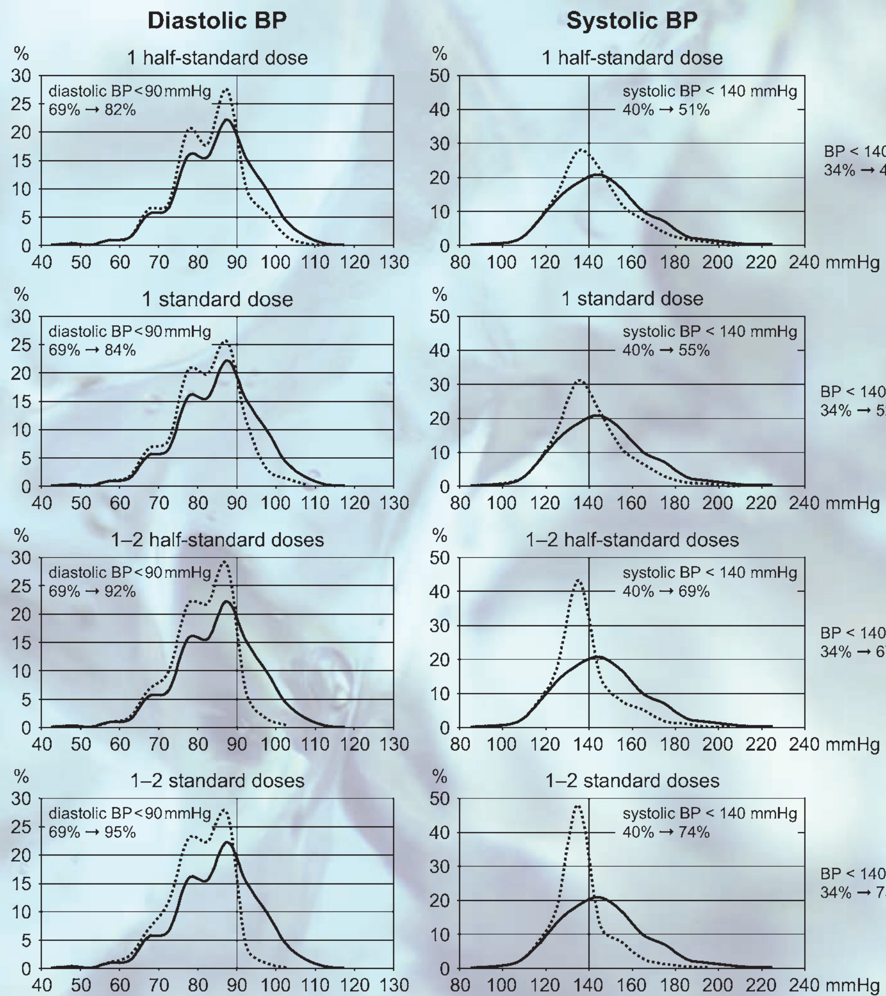
NATIONAL INSTITUTE FOR HEALTH AND WELFARE

Teemu Ahola

# Antihypertensive Drug Therapy in Finland

## Utilization of Antihypertensive Medication, Control of Blood Pressure, and Achievable Reduction of Cardiovascular Morbidity with Intensified Treatment

RESEARCH

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### ACADEMIC DISSERTATION

To be presented with the permission of the Faculty of Medicine, University of Turku, for public examination in the auditorium of the Petrea Rehabilitation Centre, Turku on May 24th, 2013, at 12 noon.

National Institute for Health and Welfare, Department of Chronic Disease Prevention, Turku, Finland
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To the memory of my father

## Abstract

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Hypertension has been identified as one of the major risk factors causing premature death. According to earlier studies, antihypertensive drugs have been underused and control of hypertension is proven to be poor in Finland and some other countries. It is well known that lowering blood pressure significantly reduces cardiovascular morbidity and mortality. According to national and international guidelines, antihypertensive drug therapy is chosen individually after taking into account indication, cardiovascular risk profile, target organ damages, and coexisting disorders. Healthy lifestyle also has a significant role in the treatment of hypertension. However, combination antihypertensive medication is usually required to reach the target blood pressure. Still, limited data exists on the utilization of antihypertensive drugs and drug combinations (including triple therapy) in relation to concomitant comorbidities in nationwide population studies, and in Finland such data, practically, does not exist.

The purpose of this thesis was to assess the prevalence and control of hypertension and the rationality of treatment (i.e., drug selection and drug combinations in accordance with national and international guidelines) among at least 30 years old patients with diabetes (I), coronary heart disease (II), and uncomplicated essential hypertension (III); and to assess changes in antihypertensive medication between 2000 and 2006. In addition, living habits associated with increased risk of cardiovascular disease were assessed, and the expected reduction of strokes and ischaemic heart disease events of uncomplicated hypertensive patients were calculated in theory by intensifying antihypertensive medication for those with uncontrolled BP ( $\geq$ 140/90 mmHg) (III). In the last study (IV), differences in drug therapy were compared between those entitled to reimbursement for hypertension medication cost and those without this entitlement. New onset diseases during the follow-up time were also noted. Moreover, differences in drug therapy in 2006 between recently treated and formerly treated were assessed after adjustment with age, sex, and living area (IV).

