular co-morbidity were excluded. Data on antihypertensive drug dispenses were derived from the Prescribed drug registry. In study IV the change in medication adherence, measured by proportion of days covered (PDC), over two years was evaluated for patients with both controlled and uncontrolled hypertension, dispensed three or more antihypertensive drugs. In studies II-IV high medication adherence was defined as $PDC \geq 80\%$.

Results Higher blood pressure before the exercise test and a rapid rise in blood pressure during the test resulted in an increased risk of hypertension ten years post exercise testing. Treatment resistant hypertension is present in 8-17% of hypertensive patients in Swedish primary care. The increased risk of cardiovascular events in this population is mainly associated with an increased risk of heart failure. Antihypertensive medication adherence does not seem to differ between patients achieving target blood pressure and patients with treatment resistant hypertension.

Conclusions Modified blood pressure screening during an exercise test can help identify patients with increased risk of developing hypertension. Treatment resistance to antihypertensive treatment is not a negligible problem, and these patients have an increased risk of heart failure despite adherence to antihypertensive treatment. Awareness of high blood pressure and adherence to antihypertensive treatment must be increased in order to reduce the burden of disease caused by high blood pressure.

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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 L Holmqvist, L Mortensen, C Kanckos, C Ljungman, K Mehlig, K Manhem. Exercise blood pressure and the risk of future hypertension. *J Hum Hypertens* 2012; 26:691-695.
- II L Holmqvist, K Bengtsson Boström, T Kahan, L Schiöler, J Hasselström, P Hjerpe, B Wettermark, K Manhem. Prevalence of treatment-resistant hypertension and important associated factors - results from the Swedish Primary Care Cardiovascular Database. *J Am Soc Hypertens* 2016; 10(11):838-846.
- III L Holmqvist, K Bengtsson Boström, T Kahan, L Schiöler, J Hasselström, P Hjerpe, B Wettermark, K Manhem. Cardiovascular outcome in treatment resistant hypertension - results from the Swedish Primary Care Cardiovascular Database. *Submitted*
- IV L Holmqvist, K Bengtsson Boström, T Kahan, L Schiöler, M Qvarnström, J Hasselström, P Hjerpe, B Wettermark, K Manhem. Drug adherence in treatment resistant and in controlled hypertension - results from the Swedish Primary Care Cardiovascular Database. *Manuscript*

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SAMMANFATTNING PÅ SVENSKA

Bakgrund

Högt blodtryck är en vanligt förekommande sjukdom. Cirka 50% av alla vuxna personer i Sverige över 65 års ålder beräknas vara drabbade och i hela den vuxna befolkningen i världen beräknas drygt 20% ha förhöjt blodtryck. Riskerna för att drabbas av stroke, hjärtinfarkt, hjärtsvikt eller nedsatt njurfunktion är betydligt högre för de individer som har högt blodtryck jämfört med de som har normalt blodtryck. De ökade riskerna som är förknippade med förhöjt blodtryck kan till stor del minskas med den behandling som idag är lättillgänglig och effektiv. Ett problem med högt blodtryck är att symtomen är få vilket bidrar till att många är ovetande om sitt förhöjda blodtryck. Ett annat problem är att många patienter med högt blodtryck inte når målbloodtryck trots behandling. Personer med högt blodtryck trots behandling med flera läkemedel tros utgöra en specifik grupp som kräver större behandlingsinsatser. En av orsakerna till dåligt reglerat blodtryck kan vara dålig följsamhet till läkemedelsbehandling vilket är en stor utmaning för en sjukdom med få symtom.

Syfte

Det övergripande syftet med denna avhandling var att skapa mer kunskap kring högt blodtryck i den kliniska vardagen. Avhandlingens fyra delarbeten belyser både upptäckt högt blodtryck och högt blodtryck hos individer med omfattande läkemedelsbehandling. Syftet var att studera om, och med vilket blodtrycksmått, man kan förutsäga om en person kommer att få högt blodtryck senare i livet genom att analysera blodtrycksreaktionen under belastning i form av ett arbetsprov på träningscykel. Vidare syftade avhandlingen till att i en stor primärvårdskohort med vuxna patienter med högt blodtryck undersöka hur många patienter med läkemedelsbehandlat högt blodtryck som inte uppnår målbloodtryck trots behandling med tre, eller fler läkemedel (behandlingsresistent högt blodtryck). Syftet var också att kartlägga utfallet avseende totaldöd, död orsakad av hjärt-/kärlsjukdom, stroke och hjärtsvikt i denna patientgrupp. Det fjärde delarbetets syfte var att jämföra den tvååriga följsamheten till omfattande läkemedelsbehandling hos personer med välbehandlat respektive icke välbehandlat högt blodtryck.

Resultat

Högre blodtryck före start av arbetsprov samt snabb stegring av blodtryck under arbetsprov resulterade i förhöjd risk att drabbas av diagnosen högt blodtryck tio år efter genomfört arbetsprov. Av de individer i en svensk primärvårdsbefolkning som erhåller tre eller fler läkemedel mot högt blodtryck har 8-17% trots denna behandling inte välreglerat blodtryck. Risken att drabbas av hjärt-/kärlsjukdom i denna patientgrupp var framförallt kopplad till en ökad risk för hjärtsvikt. Gruppen uppvisade dock inte någon ökad risk att insjukna i stroke jämfört med patienter utan behandlingsresistent högt blodtryck. Läkemedelsföljsamheten verkar inte skilja sig mellan patienter som uppnår målbloodtryck respektive patienter som inte når uppställda mål.

Slutsats

Modifierad screening vid arbetsprov kan bidra till att patienter med ökad risk för högt blodtryck identifieras. Dålig målluppfyllelse avseende blodtryck hos individer med omfattande läkemedelsbehandling är vanligt och denna grupp av patienter har en ökad risk att drabbas av hjärtsvikt trots att följsamheten till behandling är jämförbar med individer som uppnår uppställda blodtrycksmål. Medvetenheten om högt blodtryck, målluppfyllelsen för patienter med högt blodtryck och följsamheten till behandling mot högt blodtryck måste öka om sjukdomsördan orsakad av högt blodtryck ska kunna minska. Både professionen och patienten behöver tydliga mål för behandling och en tydlig struktur avseende uppföljning för att behandlingsresultatet skall bli bra.

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ABBREVIATIONS

ABPM	Ambulatory blood pressure measurement
ACE	Angiotensin converting enzyme
ATC	Anatomic therapeutic chemical
aTRH	Apparent treatment resistant hypertension
BMI	Body mass index
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
ESH	European Society of Hypertension
HBPM	Home blood pressure measurement
ICD	International classification of disease
LDL	Low density lipoprotein
PDC	Proportion of days covered
PHCC	Primary health care centre
RCT	Randomized controlled trial
RDN	Renal denervation
SBP	Systolic blood pressure
SPCCD	Swedish Primary Care Cardiovascular Database
TIA	Transient ischemic attack
TRH	Treatment resistant hypertension
WHO	World Health Organization

INTRODUCTION

Hypertension is the most important contributor to global burden of disease worldwide (1). Despite the evident risks for life threatening disease and death that high blood pressure constitute and the known benefits of treatment many patients do not reach blood pressure goals (2; 3).

History

The first time blood pressure was measured was by the priest and botanic Stephen Hales in 1769. He measured the blood pressure of a horse in the carotid artery by inserting a brass tube connected to a water column. The blood rose to about 8 feet, 8 inches, about 180 mm Hg and then sunk gradually to zero and the horse died. Luckily, about 100 years later the sphygmomanometer for measuring blood pressure around the forearm was invented, a technique still in use (4).

Blood pressure measurement

Today blood pressure at clinical appointments (office blood pressure) is, measured in a standardized way after 5-10 minutes of rest and after avoiding coffee, tobacco and heavy exercise 30 minutes before the measurement. The patient should be in a supine or seated position, resting their back and having the feet on the floor. The arm should be resting at the same level as the heart (5). To avoid under- or overestimations the right width of blood pressure cuff is essential (6; 7). In manual measurement of blood pressure, after filling the cuff with air you release it slowly and use your stethoscope to listen for the Korotkoff sound in the brachial artery. What you hear is the turbulent flow in the artery when the pressure off the cuff is equal to the pressure that the left ventricle of the heart, i.e. systolic blood pressure. As pressure drops in the cuff when air is released there will be repetitive pulse beats of turbulent blood flow until the cuff pressure is the same as the diastolic blood pressure and no turbulence is present (8).

Automated blood pressure measurements performed in the clinic are suggested to replace manual office blood pressure since they seem to have a better correlation with out of office blood pressure values (9). The difference from standard office blood pressure measurement is that the patient is left alone in the examination room with an automated, oscillometric blood pressure measurement device around the forearm. Repeated measurements are performed and a mean value of these readings is reported. The advantage of this technique is reduced artefact from white-coat effect and hence reduced unnecessary treatment (10).

Ambulatory blood pressure measurement (ABPM) is highly recommended when diagnosing hypertension, especially in patients with suspected white coat effect i.e. high office blood pressure but normal out of office blood pressures. ABPM is performed during 24 hours when the patients wear a portable blood pressure measurement device with repeated blood pressure measurements during day and night and perform normal daily life activities (11).

Home blood pressure measurement (HBPM), using an automated oscillometric blood pressure device, is a measurement technique with increasing usage. Recommendations state that the patient should measure blood pressure repeatedly, in the morning and at night during seven days and a calculation of the mean value is used for evaluation (12).

It has been suggested that out of office blood pressure measurement carries better prognostic information than office blood pressure measurements (13; 14). Also, HBPM is described to improve medication adherence and blood pressure control from an investigation where self-titration of antihypertensive medications was performed (15).

Blood pressure development during life

During a life time blood pressure changes although differently for women and men were young women have lower systolic and diastolic blood pressure levels than young men (16). After the age of fifty the systolic blood pressure of women increases further reaching the same levels as men, and surpasses men in the most elderly population (17). The reasons for this are not totally understood but hormonal factors are thought to be part of the explanation.