The material was based on two different data. The data of Health 2000 Survey were based on a well-representative sample of Finnish adult population (n=6209, 30-99 years old). Subjects participated in interviews, a thorough clinical health examination and laboratory analyses between 2000 and 2001. The massive database of the Social Insurance Institution (SII) of Finland included the data of prescriptions and the entitlements to drug reimbursement for medication costs (in 2000-2001 and in 2006-2007) and included 1.59 million Finnish patients aged 30 years or older. In addition to the above, the database of SII included practically 100% of the prescriptions on antihypertensive and lipid-lowering drugs purchased by the Finnish population between September 1st and November 30th in 2000 and 2006.

Results of this thesis indicate that control of BP at the beginning of the 2000s has been alarmingly poor. On the contrary, between 2000 and 2006, monotherapy decreased while combination therapy, particularly that of three or more antihypertensive drugs, increased significantly. Utilization of evidence-based drug therapies, particularly angiotensin receptor blockers among adult hypertensive patients increased significantly by the end of 2006. Despite the positive change discovered in this study, underutilization of antihypertensive drugs and poor control of hypertension still remain a matter of concern. Beyond that, there seems to be an unceasing relative overuse of beta-blockers in the treatment of hypertension, especially among diabetic patients and uncomplicated hypertensive patients. Moreover, quite surprisingly, beta-blockers seem to be chosen as first line agents far more often than other antihypertensive agents, even among recently treated hypertensive patients without compelling indication for their use. However, as calculated in this study, intensifying the treatment of uncomplicated hypertensive patients by one-half standard dose of BP-lowering regimen for those whose BP exceeded the limit of 140/90 mmHg, would increase the control of hypertension from 34% to 48%, reduce strokes by 18%, and reduce ischaemic heart disease events by 13%.

According to the results of this thesis, it can be concluded that more rational selections of antihypertensive drugs and drug combinations are needed. Physicians should take into account more precisely related or absent comorbidities, cardiovascular risk factors and other individual characteristics when choosing antihypertensive agents for hypertensive patients. Results of this thesis can be utilized in daily clinical practices, in order to benefit Finnish physicians and hypertensive patients in the long run.

**Keywords**: blood pressure, drug therapy, hypertension, diabetes, coronary heart disease, uncomplicated essential hypertension, cardiovascular morbidity, combination therapy

## Tiivistelmä

Teemu Ahola, Kohonneen verenpaineen lääkehoito Suomessa.
Verenpainelääkkeiden käyttö, verenpaineen hallinta, ja tehostetulla hoidolla saavutettavissa oleva sydän- ja verisuonisairauksien vähentyminen.
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Kohonnut verenpaine on identifioitu yhdeksi tärkeimmistä ennenaikaista kuolleisuutta aiheuttavista riskitekijöistä. Verenpainelääkkeet ovat olleet alikäytettyjä ja verenpaineen hoitotavoitteessa mukana olevien osuus on todettu pieneksi sekä Suomessa että muissa maissa. Tiedetään myös, että verenpaineen alentaminen vähentää merkitsevästi sydän- ja verisuonisairauksia sekä kuolleisuutta. Kansallisen ja kansainvälisten hoitosuositusten mukaan verenpaineen lääkehoito valitaan yksilöllisesti käyttötarkoitus, potilaan riskitekijät, kohde-elinvauriot ja liitännäissairaudet huomioiden. Myös terveellisten elintapojen merkitys korostuu kohonneen verenpaineen hoidossa. Hoitotavoitteeseen pääsy edellyttää kuitenkin useimmiten lääkeyhdistelmien käyttöä. Silti väestötason tutkimuksia verenpaineen lääkehoidosta ja yhdistelmähoidosta (mukaan lukien kolmen verenpainelääkkeen yhdistelmät) liitännäissairauksiin suhteutettuna on käytettävissä toistaiseksi hyvin niukasti, ja Suomesta nämä käytännössä puuttuvat.