Blood pressure is a result of several factors such as cardiac output, blood volume and arterial diameter and stiffness. It is known from population studies that the cause of the systolic blood pressure rise in elderly hypertensive patients is linked to stiffening of large arteries while increase in diastolic blood pressure in middle age hypertensive patients is related to the total peripheral resistance in primarily arterioles (16). Several factors such as high cholesterol levels, smoking, and diagnosis of diabetes/insulin resistance are involved in the development of arteriosclerosis which in turn, leads to stiff arteries. Life-style factors such as diet and daily physical activity are components that contribute to the development of vascular changes, and partially explain the age related blood pressure increase found in urban compared to populations living a traditional life-style without contact to civilization (18).

Definition of hypertension

The definitions of hypertension are the same in different parts of the world. The prevailing guidelines are ESH 2013 (European), JNC 8 (North-American) and NICE-criteria (British) (5; 19; 20). To diagnose hypertension repeated office blood pressure measurements at different occasions are required. According to guidelines there is a grading of hypertension according to blood pressure levels (Table 1).

Etiology of hypertension

The majority (95%) of patients with hypertension are defined as having primary hypertension where no specific causative factor can be identified. Genetic predisposition and multiple life-style dependent factors such as overweight, sedentary life-style, smoking, alcohol consumption, sleep-apnea, stress and smoking are involved in the preservation of blood pressure increase (4).

Table 1. Definitions and classification of office blood pressure levels (mm Hg). ESH/ESC guidelines for the management of arterial hypertension. Published by Mancia G. et.al. in European Heart Journal 2013.

Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

Patients with a specific cause of hypertension are defined as having secondary hypertension. Secondary causes to hypertension should be considered in younger patients and in patients where blood pressure is difficult to control. Conditions associated with secondary hypertension are mainly hormonal such as primary aldosteronism, hyperthyreosis, Cushing and feochromocytoma. Apart from primary aldosteronism, which has a prevalence of 5-10% in the general hypertensive population, these conditions are rare (21). Renal artery stenosis, coarctatio aorta and other congenital or acquired vessel or heart diseases may also be considered in relation to secondary hypertension (4).

Hypertension prevalence

The prevalence of hypertension in the adult population in Sweden was, through limited screening studies, estimated to approximately 27% according to the systematic literature review “Moderately Elevated Blood Pressure” published by the Swedish council on Technology Assessment in Health Care in 2004 (22). From the national public health survey in Sweden 2015 it is estimated that hypertension has a prevalence of approximately 20% in the entire adult population, rising to around 50% in individuals over 65 years (23).

In 2005 it was estimated that 29% of the world population would suffer from hypertension in 2025 (24). The World Health Organization, WHO, has estimated that right now 1 billion individuals worldwide suffer from hypertension (25). Unpublished data from the “PURE” study reveals decreasing prevalence of hypertension in western high-income countries (26). Further, in a pooled analysis of 19.1 million participants worldwide, published in 2016, the global age-standardised prevalence of hypertension was 24% for men and 20% for women. However, hypertension prevalence has shifted in geographical trends during the last forty years. The highest numbers are now found in low-income countries in south Asia and sub-Saharan Africa (27).

Hypertension awareness

It is a global challenge to find strategies for good blood pressure control. Already in 1972 the concept “rule of halves” was introduced (28). Largely this imply that 50% of hypertensive patients are aware of their condition, 50% of the aware patients have treatment and 50% of the treated patients have sufficient treatment and reach target blood pressure. There are indications that this rule still exists in the hypertensive patient population as suggested by Weinehall et. al. in 2002 (29). A slight trend towards better control rate has been seen in parts of the world like northern Sweden (30) and Canada (31). One Swedish publication even suggest that the awareness, treatment end control rate now follow the “rule of thirds” (32).

One way to handle the problem of hypertension unawareness could be to introduce a screening program in the community since the consequences of undiagnosed and untreated hypertension on a group level are important. The issue of screening has been a current issue during many years and the WHO criteria for screening, published by Wilson and Jungner in 1968, are to a large extent met in hypertension (33). The criteria state that the disease in question should have a latent/symptom-free phase, be an important health problem which is possible to diagnose with a suitable test and that there should be an agreed policy on how to treat the condition. One important criterion is however not met, namely the cost-benefit criteria. It would be far too costly to screen the whole adult population, in other words it is not considered cost-effective. The report on hypertension from the Swedish council on Technology Assessment in Health Care established in 2004 that there is no indication for blood pressure screening of the whole population but so called opportunistic screening could be applied (22). This was also emphasized by Vasan et. al. who conclude that screening for hypertension in high-risk patients can be cost-effective (34). This approach seems reasonable and applicable to today’s health care.

Blood pressure during exercise testing

One way to perform opportunistic screening is to interpret and react to every single raised blood pressure that is obtained in health care. The population referred for exercise testing is diverse in terms of cardiovascular risk profile and not always classified with high risk. According to guidelines for exercise testing the individuals with intermediate cardiovascular risk presenting with chest pain could be evaluated for ischemic heart disease with exercise testing (35). Generally exercise testing is indicated for investigation of suspected ischemic heart disease, arrhythmias and assessment of physical capacity and is also a useful tool for prognostic considerations in coronary artery disease (36). The normal blood pressure reaction to exercise is that vagal tone is withdrawn and sympathetic stimulation increased which leads to an increase in heart rate, stroke volume, cardiac output and initially in peripheral resistance resulting in a blood pressure increase.

During exercise testing blood pressure is monitored repeatedly, mainly to find indications on coronary artery disease such as a sudden decrease in blood pressure or a failure to increase blood pressure during exercise (37). A drop in blood pressure during exercise indicates that the test must be terminated, likewise a systolic blood pressure

≥ 250 mm Hg is a relative indication for test termination. When we initiated study I for this thesis the clinical question was how to interpret and handle blood pressure response during exercise. The exaggerated blood pressure response to exercise had already been suggested by several investigators as a predictor for both hypertension (38-42), cardiovascular disease and death (43; 44). However, there was no consensus on which blood pressure measurement during exercise that was the best predictor of future hypertension. Some investigators suggested a cut-off between 200-230 mm Hg (40) to define hypertensive reaction to exercise and yet others suggested recovery blood pressure after exercise to be a valid predictor for future hypertension (42). A number of scientific investigations on blood pressure reaction during exercise tests are performed only in middle-aged healthy men resulting in a problem of generalizability (45). The diversity in results from previous studies due to different populations, different methodology and different blood pressure measurements made us initiate study I, and our aim was to identify the blood pressure reaction with the best prognostic value regarding future hypertension.

Treatment of hypertension

According to hypertension guidelines antihypertensive drug treatment should be initiated first after life-style interventions such as increase in physical activity, losing weight, smoking cessation, reduced alcohol intake and initiating a diet with less fat, salt and more vegetables. At the same time, to await results from life-style changes should not postpone the initiation of drug therapy (5). Numerous studies have shown that these interventions can be effective in reducing blood pressure (46) but also that it is hard to be compliant to these life-style changes especially in the long term (47). For example, losing 5 kg of weight may reduce blood pressure by approximately 4 mm Hg (48) and physical activity, such as aerobic exercise, has been shown to reduce systolic blood pressure by 7 mm Hg (49) or as much as 11 mm Hg in hypertensive patients depending on the dose and form of exercise (50).

Initiation of antihypertensive drug treatment should be performed when life-style changes have not had sufficient effect on reducing blood pressure. The intensive development of different antihypertensive agents during the 80s and 90s has resulted in a variety of antihypertensive drugs to choose from. Already in 2004 the Swedish report on hypertension established that the three most effective and best tolerated antihypertensive drug classes were thiazide diuretics, angiotensin converting enzyme (ACE) inhibitors/angiotensinogen receptor blockers and calcium channel blockers. From numerous randomized controlled trials (RCT), it is well documented that these drug classes have equal blood pressure reduction capacity, result in the same risk reduction and are fairly equal in tolerability (22). Prevailing international guidelines from Europe, Great Britain and North America agree on these three agents being the first choice for antihypertensive treatment initiation. However, European Society of Hypertension (ESH) guidelines also include beta-blockers in first line treatment even though there are conflicting results on the risk-reducing effect by beta-blockers (51). Often there is need for more than one antihypertensive drug class to control blood pressure and combination therapy with several recommended agents is needed (Figure 1). When evaluating the hypertensive patient it is also important to have the broad perspective of the cardiovascular risk profile including parameters such as body mass

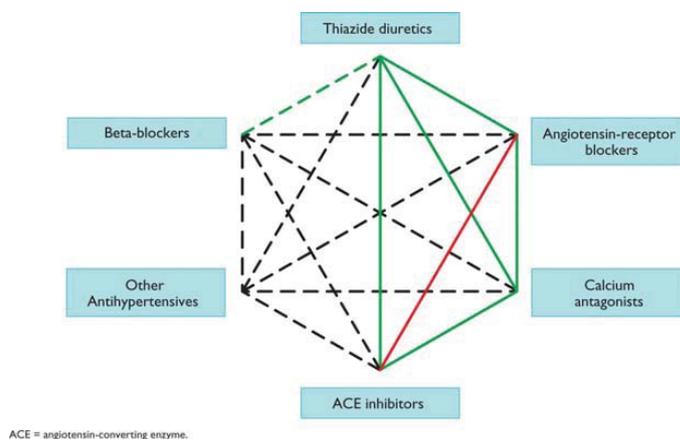


Figure 1. Possible combinations of classes of antihypertensive drugs. Green continuous lines: preferred combinations; green dashed line: useful combination (with some limitations); black dashed lines: possible but less well-tested combinations; red continuous line: not recommended combination. Although verapamil and diltiazem are sometimes used with a beta-blocker to improve ventricular rate control in permanent atrial fibrillation, only dihydropyridine calcium antagonists should normally be combined with beta-blockers. Published by Mancia G. et.al. in European Heart Journal 2013.

index (BMI), lipids, blood glucose and renal function. It is recommended to assess these other risk factors and consider them when evaluating the total risk for cardiovascular events and chronic kidney disease. A helpful tool for estimating the total cardiovascular risk in patients is the SCORE diagram. This risk chart can give an assessment of the absolute risk of suffering from a cardiovascular event within ten years and consider age, gender, blood pressure level, level of total cholesterol and smoking status (52). The limitations of the SCORE diagram are, among other aspects that the estimation does not consider diagnose of diabetes and does not give the absolute risk for individuals above 65 years of age.