Tutkimuksen tavoitteena oli selvittää vähintään 30-vuotiaiden, diabetesta (I), sepelvaltimotautia (II) ja essentiaalista komplisoitumatonta kohonnutta verenpainetta (III) sairastavien suomalaisten kohonneen verenpaineen esiintyvyyttä, hoitoisuutta ja hoidon rationaalisuutta (lääkevalintoja ja -yhdistelmiä suhteessa kansallisiin ja kansainvälisiin hoitosuosituksiin) sekä arvioida hoidossa tapahtuneita muutoksia vuosina 2000–2006. Lisäksi selvitettiin valtimotaudin riskiin liittyviä elintapoja em. kohderyhmissä (I-III) sekä arvioitiin, kuinka paljon komplisoitumatonta essentiaalista kohonnutta verenpainetta sairastavien henkilöiden sydän- ja aivoinfarkteja voitaisiin teoriassa vähentää tehostamalla verenpaineen lääkehoitoa niillä, joiden verenpaine ei ollut hoitotavoitteessa (RR≥140/90 mmHg) (III). Viimeisessä osatyössä (IV) verrattiin verenpainelääkevalintoja erityiskorvausoikeutettujen ja oikeuttamattomien henkilöiden välillä. Myös seuranta-aikana ilmaantuneet uudet liitännäissairaudet huomioitiin. Lisäksi verrattiin vuoden 2006 lääkevalintoja uusien ja pidempään verenpaineen lääkehoidossa olleiden potilaiden välillä niin, että ikä, sukupuoli ja alue oli vakioitu (IV).

Tutkimukseen käytettiin kahta aineistoa. Terveys 2000 tutkimusaineisto perustui edustavaan suomalaiseen aikuisväestöotokseen (n = 6209, 30–99-vuotiasta henkilöä). Tutkimushenkilöt osallistuivat vuosina 2000–2001 haastatteluihin,

perusteelliseen kliiniseen terveystarkastukseen sekä laboratoriotutkimuksiin. Kelan reseptitiedoista ja erityiskorvausrekistereistä (2000–2001 ja 2006–2007) koottu jättiaineisto käsitti yhteensä 1,59 miljoonaa vähintään 30-vuotiasta suomalaista. Erityiskorvausrekisterien lisäksi Kelan aineisto sisälsi 100 % kaikista verenpaine- ja kolesterolilääkeostoista Suomessa syyskuun alusta marraskuun loppuun vuosilta 2000 ja 2006.

Tämän väitöstutkimuksen tulokset osoittavat, että verenpaineen hoitotavoitteessa olleiden osuus oli hälyttävän pieni 2000-luvun alussa. Toisaalta vuosina 2000-2006 monoterapian osuus väheni ja yhdistelmähoito, etenkin vähintään kolmen verenpainelääkkeen yhdistelmien osalta, lisääntyi huomattavasti. Näyttöön perustuvien terapioiden, erityisesti angiotensiinireseptorin salpaajien käyttö, lisääntyi huomattavasti vuoden 2006 loppuun mennessä. Tutkimuksessa todetuista positiivisista muutoksista huolimatta verenpainelääkkeiden liian vähäinen käyttö ja taudin hoitotavoitteessa mukana olevien pieni osuus huolestuttavat edelleen. Lisäksi beetasalpaajien suhteellinen yliedustus kohonneen verenpaineen hoidossa näyttää jatkuvan etenkin diabeetikoilla ja essentiaalista komplisoitumatonta kohonnutta verenpainetta sairastavilla. Oli melko yllättävää, että jopa uusille verenpainepotilaille määrättiin ensilinjan lääkkeenä kaikista verenpainelääkkeista muita useammin beetasalpaajia, vaikka ehdotonta indikaatiota sen käytölle ei ollutkaan. Toisaalta, kuten tässä tutkimuksessa osoitettiin, tehostamalla essentiaalista komplisoitumatonta kohonnutta verenpainetta sairastavien hoitoa lisäämällä tarvittaessa vain puolikas verenpainelääkeannos niille, joiden verenpaine ylitti rajan 140/90 mmHg, voitaisiin hoitotavoitteessa olevien osuutta lisätä 34 %:sta 48 %:iin ja samalla vähentää aivoinfarkteja 18 %:lla ja iskeemisiä sydäntapahtumia 13 %:lla.

Tämän tutkimuksen perusteella voidaan todeta, että verenpaineen hoitoon käytettävien lääkkeiden valinnan tulisi olla rationaalisempaa. Lääkäreiden tulisi verenpainelääkkeitä valitessaan tarkemmin huomioida potilaan liitännäissairaudet, sydän- ja verisuonisairauksien riskitekijät sekä muut yksilölliset tekijät. Tämän väitöskirjan tuloksia voidaan soveltaa suoraan kliiniseen käytännön työhön lääkäreiden avuksi ja potilaiden parhaaksi.

**Avainsanat**: verenpaine, lääkehoito, kohonnut verenpaine, diabetes, sepelvaltimotauti, komplisoitumaton essentiaalinen kohonnut verenpaine, sydän- ja verisuonitautisairastuvuus, yhdistelmälääkehoito

## Contents

## List of original publications

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

I Ahola TL, Jula AM, Kantola IM, Mäki J, Klaukka T, Reunanen A. Positive change in the utilization of antihypertensive and lipid-lowering drugs among adult diabetics in Finland. Results from large national database between 2000 and 2006. *J Hypertens* 2009, 27:2283-2293.

II Ahola TL, Kantola IM, Puukka P, Kattainen A, Klaukka T, Reunanen A, Jula AM. Positive change in the utilization of antihypertensive and lipid-lowering drugs among adult CHD patients in Finland: results from a large national database between 2000 and 2006. *Eur J Cardiovasc Prev Rehabil* 2010, 17:477-485.

III Ahola TL, Kantola IM, Mäki J, Reunanen A, Jula AM. Adding a low-dose antihypertensives regimen would substantially improve the control of hypertension and reduce cardiovascular morbidity among uncomplicated hypertensive patients. *Eur J Prev Cardiol* 2012, 19:712-722.

IV Ahola TL, Jula AM, Kantola IM, Puukka P. Beta-blockers are relatively overused in Finland. Submitted.

## Abbreviations

| | |
|---|---|
| *ABCD* | Appropriate Blood Pressure Control in Non-insulin-dependent Diabetes Mellitus |
| *ACCOMPLISH* | Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension |
| *ACCORD* | Action to Control Cardiovascular Risk in Diabetes |
| *ACTION* | A Controlled Trial Investigating Outcomes of Exercise Training |
| *ADVANCE* | Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation |
| *ALLHAT* | Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial |
| *ANBP2* | Second Australian National Blood Pressure Study |
| ACE | AngiotensinConverting Enzyme |
| ARB | Angiotensin Receptor Blocker |
| ASA | Acetylsalicylic Acid |
| *ASCOT* | Anglo-Scandinavian Cardiac Outcomes Trial |
| BB | Beta-blocker |
| *BENEDICT* | Bergamo Nephrologic Diabetes Complications Trial |
| BHS | British Hypertension Society |
| BMI | Body Mass Index |
| BP | Blood Pressure |
| CABG | Coronary Artery Bypass Grafting |
| *CAFE* | Conduit Artery Function Evaluation |
| *CAMELOT* | Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Trombosis |
| *CAPPP* | Captopril Prevention Project |
| CCB | Calcium Channel Blocker |
| CHD | Coronary Heart Disease |
| CHF | Chronic Heart Failure |
| *DAVIT* | The Danish Verapamil Infarction Trial |
| *ELSA* | European Lacidipine Study on Atherosclerosis |
| ESC | European Society of Cardiology |
| ESH | European Society of Hypertension |
| *EUROASPIRE* | European Action on Secondary Prevention through Intervention to Reduce Events |
| *EUROPA* | European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease |
| *FACET* | Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial |
| FCCH | Finnish Current Care Hypertension |

| | |
|---|---|
| FDMS | Formerly Diagnosed Moderately to Severely |
| *FEVER* | Felodipine Event Reduction |
| FHA | Finnish Heart Association |
| H2000 | Health 2000 Survey |
| HDL | High Density Lipoprotein |
| *HOPE* | Heart Outcomes Prevention Evaluation |
| *HOT* | Hypertension Optimal Treatment |
| *HYVET* | Hypertension in the Very Elderly Trial |
| *IDNT* | Irbesartan Diabetic Nephropathy Trial |
| IHD | Ischaemic Heart Disease |
| *INSIGHT* | International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment |
| *INVEST* | International Verapamil Sustained Release Trandolapril Study |
| *IRMA-2* | IRbesartan in MicroAlbuminuria, Type 2 Diabetic Nephropathy |
| *I-SEARCH* | International Survey Evaluation Microalbuminuria Routinely by Cardiologist in patients with Hypertension |
| *JIKEI Heart* | Japanese Investigation of Kinetic Evaluation in Hypertensive Event and Remodeling Treatment |
| JNC6 | Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure |
| JNC7 | Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure |
| *JMIC-B* | Japan Multicenter Investigation for Cardiovascular Diseases-B |
| *MDPIT* | Multicenter Diltiazem Post-Infarction Trial |
| *NHANES* | National Health and Nutrition Examination Survey |
| *NORDIL* | Nordic Diltiazem Study |
| LDL | Low Density Lipoprotein |
| *LIFE* | Losartan Intervention for Endpoint Reduction |
| *ONTARGET* | Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial |
| *OPTIMAAL* | Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist |
| *PEACE* | Prevention of Events with Angiotensin-Converting Enzyme Inhibition |
| *PREVESE* | Secondary Prevention of Myocardial Infarction in Spain |
| PTCA | Percutaneus Transluminal Coronary Angioplasty |
| *QUIET* | Quinapril Ischemic Event Trial |
| RAS | Renin-Angiotensin System |
| RDMS | Recently Diagnosed Moderately to Severely |
| *RENAAL* | Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan |
| *SCOPE* | Study on Cognition and Prognosis in the Elderly |