Optimal target blood pressure level

The optimal target blood pressure for individuals with different cardiovascular risk profile is under debate. There is a consensus in prevailing guidelines that optimal blood pressure goal should be <140/90 mm Hg in adult individuals. Only the American guidelines recommend a blood pressure level of <150/90 mm Hg in the general population aged ≥ 60 years. Observational data indicate that it is beneficial for the stroke risk with a blood pressure down to at least 115/75 mm Hg (53). More recently the association between blood pressure level in different age groups and different cardiovascular diseases were thoroughly investigated and presented with the conclusion that the lower blood pressure (90-114 mm Hg), the better outcome in all age-groups and for all cardiovascular diseases (2). The debate regarding appropriate target blood pressure level is even more intense since the publication of a randomized control trial

in non-diabetic patients with high cardiovascular risk where it was found that patients with more strict systolic blood pressure control (<120 mm Hg) had a more beneficial outcome regarding fatal and nonfatal major cardiovascular events and death and all-cause mortality (54). Major criticism has been raised against the methodology of the study, especially against the blood pressure measurements that were performed with an unobserved automated office blood pressure registration (55).

Earlier guidelines recommended a lower blood pressure target for diabetic patients but because of lack of proof from RCT's that blood pressure <130/80 mm Hg could influence major cardiovascular events the shift to higher blood pressure targets for patients with diabetes type 2 has been performed (56). In Sweden the current recommended blood pressure target for patients with diabetes type 2 is <140/85 mm Hg and was a consensus agreement published in 2014 (57). Future investigations will hopefully clarify this complicated and important question.

Another subject under current debate is whether the "J-curve-phenomenon" applies to hypertensive patients, especially hypertensive patients with diabetes. The J-curve-phenomenon refers to an observation that it seems to be a linear relation between blood pressure level and outcome where lower is better but only down to a certain point where the curve turns up again suggesting that really low blood pressures could be associated with worse outcome. It could also be that low blood pressure is associated with higher degree of comorbidity, which of course would influence outcome. It is important to evaluate whether the blood pressure is low due to natural cause or is an effect of treatment. In an observational study by Adamsson-Eryd and co-workers the J-curve seems to uncurl when outcome is evaluated in a population with diabetes without obvious cardiovascular disease showing the highest outcome benefits in patients with the lowest blood pressure (110-119 mm Hg) (58).

Treatment resistant hypertension

Definitions of treatment resistant hypertension

European guidelines advocate the definition of treatment resistant hypertension (TRH) to be uncontrolled blood pressure (>140/90 mm Hg office blood pressure) despite treatment with 3 or more antihypertensive drug classes of which one is a thiazide diuretic (5). The definitions of TRH differ to some extent between North America and Europe where the largest difference is that American guidelines also include patients who have a controlled blood pressure (<140/90 mm Hg) on 4 or more antihypertensive drug classes, of which one is a diuretic if tolerated (59).

True/apparent treatment resistant hypertension

The definitions of TRH all require that secondary cause of hypertension has been excluded. The secondary causes are mentioned above but there are also causes that are not related to specific diagnoses but to poor blood pressure technique, medication non-adherence or the white-coat effect (59). These causes can be summarised as pseudo resistance to treatment. When studying the hypertensive population a term called apparent TRH (aTRH) is often used. This means that all possible causes of uncontrolled hypertension have not been excluded in an integrated way but the patient fulfils

the criteria for TRH (60). The term true TRH refers to uncontrolled hypertension both in the office blood pressure measurement and in the 24-h ambulatory blood pressure measurement. The proportions of these populations are illustrated in Figure 2.

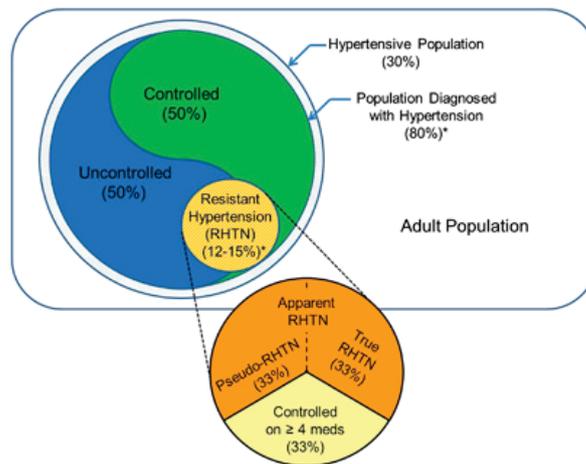


Figure 2. Venn diagram of the prevalence of resistant hypertension. Area of subpopulations drawn to scale with estimated prevalences in percentages. Prevalences were estimated primarily from epidemiology studies performed within the United States.*Estimated prevalence among all hypertensive individuals. Published by Judd E. et.al. in J Hum Hypertens. 2014 Aug; 28(8): 463-468

Renal denervation – a plausible therapy for resistant hypertension

Around 2009 the interest for TRH grew immensely since the introduction of invasive therapeutic possibilities such as renal denervation (RDN). The theory of RDN mechanism is to diminish the sympathetic drive on blood pressure by reducing the sympathetic nerve activity in the renal arteries through catheter based technique (61). The market for devices for performing these new techniques grew rapidly and RDN was performed in Europe, mostly in Germany, and the North America. Positive results regarding blood pressure lowering effect was seen in uncontrolled trials (62). To be able to study the effect of RDN in a more controlled way a study program was initiated to perform controlled studies in different ways and finally a sham-controlled study (SYMPPLICITY III trial) was carried out (63).

In Sahlgrenska University Hospital a multidisciplinary Health Technology assessment was performed before the planned introduction of RDN. During that process it was evident that the prevalence of TRH in Sweden was unknown. If RDN was to be implemented as a standard method of treating hypertension in the future it would be necessary to have an estimation of how many patients that could be eligible for this technique. Hence, study II was initiated where we aimed at describing the prevalence of TRH in primary health care in Sweden.

Hypertension prognosis

It is estimated that the life expectancy in hypertensive men and women is 5.1 and 4.9 years shorter compared to normotensive individuals (64). The increased risk for cardiovascular and chronic kidney disease that hypertension carries can to a great extent be diminished by efficient treatment (3). In a large population study in primary care the association between blood pressure levels and different specific cardiovascular outcomes were analyzed. This study showed that peripheral artery disease and heart failure are common early manifestations of target organ damage in relation to blood pressure (2). From the Swedish heart failure registry we know that 61% of patients with heart failure with preserved ejection fraction have hypertension (65). Further it is also well known that the risk for atrial fibrillation is higher in hypertensive patients (66).

The prognosis for patients with TRH is less thoroughly studied. We know from sub studies of clinical trials like “ALLHAT” that patients with TRH have worse prognosis compared to patients with controlled hypertension (67). Also, in a North American cohort study of >200 000 hypertensive patients the patients with TRH had an increased risk of cardiovascular events (68). Thus, in study III we aimed to evaluate the cardiovascular risk associated with TRH in Swedish primary care.

Medication adherence

“Keep a watch on the faults of the patients, which often make them lie about the taking of things prescribed” Hippocrates

Medication adherence is a challenging task in all chronic illnesses and is estimated by WHO to be approximately 50%. The definition of medication adherence suggested by the WHO is “the extent to which a person’s behaviour corresponds with agreed recommendations from a health care provider” (69). In a population based study, healthy individuals were asked how much longer survival it would be required for them to make it worth taking a prescribed medicine. Twelve percent reported that it would be required ten years of extended life-time for them to fulfil the prescribed treatment (70). The barriers to comply with treatment were reviewed in 2011 and could be categorized into patient related, physician related and health care system related (71).

Hypertension is a disease with few symptoms which makes medication adherence even more challenging (72). We know from a Swedish study that the adherence over time to antihypertensive medication decreases with 26% during the first year of treatment in incident hypertensive patients (73). Decline in medication adherence over time has also been described in secondary prevention after stroke (74), after myocardial infarction (75) and in heart failure patients (76). Low medication adherence in hypertension is associated with young age, male sex and mild-to-moderate blood pressure elevation (73). Drug class, however, does not seem to have an association to medication persistence (77). There is solid evidence that high adherence to antihypertensive treatment results in reduction of cardiovascular risk. For example 10% lower risk for coronary artery disease (78), 11% lower risk for heart failure (79) and 22% lower risk for cerebrovascular disease have been found in relation to antihypertensive treatment adherence (80).

Medication adherence in treatment resistant hypertension

In apparent TRH low medication adherence is a common cause of uncontrolled blood pressure (81). In a recent review the prevalence of insufficient medication adherence in apparent TRH was varying between 7 and 66% in different populations and as a result of different adherence measurements (82).

We initiated study IV after the SYMPLICITY III trial results were made official (63). This first sham-controlled RDN study did not show a significant blood pressure reduction as a result of active treatment. These results were surprising to many hypertension researchers and immediately a debate was initiated dealing with factors that could have influenced the results. One criticism was directed towards the fact that some operators only did one single RDN within the study program. Maybe this could have led to a low quality in the procedure. Also the medication adherence during the study was not thoroughly monitored and therefore it cannot be ruled out that an enhanced medication adherence in both groups would have influenced the results. This is defined as the Hawthorne effect and imply that people who know that they are being observed (controlled) within a study often act differently than they regularly do (83). It is possible that all patients in the SYMPLICITY III study had an enhancement of medication adherence and therefore the blood pressure control was increased in both groups. It has even been suggested that TRH does not exist in a patient population with perfect medication adherence (84). Also, it is suggested that screening for medication non-adherence should be mandatory before classifying patients with TRH (5).