| | |
|---|---|
| *SHEP* | Systolic Hypertension in the Elderly Program |
| SII | Social Insurance Institution of Finland (Kela) |
| *STOP-2* | Swedish Trial in Old Patients with Hypertension-2 |
| *Syst-Eur* | Systolic Hypertension in Europe |
| *TASPIC-CRO* | Treatment and Secondary Prevention of Ischemic Coronary events in Croatia |
| *TNT* | An analysis of the Treating to New Targets |
| *TRANSCEND* | Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease |
| *UKPDS* | United Kingdom Prospective Diabetes Study Group |
| *VALIANT* | Valsartan in Acute Myocardial Infarction Trial |
| *VALUE* | Valsartan Antihypertensive Long-term Use Evaluation |
| *VHAS* | Verapamil in Hypertension and Atherosclerosis Study |
| WHO-ISH | World Health Organization – International Society of Hypertension |

# 1 Introduction

Hypertension has been identified as the leading risk factor for mortality [1]. Antihypertensive drugs are underused, and control of hypertension is poor both in Finland and some other countries [2-5].

While some drugs and drug combinations may be more efficient at reducing cardiovascular morbidity, no category of drugs appears to be inferior in their ability to reduce BP [6, 7]. Many studies support the view that the reduction of BP *per se* is more important than the individual properties of the specific drug, for decreasing cardiovascular risk among hypertensive patients [8-10]. There is evidence that lowering systolic BP by 10 mmHg or diastolic BP by 5 mmHg reduces events of stroke by approximately 41% and of ischaemic heart disease (ICH) by approximately 22% [11].

According to national and international guidelines, each agent can be preferentially prescribed under specific conditions [12-15]. However, combination therapy is usually required to achieve a proper control of BP [7]. Nevertheless, the European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines for management of arterial hypertension [16], published in 2003, demonstrated evidence that specific drug classes may differ in some effect, or in special groups of patients. Beyond that, national [12, 13] and international guidelines [16] have emphasized that physicians should tailor a drug treatment to an individual patient after taking into account the cardiovascular risk profile, target organ damages, and other coexisting disorders (renal disease, diabetes, etc.). ESH and ESC guidelines for the management of arterial hypertension [16] also listed indications and contraindications for the major classes of antihypertensive drugs. Moreover, the guidelines emphasized the importance of low-dose combination therapy and established the renoprotective effects of ACE inhibitors and ARBs [13, 16]. According to recent guidelines, the most rational three-drug combination appears to be a blocker of renin-angiotensin system (RAS), a calcium channel blocker (CCB), and a diuretic, although other drugs, such as a beta-blocker (BB) or an alpha-blocker, may be used in specific indications, depending on the clinical circumstances [7].

However, the available data is limited, if any, on the utilization of antihypertensive drugs and drug combinations (including triple therapy) in relation to concomitant comorbidities in all-inclusive nationwide studies.  In Finland, such data, practically, does not exist.

The aim of this thesis was to assess the utilization of antihypertensive drugs in Finland between 2000 and 2006, and to assess trends in the utilization of antihypertensive drugs and drug combinations among diabetic patients, CHD patients, and uncomplicated hypertensive patients. The ultimate purpose was to assess whether these treatments are in line with the guidelines of hypertension management. Beyond that, the longitudinal nationwide drug utilization study presented in this thesis analyzes changes in monotherapy, in dual-therapy, and in drug combinations containing at least three drugs, in relation with changes in concomitant disease profiles on the individual level. In addition, this thesis was also designed to assess the control of hypertension in above-named subgroups, and to calculate the expected reductions in BP and cardiovascular morbidity among uncomplicated hypertensive patients, with intensified antihypertensive treatment.

# 2 Review of the Literature

## 2.1 BP threshold for drug therapy according to guidelines

### 2.1.1 Patients with essential hypertension (including uncomplicated hypertensive patients)

Typical for hypertension management guidelines in the nineties and early 2000s was a fairly conservative approach in relation to initiation of antihypertensive drug therapy. Even at relatively high levels of BP, such as 140-159/90-99 mmHg, drug treatment was recommended to be started with lifestyle modifications and non-pharmacological interventions. If this, after several months of follow-up including re-measurements of BP, did not achieve required targets, initiation of antihypertensive drug therapy was recommended. For the general population (those without additional cardiovascular risk factors), the mean BP of 160/100 mmHg was the most common threshold for drug therapy during the nineties [17] and early 2000s [12]. However, each guideline categorized BP levels into certain ranges and gave specific recommendation as to when to commence antihypertensive medication. Specific BP thresholds and/or ranges of systolic and diastolic BP for initiation of drug therapy, taking into account target organ damages and cardiovascular risk levels, are presented in detail in Table 1 (columns "General population" and "Uncomplicated hypertension"). The Finnish Current Care Hypertension (FCCH) guidelines (2002) [12] placed significant importance on target organ damages and other cardiovascular risk factors. Evaluation of cardiovascular risk, particularly in the ESH guidelines (2003) [16], took a very important role instead of a certain BP value in itself. In addition, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) [18], recommended for the first time to initiate treatment of hypertension with a two-drug combination instead of monotherapy if the BP exceeded 160/100 mmHg.