This scientific discussion emphasize the importance of medication adherence, and constitutes the background to study IV where we aimed at investigating the adherence to treatment in hypertensive individuals dispensed 3 or more drug classes comparing TRH with non TRH patients.

AIMS

Study I

To identify the best blood pressure measurement for predicting future hypertension during exercise testing. Further, we aimed to create a feasible risk chart regarding blood pressure reaction during exercise that could predict the risk of future hypertension in the clinical setting.

Study II

To determine the prevalence of treatment resistant hypertension (TRH) according to different definitions in a hypertensive cohort with known medication adherence in primary health care in Sweden. Further we aimed to evaluate the use of mineralocorticoid receptor antagonists in TRH and to describe the association of different comorbidities in this patient group.

Study III

To assess the risk for cardiovascular morbidity and mortality, beyond blood pressure level, in patients with treatment resistant hypertension (TRH) compared to hypertensive patients with no TRH in a primary care setting of hypertensive patients.

Study IV

To describe the medication adherence over a time period of two years in patients with treatment resistant hypertension. We also aimed to compare the adherence to a population of patients with controlled blood pressure treated with three or more antihypertensive drug classes and to find factors associated with change in adherence over time.

PATIENTS AND METHODS

Study I

All patients (N=1047) who performed an exercise test at the Department of Clinical Physiology at Sahlgrenska University hospital/Östra between May 1996 and December 1997 were considered for inclusion in the study. Individuals who already had hypertension or antihypertensive treatment, had moved abroad or who had died during follow up were excluded (n=441). In 2006 and 2007 we distributed questionnaires to the remaining 606 patients. The questionnaire included questions on whether the patient had developed hypertension or started antihypertensive treatment during follow up (Figure 3).

The exercise test was performed after referral from either primary health care or currently hospitalized patients or as part of health examinations. The most common cause for referral was chest pain. The test was performed according to the Bruce protocol, a graded symptom-limited test with bicycle ergometry (85). All blood pressures were measured manually with auscultatory technique by the attending nurse.

We considered different blood pressure measurements during the exercise test as predictors for development of hypertension including systolic blood pressure (SBP) at rest before the test, maximal SBP, SBP rise rate and SBP during recovery.

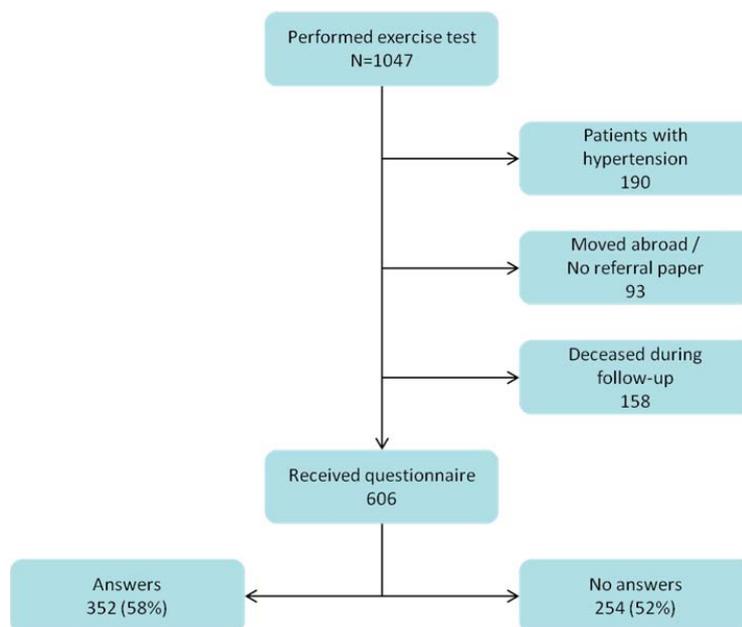


Figure 3. Flow chart of the study population in study I.

The Swedish Primary Care Cardiovascular Database (SPCCD) (Study II-IV)

Clinical data from 74 751 patients attending primary care with hypertension according to International Classification of Diseases 10th revision codes (ICD-10), were collected From 1 January, 2001 through 31 December, 2008 into the Swedish Primary Care Cardiovascular Database (SPCCD). The SPCCD included all patients age ≥ 30 years with a recorded diagnosis of hypertension visiting any of the 48 participating primary health care centers (PHCCs) during the time period. The PHCCs were 24 out of 25 available PHCCs in the rural region of Skaraborg and a selection of 24 PHCCs from the urban region of south west Stockholm, Sweden. Data on age, sex, BMI, smoking status, co-morbidity and blood pressure levels were derived from electronic medical records from single visits (86). Using unique personal identification numbers made it possible to link the data extracted from medical records to the Prescribed Drug Register, the National Patient Register and the Cause of Death Register. Furthermore, the data was synchronized with Census data (migration, country of birth) and National registers of education and income from Statistics Sweden (Figure 4). The Prescribed Drug Register has a full coverage of the dispensed prescriptions to the whole population of Sweden since 2005 (87).

The PHCCs were recommended to follow national guideline recommendations for blood pressure measurements. Office blood pressure was measured in a seated or supine position, according to prevailing recommendations, by a physician or a nurse using either oscillometric or auscultatory measurement techniques.

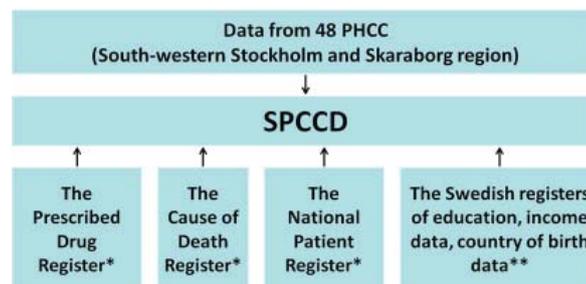


Figure 4. The Swedish Primary Care Cardiovascular Database (SPCCD). Data from 48 primary health care centres. *Registers held by the Swedish National Board of Health and Welfare. **Register held by Statistics Sweden.

Study II

This registry-based descriptive study was limited to patients, in the SPCCD, who had a valid recorded blood pressure after July 1, 2006 (N=59 032), were treated with at least one antihypertensive drug, and who had identifiable dispensed drugs in the Prescribed drug registry after January 1, 2006. Number of excluded patients are visualized in Figure 5.

We assessed different definitions of TRH according to European and American guidelines (5; 59).

The index blood pressure was the first measured blood pressure after July 1st 2006 in the database.

All the definitions included the index blood pressure and 3 or more antihypertensive medications. We described both uncontrolled TRH (BP \geq 140/90 with 3 or more drugs) and controlled TRH (BP <140/90 with 4 or more drugs). We also specifically calculated the prevalence of treatment resistant hypertension in patients treated with mineralocorticoid receptor antagonists. The complete definitions are presented in Table 2 page 32. We considered drugs dispensed up to 180 days prior to the index blood pressure. To assess the medication adherence we calculated the “Proportion of Days Covered” (PDC). This is a measurement based on the number of days the patient is supplied medication during a specific time interval (88). An elevated blood pressure with an average PDC \geq 80 % is the definition of TRH used, hence an average PDC for the individual antihypertensive drug classes for each patient was calculated.

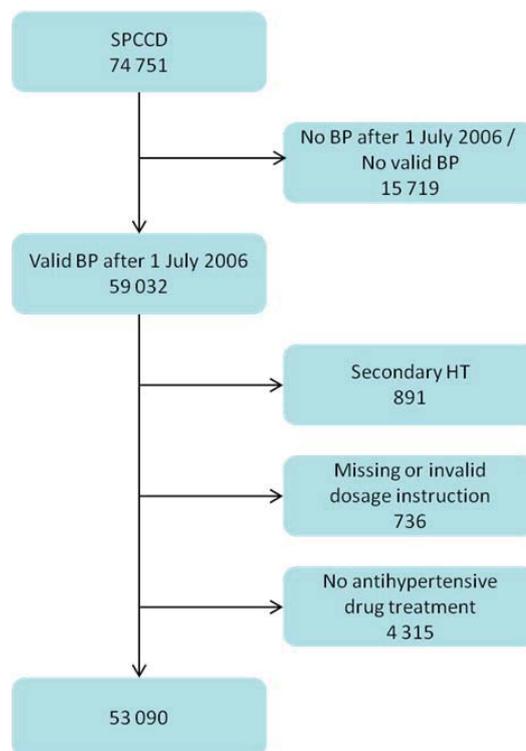


Figure 5. Flow chart of study population in study II.

Study III

In this cohort-study we compared the outcome of patients with TRH to patients with non TRH and used the same patient cohort from the SPCCD as in study II. With respect to TRH we restricted the analysis to definitions including uncontrolled TRH. Hence, patients with blood pressure $\geq 140/90$ despite treatment with 3 or more anti-hypertensive drug classes were defined as TRH whereas the treated hypertensive patients, regardless of blood pressure level, constituted the control group. Patients who were diagnosed with ischemic heart disease, heart failure, stroke or transient ischemic attack (TIA) prior to the index blood pressure were excluded. All exclusion criterias and numbers of excluded patients are presented in the flow-chart (Figure 6).

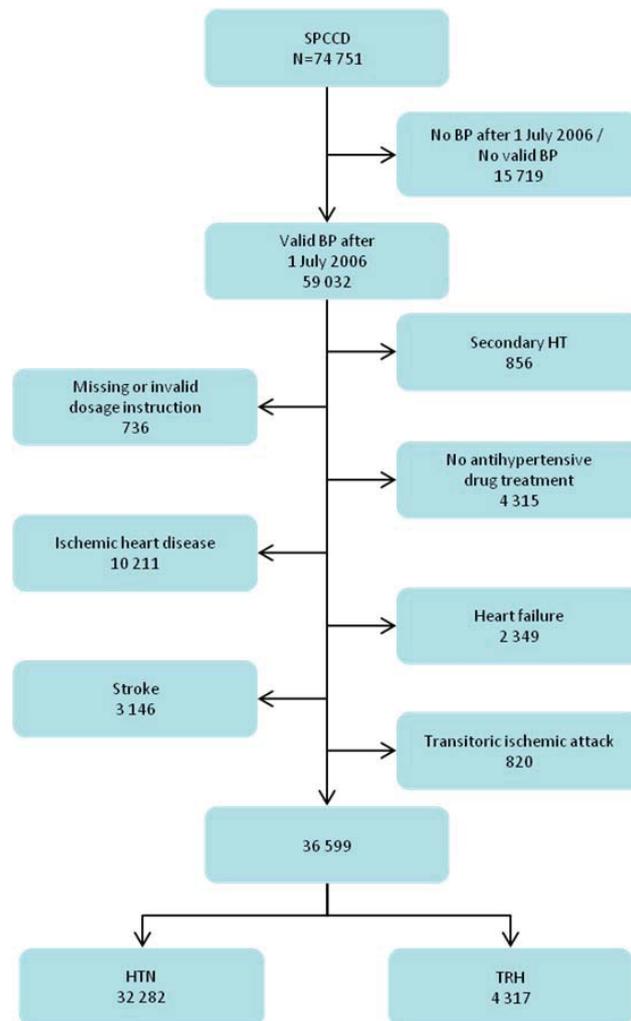


Figure 6. Flow chart of the study population in study III. BP=Blood pressure, HT=Hypertension, HTN=non-treatment resistant hypertension, TRH=Treatment resistant hypertension.

The outcome parameters were cardiovascular mortality, all cause mortality, ischemic heart disease, heart failure, stroke and TIA. Data on outcome was retrieved from the National Patient register for ICD-diagnoses from both outpatient clinics and hospitals and the Cause of Death register. The diagnose heart failure refer to patients diagnosed during hospitalization. Time to follow-up was from July 2006 to December 2012 at the most.

Study IV

This cohort study included hypertensive patients with dispense of 3 or more antihypertensive drugs from the Swedish primary care cardiovascular database (SPCCD) from 2006 to 2008. All patients with a blood pressure measurement after 1 July 2006 were eligible for inclusion, but only patients with a PDC $\geq 80\%$ on 3 or more antihypertensive drug classes were included. Two comparable patient groups were formed according to their baseline blood pressure level, $\geq 140/90$ mm Hg (TRH) and $< 140/90$ (controlled). We excluded patients with a history of ischemic heart disease, heart failure, stroke or TIA. Also, patients with a PDC $< 80\%$, with multi dose dispensing or with diagnosed secondary hypertension were excluded.

We measured drug adherence longitudinally through PDC level during 365 and 730 days after the index blood pressure which was the last measured blood pressure in the database. Adherence to treatment with 3 or more antihypertensive drug classes, at these time points, was the defined outcome in the study. To be classified as adherent a continuous PDC $\geq 80\%$ for 3 antihypertensive drugs during the defined time periods was required. PDC was measured by counting numbers of days supplied by medications divided by the number of days in the measurement period (i.e 365 or 730 days) (Figure 7).

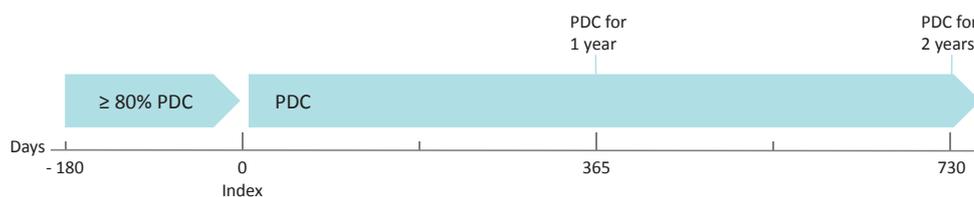


Figure 7. Illustration of the study design. Mean PDC of $\geq 80\%$ for three antihypertensive drug classes during 180 days before index blood pressure was mandatory for inclusion. The time axis is individual for each patient. All index blood pressures are measured after 1 July 2006. PDC=Proportion of days covered.

Statistics

Study I

To compare the groups by incident hypertension we used the Chi-2 and the Students t-test for categorical and continuous variables respectively. To model the dependence on probability for hypertension we used multiple logistic regression analysis. We

chose the most predictive models for hypertension by applying the Akaike information criteria, Hosmer-Lemeshow test and area under the ROC-curve. All models were adjusted for age, sex, BMI and smoking. To make the results more comprehensible we created a risk chart describing the absolute risk of developing hypertension 10 years after an exercise test. The risk chart was based on the model with the best predictive value which included systolic blood pressure before exercise and increase in SBP over time and workload. Statistical analysis was made using SAS 9.2.

Study II

We presented the baseline data as means +/- SD or percentages as appropriate. For between group comparisons we used the Chi-2 and the Students t-test for categorical and continuous variables respectively. To describe the prevalence in each category we used the treated hypertensive study population as a denominator.

To model the dependence of having TRH from different patient characteristics and co-morbidities we used a Poisson regression analysis (89). We made adjustments for age, sex, smoking and co-morbidity. Data are presented as prevalence ratios with 95% confidence intervals (CI). Statistical analysis was made using SAS 9.3.

Study III

Baseline data was presented as means +/- SD or percentages as appropriate. To compare the groups we used Poisson regression analysis (89) for unadjusted model and Cox-regression analysis to adjust for the possible confounders age, sex, smoking, BMI, level of education, country of birth, level of income, diabetes (type I and II) and atrial fibrillation. We performed the analysis in a stepwise manner and adjusted for possible confounding factors in three different models.

To strengthen the validity of the study we used multiple imputation for missing data on smoking and body mass index. Multiple imputation is a way of dealing with missing data. Imputed data is created by using observed data in multiple regression models and the advantage over single imputation is that it accounts for the uncertainty associated with the missing values (90). We compared results from the Cox-regression analysis from complete/observed data with results from data derived from multiple imputation. Statistical analysis was made using SAS 9.3.

Study IV

We presented the baseline data as means +/- SD or proportions as appropriate. Differences in baseline data were evaluated using the Students t-test and the Chi-2 for continuous and categorical variables. To test between group differences in PDC-level we applied the Mann-Whitney-U-test. To describe factors associated with non-adherence in this population, treated with 3 or more antihypertensive drug classes we used a Poisson regression analysis (89). Non-adherence was the outcome measure in the regression analysis and was defined as PDC <80% at 1 or 2 years. Co-variates with influence on adherence level were treatment resistant hypertension, age, sex, diabetes mellitus, renal function, and educational level, country of birth, annual income, and index blood pressure level. Statistical analysis was made using SAS 9.3.

RESULTS

Study I

The response rate to the questionnaire was 58% (352/606). Because of incomplete information in the questionnaire or resting blood pressure before exercise of ≥ 180 mm Hg before the exercise test we excluded 58 patients. Among the remaining 294 patients, 9 subjects were diagnosed with cardiovascular disease (myocardial infarction, angina pectoris or stroke) at the time of the exercise test. Of the evaluated patients 244 were outpatients and 35 were hospital-admitted. Fifteen patients had unknown referral status. Individuals who were hypertensive at follow-up had a higher BMI and were more often found to be smokers at the time of the exercise test.

Out of 294 subjects, 67 (23%) reported hypertension at the 10-12 year follow-up in 2007-2008.

Patients who were hypertensive at follow-up had on average a higher SBP before the exercise test and had a steeper rise in SBP during the test compared to patients who stayed normotensive (Figure 8).

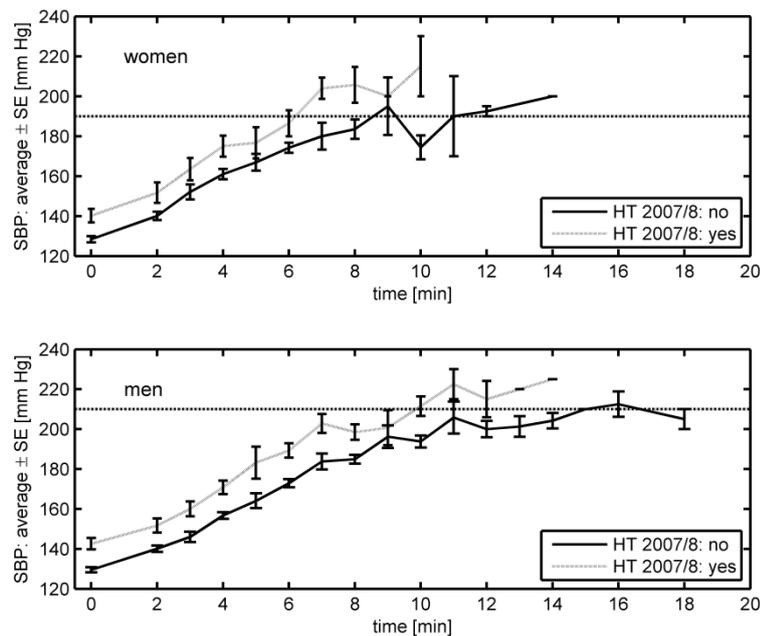


Figure 8. Systolic blood pressure during exercise (mean value \pm 1 s.e.) by incident hypertension as a function of time, separately for women and men. The horizontal line indicates 190 mm Hg for women and 210 mm Hg for men, respectively.

From the multiple logistic regression analysis we found that the best model to predict hypertension at follow-up was SBP before exercise in combination with blood pressure increase over time (OR 1.63; 95% CI 1.31-2.01). To describe the absolute risk of developing hypertension from the best predictive model we created a risk chart based on systolic blood pressure before exercise (SBP_0), rate of increase in SBP over time (rate [mm Hg/min]) and BMI (Figure 9).