The ESH/ESC guidelines (2007) [19] emphasized individual cardiovascular risk beyond BP level, in the evaluation of treatment strategy. In brief, between 1994 and 2009, the guidelines have moved slowly into more aggressive initiation of antihypertensive pharmacotherapy. There are numerous studies from the past twenty years, which have affected the development of these guidelines and when to initiate antihypertensive drug therapy. Of these McMahon et al. [20], Collins et al. [11], the meta-analysis of Staessen et al. [21], Vasan et al. [22], the meta-analysis of Lewington et al. [23], the STOP trial [24], MRC trial [25], SHEP trial [26], Syst-Eur trial [27], HOT trial [28], VALUE trial [29], FEVER trial [30], and ASCOT trial [31], are the most important. See also Table 2 (Description of major clinical trials of primary hypertensives).

Worth mentioning is also the fact that the guidelines for initiation of antihypertensive medication among uncomplicated hypertensive patients have departed from those for "General" hypertensive patients but not earlier than in the ESH/ESC guidelines published in 2007.

### 2.1.2 Diabetic patients

According to the Finnish Heart Association (FHA) working group recommendation (the current national guideline during the health 2000 Survey) published in 1994 [32], the BP threshold for drug therapy was not separately specified for diabetic patients. The recommendation followed the same principals as made for general hypertensive patients. In 1997, the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC6) [17] gave for the first time a specific recommendation for the initiation of antihypertensive medication for diabetic patients. The JNC6 set the threshold to 130-139 mmHg for systolic BP and 85-89 mmHg for diastolic BP. In 2002, the FCCH guidelines [12] set the BP threshold for drug therapy to 140/90 mmHg for diabetic patients; however, the FCCH guidelines recommended to consider treatment with BP 130-139/85-89 mmHg in the case of Type 1 diabetes or renal failure.

In 2003, ESH guidelines [16] lowered the threshold limit to 130/85 mmHg, and the JNC7 [18] accordingly, to 130/80 mmHg. The FCCH guidelines in 2005 [13], however, kept the previous slightly higher threshold of 140/90 mmHg.

Due to poor and somewhat controversial trial evidence, the ESH guidelines increased the threshold for initiation of drug therapy back to the level of 140/90 mmHg in 2009 [7]. Besides, it reappraised that initiation of BP-lowering treatment in the high normal BP range (130-139/85-89 mmHg) is unsupported by prospective trial evidence unless microalbuminuria or proteinuria is involved. The FCCH guidelines, published in 2009 [14], hold the threshold of 140/90 mmHg for initiation of antihypertensive drug therapy.

In brief, scientific evidence from randomized clinical trials led the guidelines in early 2000s and mid-2000s to recommend lowering the BP target for diabetic patients. Consequently, this forced to earlier initiation of antihypertensive treatment in addition to lifestyle modifications. Recommendations favouring more aggressive treatment were probably generated by some trials, such as the HOT trial [28], and the

post hoc analyses of the Syst-Eur trial [33]. There are numerous other studies made in the course of the past twenty years, which have directly or indirectly affected the development of these guidelines. Collins et al. [11], Peterson et al. [34], Curb et al. 1996 [35], UKPDS38 [36], UKPDS39 [8], ABCD [37-39], the MICRO-HOPE substudy [40], the FEVER trial [30], and the ADVANCE trial, are the most important.
Nonetheless, after the publication of recent guidelines, there is evidence that no benefit has been achieved for diabetic patients if the systolic BP is intensively lowered below 130 mmHg [41, 42], or below 120 mmHg [43], as compared with those with a target systolic BP <140 mmHg. According to the meta-analysis of Sarwar et al. [44] diabetes itself doubles the risk of vascular disease, independent of other conventional risk factors.

Description of major clinical trials concerning hypertension and diabetes is shown in Table 3. See also Table 1 (BP thresholds for drug therapy according to guidelines from 1994 to 2009, column “DM”).