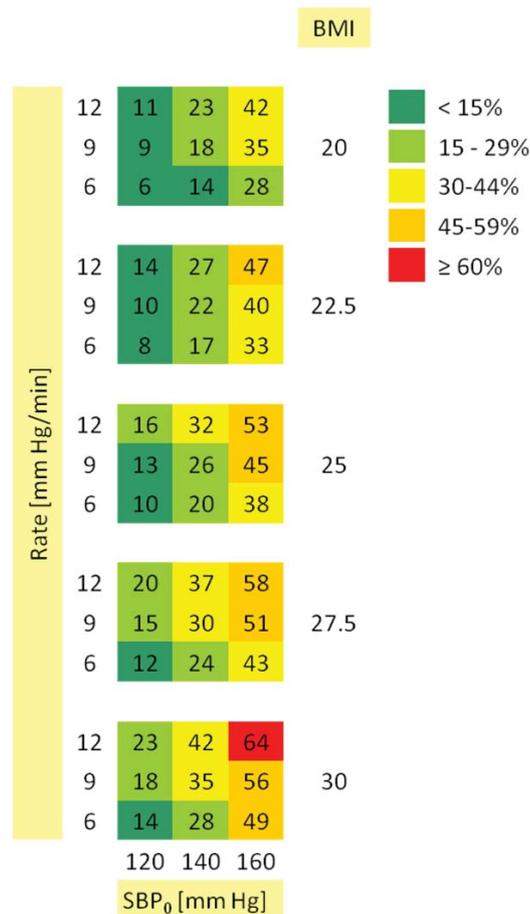


Figure 9. Predicted probability for 10-year incidence of hypertension (%). Chart based on systolic blood pressure before exercise, rate of blood pressure increase over time and body mass index (BMI).

Study II

We identified 53 125 individuals diagnosed with hypertension who had at least one dispensed antihypertensive drug during the study period. Compared to the non-TRH group, patients with TRH were older, had a higher systolic blood pressure and more co-morbidity.

According to the five different definitions applied the prevalence of TRH was 8-17%. The highest prevalence was found when combining controlled and uncontrolled TRH. The lowest prevalence was found in the definition including mineralocorticoid receptor antagonist treatment. Women had higher prevalence of uncontrolled TRH. But, when combining controlled and uncontrolled TRH, there was no gender difference. The prevalence of TRH increased with age, but a substantial proportion of TRH was observed in the youngest age group, 30-49 years (Table 2).

Table 2. The prevalence of treatment resistant hypertension (TRH) in women and men by the different definitions.

Definitions of TRH	Women (n=29 917)		Men (n=23 173)		Difference in prevalence Women and Men P		
	SBP±SD (%)	DBP±SD (mm Hg)	SBP±SD (%)	DBP±SD (mm Hg)			
1a) SBP ≥140 and/or DBP ≥90 mm Hg with 3 or more drugs dispensed, of which one is a thiazide diuretic	9.4	153±15	79±10	8.4	151±13	82±10	<0.001
1b) SBP ≥140 and/or DBP ≥90 mm Hg with 3 or more drugs dispensed, regardless of drug class	14.5	153±14	79±10	13.4	151±13	82±10	0.002
2) SBP <140 and/or DBP <90 mm Hg with 4 or more drugs dispensed, regardless of drug class	2.9	125±10	71±9	3.8	125±10	72±9	<0.001*
3) TRH according to any of the definitions 1a, 1b or 2	17.4	148±17	78±11	17.2	145±17	80±11	0.5
4) SBP ≥140 and/or DBP ≥90 mm Hg with 3 or more drugs dispensed, of which one is an MRA	1.2	151±15	77±11	0.9	152±15	80±11	0.002
5) SBP ≥160 mm Hg with 3 or more drugs dispensed, regardless of drug class	4.5	170±12	82±11	3.7	169±11	85±11	<0.001

SD=standard deviation; TRH=treatment-resistant hypertension; MRA=Mineralocorticoid receptor antagonist. SBP/DBP represent means +/- SD. *Significantly more men.

We found that diabetes mellitus (type I and II) (prevalence ratio [PR] 1.59; 95% CI 1.53-1.66), ischemic heart disease (PR 1.25; 95% CI 1.20-1.30), heart failure (PR 1.55; 95% CI 1.48-1.64), atrial fibrillation (PR 1.33; 95% CI 1.27-1.40) and chronic kidney disease (PR 1.38; 95% CI 1.23-1.54) were all associated with having TRH. Stroke/TIA (PR 1.04; 95% CI 0.98-1.09) or being a smoker (PR 0.97; 95% CI 0.89-1.05) was however not associated with having TRH (Figure 10).

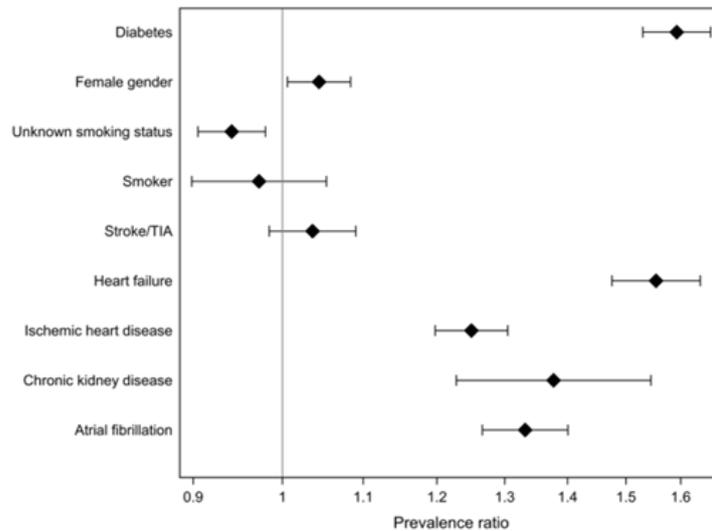


Figure 10. Prevalence ratios for treatment resistant hypertension (TRH) associated with patient characteristics and cardiovascular diagnosis.

Study III

We found 4 317 patients with TRH and 32 282 with non-TRH among the 36 599 patients with treated hypertension and without a history of previous cardiovascular disease, corresponding to a TRH prevalence of 12%.

Regarding baseline characteristics, patients with TRH, compared to non-TRH, were older, less often smokers, had higher SBP, lower estimated glomerular filtration rate (eGFR), and were more often diagnosed with diabetes mellitus and atrial fibrillation.

The mean follow-up time was 4.3 years regarding total mortality, cardiovascular mortality, ischemic heart disease, heart failure, stroke and TIA. During follow-up a total of 3 851 patients died, 31% of deaths were caused by cardiovascular disease. In the whole study population of 36 599, 2 048 patients were diagnosed with ischemic heart disease and 1 476 with heart failure, 1 666 with stroke and 473 with TIA. When comparing the TRH and the non-TRH patients with respect to the specific cardiovascular outcomes through a regression analysis we found in the unadjusted model that pa-

tients with TRH had a significantly higher incidence rate ratio (IRR) for all outcomes compared to patients with non-TRH. However, in the fully adjusted model patients with TRH had a remaining increased risk of total mortality (HR 1.12; 95% CI, 1.03-1.23), cardiovascular mortality (HR 1.20; 95% CI, 1.03-1.40), and heart failure (HR 1.34; 95% CI, 1.17-1.54). The risk for ischemic heart disease, stroke and TIA was not significantly increased (Figure 11). The results from the different models derived from the Cox-regression analysis illustrate the impact of blood pressure level, of socioeconomic situation and of metabolic disturbances on the specific outcomes. The results were consistent when data from complete cases before imputation (smoking, BMI, LDL and eGFR) were compared to the results with the imputed data set.

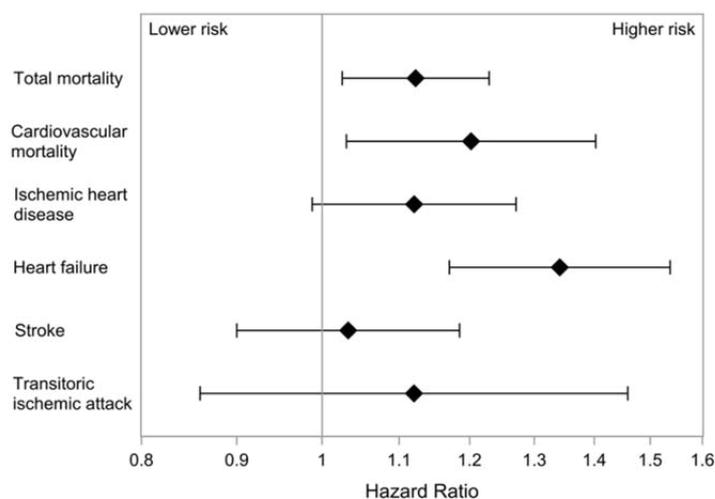


Figure 11. Results from the Cox regression analysis comparing patients with treatment resistant hypertension and patients with non-treatment resistant hypertension. Adjustment for age, sex, smoking, diabetes mellitus, atrial fibrillation, BMI, systolic blood pressure, eGFR, LDL, cancer, country of birth, education and income level.

Study IV

In the population eligible for inclusion we found 3 508 patients with TRH (blood pressure $\geq 140/90$ mm Hg) and 2 338 patients with controlled hypertension (blood pressure $< 140/90$ mm Hg) despite adherence to 3 or more antihypertensive drug classes. The mean systolic blood pressure in the TRH group was 152 mm Hg and 128 mm Hg in the controlled group. Patients with TRH were found to be older (69.1 vs. 65.8 years, $p < 0.0001$) and to have higher LDL-levels (3.2 vs. 3.1 mmol/L, $p < 0.0001$). In the TRH group there were a smaller proportion of patients with diabetes compared to controlled patients (28.5 vs. 31.7%, $p = 0.009$). Further, in the TRH group there were more women (61 vs. 57%, $p = 0.003$) and a lower mean annual income level. Number of drugs exceeding the 3 that was mandatory to be included in the study were similarly distributed between the groups.

At the time of the index blood pressure every patient included had a PDC level $\geq 80\%$. During the first year of the study the decline in proportion of patients keeping the PDC level $\geq 80\%$ declined to 89% in both groups with a further decline in the controlled group to 87% compared to the TRH group who stayed at 89% even at 2 years.

From the Poisson regression analysis we found that having TRH was not associated with a PDC $< 80\%$ at 1 (RR 0.99; 95% CI 0.79-1.23) or 2 years (RR 0.87; 95% CI 0.71-1.08). Being diagnosed with diabetes was associated with staying at a high PDC level (RR 0.82; 95% CI 0.68-0.98). However, being born outside Europe was associated with having a lower adherence level after 1 (RR 2.05; 95% CI 1.49-2.82) and 2 years (RR 2.27; 95% CI 1.70-3.03) (Figure 12).

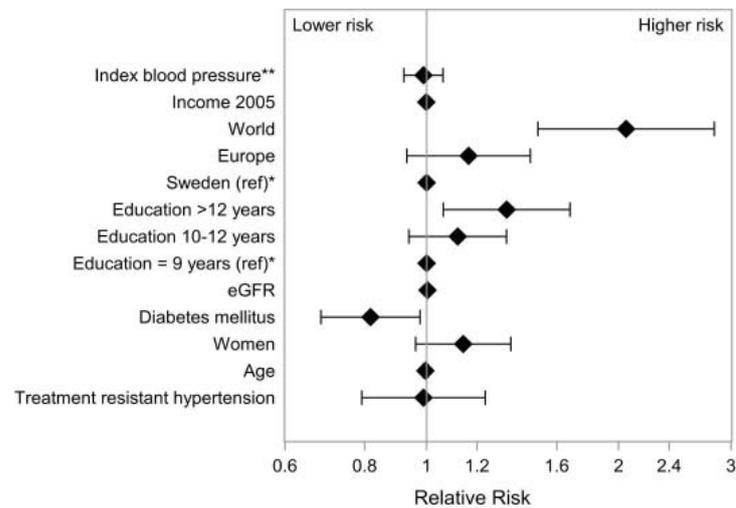


Figure 12. Forest plot describing the associations from different factors on having PDC $< 80\%$ at 1 year. Positive association (> 1.0). Negative association (< 1.0). *Reference categories for the regression analysis. **RR for every 10 mm Hg index blood pressure increase for having PDC $< 80\%$.

DISCUSSION

Is it possible to predict onset of hypertension using data from exercise testing?

The exercise test is primarily designed to reveal arrhythmias and cardiac ischemia. The idea of using the test for additional scientific questions stems from the fact that during every single test much hemodynamic data can be collected. Other underlying causes are the wish to have prognostic tools for cardiovascular disease at an early stage and to predict disease development for the future. The importance of identifying individuals with increased risk of future hypertension could on the other hand be questioned since there are scarce evidence that treatment should be initiated in pre-hypertension (91), and it is important to focus on proper blood pressure measurement (office blood pressure, ambulatory blood pressure monitoring and home blood pressure) proven to be linked to cardiovascular outcome. There have been several scientific attempts to use the exercise test as a predictive tool for a variety of diagnoses and outcomes. It has been suggested that the risk for future atrial fibrillation can be predicted from a high blood pressure during exercise testing (92). From a Norwegian cohort of normotensive, healthy, middle-aged men several publications have claimed the usefulness of a high blood pressure during exercise as a predictor for death due to myocardial infarction (45) and cardiovascular death (44). Further, the risk of stroke (93; 94) and the unmasking of heart failure with preserved ejection fraction (95) has been suggested to be predicted from the blood pressure reaction recorded during standardized exercise.

In study I we conclude that the best predictor for future hypertension in both men and women is high baseline blood pressure and a steep rise in blood pressure over time. Previous investigations have found a mechanistic explanation linking high blood pressure during exercise test to augmented aortic stiffness, altered endothelial function (96) and increase in carotid intima media thickness (97).

The ESH concluded in their guidelines from 2013 that exercise testing is not recommended for prediction of future hypertension mainly because of the diversity in methodology in present studies and the fact that there is no consensus regarding which blood pressure measurement that has the best predictive value (5). However, the same guidelines state that there might be an indication for ABPM in patients with hypertensive response to exercise because this blood pressure measurement can reveal masked hypertension (98).

Since the publication of our study I and the ESH guidelines in 2013 several studies with the intention to investigate the predictive value of exaggerated blood pressure response to exercise testing have been performed. It is suggested that a peak SBP of 181 mm Hg may be a predictor of future hypertension (99). Also a meta-analysis published in JACC conclude that high blood pressure during exercise, despite various definitions, can predict incident hypertension (100). However, there are also recent studies where no relation between high blood pressure at exercise and future hypertension has been identified (101).

An interesting finding is that high SBP during exercise in the elderly might rather predict a good prognosis since the possibility to produce a high blood pressure during exercise in the elderly may be a sign of preserved cardiac output (102).

In conclusion, many studies have shown that exaggerated blood pressure in response to exercise testing, independent of methodology, is a predictor for future hypertension. Still there are some different definitions of hypertensive response to exercise testing and many physicians are still not confident in interpreting the blood pressure response during the test.

One help for interpretation of the blood pressure reaction could be a simple risk chart. We have published a suggestion of how such a risk chart could be created. However, this predictive risk chart ought to be evaluated in larger populations with more strict measurements of the outcome variables before it could be introduced in clinical practice.

The exercise test holds information about the cardiovascular status of apparently healthy individuals or at least the individuals referred for exercise testing that of course is a selected population. If we can identify individuals with masked hypertension by the exercise test we might be able to diagnose more individuals with hypertension or initiate follow-up of individuals in this particular population. This could be one contribution to increase awareness regarding hypertension among physicians and patients.

What is the prevalence of treatment resistant hypertension?

Treatment resistant hypertension has various definitions in different guidelines (5; 59). In Europe a commonly used definition of TRH is blood pressure $\geq 140/90$ mm Hg despite the use of 3 or more antihypertensive drug classes, of which one is a thiazide diuretic (5). In study II our aim was to present a summary of all prevailing definitions. We found the prevalence of TRH to be between 8 and 17% depending on the definition used.

Previous attempts to describe the prevalence of TRH from hypertension RCT's (103; 104), population based studies (105; 106) and retrospective analysis of registry data (107; 108) all report a prevalence between 8-15% which make our study partly confirmatory but extend the knowledge to a larger population in Sweden with valid pharmacy refill data.

Women have been found to have more uncontrolled TRH, i.e. blood pressure $\geq 140/90$ mm Hg despite the use of 3 or more antihypertensive drug classes, both in our study II and in previous investigations (105; 106; 109). This is also in line with previous findings in the SPCCD cohort where women have been found to have higher attained blood pressure levels (110). In the study by Ljungman et. al. one explaining factor was thought to be the choice of antihypertensive drug classes, since women more often were prescribed beta-blockers and diuretics while men primarily were prescribed calcium channel blockers and ACE-inhibitors. We do not know if this prescription difference, with respect to gender, holds true for our patients with TRH but it is pos-

sible to consider that different prescriptions to men and women might contribute to our findings regarding gender differences since patients with TRH are selected from the same SPCCD cohort as the cohort mentioned above.

We found that when including a mineralocorticoid receptor antagonist into the definition of TRH a prevalence of 1.1% was found. Only 8% of patients with TRH and 4% in the group without TRH were prescribed a mineralocorticoid receptor antagonist. Explaining factors for not using mineralocorticoid receptor antagonists to a higher extent are not easily found in the present study but possible factors could be renal impairment or the fact that treatment with mineralocorticoid receptor antagonists is afflicted with several side effects. Further, mineralocorticoid receptor antagonist is a second line treatment and might be considered as an old fashioned treatment strategy since the introduction of better tolerated antihypertensive drugs during the 80's and 90's century. Mineralocorticoid receptor antagonists are considered less studied in terms of cardiovascular risk reduction compared to other treatment options.

Previous studies have however revealed that mineralocorticoid receptor antagonists are efficient regarding blood pressure lowering effect (111; 112). To test the hypothesis whether sodium retention is the most common cause of resistant hypertension Williams and co-workers designed the PATHWAY-study. In this RCT a fourth drug was added on top of standard treatment with ACE-inhibitor, calcium channel blocker and thiazide-like diuretic in patients with TRH. The mineralocorticoid receptor antagonist, Spironolactone, was found to have the best blood pressure lowering effect. This implies that TRH might be a result of fluid retention and can be diminished by diuretic therapy, especially mineralocorticoid receptor antagonist, at sufficient doses (113). Further, since the proportion of undiagnosed primary aldosteronism in the hypertensive population, and especially in the subpopulation with TRH, Spironolactone seems to be a proper drug of choice. In the PATHWAY-study the renin levels at baseline in patients with TRH were low indicating that there might be an undiagnosed disturbance in the aldosterone-renin system explaining some of the TRH cases. Our study shows that there is room for an increase in prescription of mineralocorticoid receptor antagonists and together with the evident efficacy as a blood pressure lowering agent this should encourage physicians to reappraise the use of mineralocorticoid receptor antagonists in hypertensive patients.

The diagnosis with the strongest association to TRH was diabetes mellitus. It is well known that diabetes co-exist and share common pathophysiology such as altered microcirculation with hypertension (114). High-normal blood pressure has been suggested as a predictor for onset of type 2 diabetes in extended follow-up over thirty-five years time (115). Furthermore, patients with diabetes have higher attained blood pressure levels (116) and it has been found that it is more difficult to control blood pressure in patients with diabetes (117). At the same time patients with diabetes are signed up for regular visits at the PHCC's for control of their diabetes and blood pressure, which ought to result in better control. This should be an opportunity to tailor the antihypertensive treatment to reach target blood pressure levels.