### 2.1.3 Coronary heart disease patients

Specific threshold values for systolic and diastolic BP, in the treatment guidelines between 1994 and 2009, for initiating drug therapy for hypertensive CHD patients, are presented in detail in Table 1, column “CHD”. In brief, BP threshold values for initiation of antihypertensive drug therapy for CHD patients have been in line with those for diabetic patients. However, the threshold slightly differs between these two groups of patients in some of the guidelines [12, 13, 45], as shown in Table 1. According to the FHA work group recommendation (1994) [32], the BP threshold for drug therapy was not separately specified for CHD patients and therefore followed the same principles as those for general hypertensive patients. In the early and mid 2000s, the FCCH guidelines [12, 13] set the threshold BP for drug therapy for CHD to 140/90 mmHg, while the ESH guidelines (2003) set the threshold 10/5 mmHg lower than the FCCH guidelines. Several studies have been published during the last few decades which are responsible for the development of the guidelines with respect to initiation of antihypertensive drug therapy for CHD patients. Some of these are already referred to in previous chapters; however, the HOPE trial [46], EUROPA trial [47], CAMELOT study [48], ACTION trial [49], VALUE trial [29], and PEACE trial [50], are the ones most important. See Table 4 (Description of major clinical trials concerning hypertension and CHD).

Nonetheless, the ESH/ESC guidelines (2007) [19] recommended to consider initiation of drug therapy sometimes even at normal BP values, such as 120-129/80-84 mmHg. Similarly, for diabetics, in case of CHD patients, these recommendations have been reconsidered due to scant and somewhat controversial trial evidence described widely in recent ESH guidelines in 2009 [7].

**Table 1. BP thresholds for drug therapy according to guidelines from 1994 to 2009**

| Guideline | Year | General population | DM | CHD | Uncomplicated hypertension | Remarks |
|---|---|---|---|---|---|---|
| **FHA w.g.** (32) | **1994** | **DBP 120 for few days<br>180/110-119 for ~ 1 month †<br>160-179/100-109 for 3-6 monhts ‡<br>DBP 90-99 for 6-12 months ¥** | ***not specified*** | ***not specified*** | ***not specified*** | **† start earlier with DBP 110-119 if organ damages<br>‡ start in 3(4) months if organ damages<br>‡ start in 4-6 months with DBP 100 without organ damages<br>¥ if organ damages, diabetic nephropathy or other CV risk factors** |
| **JNC6** (17) | 1997 | 160/100<br>140-159/90-99 * | 130-139/85-89 | 130-139/85-89 | 160/100<br>140-159/90-99 * | *after 12 months if non-pharmacologic therapy inssufficient |
| **WHO-ISH** (45) | 1999 | 150/95 * | 140/90 | 140/90 † | 150/95 * | * after 6-12 months if low-risk patient (CV event risk <15%/10y)<br>† if medium risk patient (CV event risk 20-30%/10y) |
| **BHS** (51) | 1999 | 160/100<br>140-159/90-99 * | 140/90 | 140/90 | *not specified* | * if target organ damage present |
| **FCCH** (12) | 2002 | 160/100 *<br>140-159/90-99 † | 140/90<br>130-139/85-89 ‡ | 140/90 | *not specified* | *in repeated measurements; † consider drug therapy after lifestyle interventions if CHV risk 20% /10year; ‡ consider treatment if DM1 or kidney failure; |
| **ESH** (16) | 2003 | 180/110 for few days *<br>140-179/90-109†<br>130-139/85-89‡ | 130/85 | 130/85 | *not specified* | * immediately; † promptly if high risk patient, within 3 monts if moderate risk patient and consider drug therapy if low risk patient; ‡ if high risk patient |
| **JNC7** (18) | 2003 | 140-159/90-99<br>160/100 * | 130/80 | *not specified* | *not specified* | * start with 2-drug combination |
| **BHS** (52) | 2004 | 160/100<br>140-159/90-99 * | 140/90 | 140/90 | *not specified* | *if CV complications or TOD or DM or CV-risk ≥20% per 10y |
| **FCCH** (13) | **2005** | **160/100 *<br>140-159/90-99 †** | **140/90<br>130-139/85-89 ‡** | **140/90** | ***not specified*** | *** in repeated measurements; † consider drug therapy if risk of CV death after lifestyle interventions 5% / 10y; mediation of lifestyle changes and other risk factors; ‡ consider treatment if DM1 or kidney failure;** |
| **ESH/ESC** (19) | 2007 | 180/110 *<br>140-179/90-109 † ‡<br>140-159/90-99 ¥ | 130/85 | 130/85<br>(120/80)£ | 180/110 *<br>160-179/100-109 §<br>140-159/90-99 # | *promptly; § after several weeks; # after several months<br>† promptly if CV risk high or very high; ‡ after several weeks if CV risk mod.; ¥ after several months if no other RF; £sometimes |
| **ESH** (7) | 2009 | 160/100 *<br>140-159/90-99† ‡ | 140/90<br>130-139/85-89§ | 140/90 ¥ | *not specified* | *promptly; † after a suitable period with with lifestyle changes if low or moderate CV risk; ‡ promptly if CV risk high; §unsupported by prospective trial evidence, unless if microalbuminuria or proteinuria; ¥controversial evidence |
| **FCCH** (14) | 2009 | 160/100<br>140/90*<br>140/90 † | 140/90<br>130-139/85-89 ‡ | 140/90 | *not specified* | * if DM, renal disease, TOD, clinically significant cardiovascular disease;<br>† consider therapy after non-pharmacologic treatment if >140 and risk of CV death >5% / 10y; ‡ consider treatment if DM1 or kidney failure |