The challenge of describing the prevalence of TRH is partly due to the fact that one must try to distinguish apparent TRH (aTRH) from true TRH. From population based

and registry based studies it is only possible to describe the prevalence of aTRH. However, there is potential to get closer to the prevalence of true TRH. Our approach was to only include patients with high medication adherence and exclude patients with known and diagnosed secondary causes to hypertension. To describe the prevalence of true TRH one would need to initiate a cohort especially designed for describing true TRH. This would be costly and require a lot of effort. By describing the prevalence of TRH you can acquire an estimate of how many patients that could be considered for a more systematic screening for secondary causes of hypertension. Further, this work can direct attention towards TRH and associated factors. Hopefully by focusing on this patient group the well known methods of controlling blood pressure such as strict medication adherence, life-style factor intervention and treating secondary causes can once again be appraised.

What is the outcome in treatment resistant hypertension?

Patients with TRH, in study III, were found to have an increased risk for heart failure during the time of follow-up. Hypertension is a well-known risk factor for heart failure (118). In the Swedish Heart Failure registry as many as 61% of the patients with heart failure with preserved ejection fraction have concomitant hypertension (65). Heart failure is a disease with poor prognosis (119) and the prognosis is comparable to several common cancer forms (120).

It has been described that controlling blood pressure is a proper way to decrease the incidence of heart failure (121). Since TRH patients per se do not reach target blood pressure levels it is not surprising that they carry an over-risk for heart failure. This has also been demonstrated in previous studies with partly different design compared to our study III. In a post-hoc analysis from patients not reaching target blood pressure in the RCT “ALLHAT” performed in the late 90’s century heart failure was significantly higher in TRH patients (67). In RCT’s the medication adherence is thought to be good but the choice of medications is limited to the study protocol which can make it more difficult to interpret in the clinical setting.

In our study III we did not, after multivariate adjustments, find an association between TRH and stroke/TIA. This was at first surprising since hypertension is a well-known risk factor for stroke (122) and lower blood pressure levels are protective especially for stroke (53). The results are however in line with a previous study assessing the cardiovascular risk for TRH (123). Possible explaining factors in our investigation can be low mean age in both groups and the fact that we are comparing two groups with hypertensive patients who both have increased risk for stroke. It has further been suggested that stroke is an entity that primarily has hypertension as a risk factor (123) while ischemic heart disease and heart failure share common risk factors with TRH beyond high blood pressure such as primary aldosteronism and sleep apnea. All these factors could partly explain the lack of differences in stroke outcome found in study III (124-126).

Diabetes was more common in the TRH group. As a result we adjusted for this variable in the multivariate analysis. It is not obvious if diabetes is a mediator or a confounder for the correlation between TRH and, for example, stroke. In the unadjusted

analysis the association between TRH and stroke was strong and when adjusting for diabetes, among other things, the association was no longer significant which might indicate that diabetes is one of the mediators of the effect from TRH on stroke (127).

Medication adherence

According to guidelines medication adherence should always be considered in patients who do not reach blood pressure target levels (5).

We evaluated the medication adherence during two years in patients dispensed 3 or more antihypertensive drug classes with high medication adherence at baseline with both uncontrolled blood pressure ($\geq 140/90$ mm Hg) and controlled blood pressure ($< 140/90$ mm Hg).

We found an equal decline in medication adherence to 3 or more antihypertensive drug classes in both patients with controlled blood pressure and patients with uncontrolled blood pressure at baseline. Since it has been described that low medication adherence is common in TRH (128) we hypothesized that this might be reflected in a difference in medication adherence between uncontrolled and controlled hypertensive patients even in this selected population with patients verified to be highly adherent at baseline. Lower adherence for TRH patients has been previously described (129). On the other hand, the same phenomenon as in our study has been observed in earlier studies from North America (68). Since we do not have data on blood pressure development during these two years it is difficult to make any further conclusions from these findings.

In paper IV we further found that having diabetes was associated with having PDC $\geq 80\%$ during both years studied. It has previously been described that blood pressure level generally is higher in patients with diabetes (130) and it has also been described that diabetes is associated with additional difficulty to control hypertension (117). Patients with diabetes ought to have a good chance of being evaluated for medication adherence since they have regular visits at the PHCC's. Further, it might be likely that patients diagnosed with a disease that produce negative symptoms in relation to insufficient medication adherence will be more compliant to other medications as well.

In the clinical setting there are several ways of evaluating medication adherence. In a Norwegian study direct observation of drug intake in the clinic was seen to reduce TRH immensely (131). This is the only way to be positive regarding if the patients are actually taking their medication, but it is of course impossible to practice this regimen in real life. Another method described is "Therapeutic drug monitoring" which implies screening for drug concentrations in blood and urine. This method has been shown cost-effective in patients with TRH (132). Registry studies are not suitable for these kinds of medication adherence assessments, but enable us to use a different method in evaluating drug adherence. To estimate prescribed medication is one way but, to investigate dispensed drugs is even more accurate and gives a better opportunity to answer the question whether the patients are taking their medication or not (133). In Sweden we have a unique pharmacy claims registry with full coverage of all

dispensed drugs to all citizens (87) which makes evaluation of medication adherence with this method accurate.

Low medication adherence in hypertension is common and maybe, by describing medication adherence in a population with multiple antihypertensive drug use we can gain more insight in this challenging subject and hopefully overcome some of the barriers to treatment that exists.

CONCLUSIONS AND FUTURE PERSPECTIVES

It is possible to predict development of hypertension from an exercise test. In fact many patients with undiscovered hypertension have high blood pressure already before the exercise test starts. Using the information from exercise testing can help find, follow and treat more hypertensive patients and could contribute to diminishing the global burden of the disease from hypertension.

The prevalence of treatment resistant hypertension varies between 8 and 17% according to which definition you chose to apply. Treatment with mineralocorticoid receptor antagonists does reduce the prevalence, but treatment resistant hypertension is still not a negligible problem in the hypertensive population. Increasing the use of mineralocorticoid receptor antagonists will probably decrease the prevalence of treatment resistant hypertension and the blood pressure levels in this hypertensive population.

Patients with treatment resistant hypertension seem to have an increased risk for heart failure, cardiovascular mortality, total mortality and ischemic heart disease compared to other patients with hypertension not resistant to treatment. Although hypertension is known to be the strongest risk factor for stroke we did not find a strong association between treatment resistant hypertension and stroke/TIA. Putting extra effort into controlling blood pressure and search for causes of secondary hypertension, especially primary aldosteronism, is recommended if we want to reduce the enhanced risk for unbeneficial cardiovascular outcomes for patients with apparent treatment resistant hypertension. Especially the increased risk for heart failure is important since heart failure has an increasing prevalence in Sweden (134) and is a disease with prognosis comparable to many cancer forms. This knowledge once again should encourage care-givers to take action to control blood pressure and try to diminish the burden of disease from hypertension.

In a patient cohort of hypertensive patients with high medication adherence to multiple antihypertensive drugs there is a similar decline in mean medication adherence over two years time between patients with treatment resistant hypertension and patients with controlled hypertension. Patients with diabetes are more prone to have a high medication adherence emphasizing that structured care-giving is beneficial for high medication adherence. The results reappraise that hypertensive patients ought to have the possibility to have structured care-giving and hopefully reminds us of the known ways to enhance blood pressure control through home blood pressure and fixed dose combinations.

LIMITATIONS

All the studies in this thesis are observational to their character and hence they all have the inherent limitations of this kind of studies such as selection bias, unknown confounding factors, missing values and misclassification.

Study I

All exercise tests during a certain time-period were eligible for inclusion but almost half of them were excluded from further analysis. We do not think that these missing data are dependent on the outcome variable, hypertension. The missing values from unanswered questionnaires could be dependent on the diagnosis of hypertension but it is impossible to know what influence this had on the effect-size. The outcome variable, hypertension, is measured through a questionnaire that was not validated, which can lead to misclassification regarding the outcome variable.

The fact that the study included patients who performed the exercise test on different indications make the study generalizable to the clinic situation in the ward of Clinical physiology where most exercise tests are performed but can also be misinterpreted since some individuals are healthy firemen and others are patients hospitalized for chest pain.

Study II-III

Patients who are unaware of their hypertension are not included in the SPCCD since they were not diagnosed in the PHCC. This bias could only be diminished by initiating a cohort study randomising individuals from the population for the purpose of screening for hypertension and TRH.

Since we have the treated hypertensive population as a denominator in the prevalence calculation the prevalence numbers should be valid regarding the prevalence of TRH in the treated hypertensive population.

We used one single blood pressure to classify patients with TRH which might produce some bias with respect to misclassification. However, analyses of blood pressure measurements in the SPCCD reveal that the last recorded blood pressure is representative of the last three measurements. Both diagnosis of hypertension, co-morbidities and outcome variables rely on registration of ICD-codes in medical records or diagnose registers. However, a validation of the diagnosis registration in one region of the SPCCD shows that the mean sensitivity for hypertension ICD-code is 83% (135).

In study III we used multiple imputation to try to diminish the influence from missing values in the SPCCD on the results. In multiple imputation you need to assume that the missing data are missing randomly i.e. not depending on the explaining variable or the outcome variable. We made this assumption for the analysis of BMI, smoking, LDL and eGFR which all had a large proportion of missing values.

In the SPCCD we miss information on several factors influencing blood pressure such as level of physical activity, alcohol consumption, perceived stress, salt-intake and sleeping disorders. The missing information on these parameters is equal for all patients and thus does not directly influence the results for between group comparisons. Also, when describing apparent TRH, like we did, it is not mandatory to exclude secondary causes of hypertension.

Study IV

In study IV we investigate individuals with known high adherence which limits the results to only describe a decline in medication adherence. Another limitation in this study is the fact that we compare the mean values of the two groups which possibly mask a true medication adherence increase in some cases and decrease in some cases. We do not follow blood pressure longitudinally and it is unknown to us whether the patients have a controlled blood pressure or not after one and two years or not. Blood pressure control might of course have had influence on medication use during this time period.

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