FHA w.g., Finnish Heart Association working group; JNC6, The Sixth Report of the Joint National Committee; WHO-ISH, World Health Organization - International Society of Hypertension; BHS, British Hypertension Society; FCCH, Finnish Current Care Hypertension; ESH, European Society of Hypertension; JNC7, The Seventh Report of the Joint National Committee; ESC, European Society of Cardiology; DBP, diastolic blood pressure; CV, cardiovascular; TOD, target organ damage; DM, diabetes mellitus; CHD, coronary heart disease; RF, risk factor

**Table 2. Description of major clinical trials of primary hypertensives**

| Trial | Publ. | Population | Study design |
|---|---|---|---|
| STOP (24) | 1991 | HBP; 70-84y | Active treatment (BBs and D) vs. plasebo |
| SHEP (26) | 1991 | ISH ; ≥60y | Active treatment (THZ ,BB) vs. plasebo |
| MRC (53) | 1992 | HBP; 65-74y | Diuretic vs. plasebo, BB vs. plasebo |
| SYST-EUR (27) | 1997 | ISH ; ≥60y | Active treatment (Nitrendine-based) vs. plasebo |
| VHAS (54) | 1997 | HBP | Verapamil vs. chlorthalidone |
| HOT (28) | 1998 | HBP | DBP≤80 vs ≤85 vs ≤90 mmHg |
| UKPDS 38 (36) | 1998 | HBP+DM | DBP <85 vs. < 105mmHg |
| UKPDS 39 (8) | 1998 | HBP+DM | Captopril vs. atenolol |
| CAPPP (55) | 1999 | HBP; 25-66y | Captopril-based vs. conventional (D and/or BB) |
| NORDIL (56) | 2000 | DBP≥100; 50-74y | Diltiazem-based vs. D and/or BB |
| INSIGHT (57) | 2000 | HBP; 55-80y | Long-acting nifedipine vs. HCTZ+amiloride |
| LIFE (58) | 2002 | ISH+LVH | Losartan-based vs atenolol-based |
| ALLHAT (59) | 2002 | HBP+≥1RF | Amlodipin vs. lisinopril vs. chlothalidone |
| ELSA (60) | 2002 | HBP | Lacidipine vs. atenolol |
| ANBP2 (61) | 2003 | HBP; 65-84y | Enalapril vs HCTZ (as add-on therapy) |
| SCOPE (62) | 2003 | HBP; 70-89y | Candesartan-based vs. plasebo |
| ALPINE (63) | 2003 | HBP; (newly detected) | Candesartan±felodipine vs. HCTZ±atenolol |
| VALUE (29) | 2004 | HBP+high CV risk;>50y | Valsartan vs. amlodipin |
| FEVER (30) | 2005 | HBP+1-2RF | HCTZ+felodipin vs. HCTZ+plasebo |
| ASCOT (31) | 2005 | HBP+≥3RF; 40-79y | CCB+ACE vs. BB+D |
| CAFE (64) | 2006 | HBP+≥3RF; 40-79y | BB±D-based vs. CCB±ACE-based |
| HYVET (65) | 2008 | SBP≥160 and ≥80y | Indapamide (±perindopril) vs. plasebo |
| ACCOMPLISH (66) | 2008 | HBP+high CV risk | ACE+CCB vs. ACE+D |
| ONTARGET (67) | 2008 | CVD or high risk DM;(69%HT) | Ramipril vs. telmisartan vs. both |

Abbreviations of the trials are described on "Abbreviations". HBP, high blood pressure; ISH, isolated systolic hypertension; DM, diabetes mellitus; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; SBP, systolic blood pressure; RF, risk factor; CV, cardiovascular; DBP, diastolic blood pressure; BB, beta-blocker; D, diuretic; THZ, thiazide; HCTZ, hydrochlorthiazide; CCB, calcium channel blocker; ACE, angiotensin converting enzyme; CVD, cardiovascular disease

**Table 2 (continued)**

| Trial | Primary message briefly | Secondary message friefly |
|---|---|---|
| STOP (24) | Active treatment reduced fatal or nonfatal strokes, MI and CV deaths | High BP in elderly should be treated with antihypertensive drugs |
| SHEP (26) | Low-dose chlorthalidone reduced incidence of stroke by 36% | Major CV event reduced, with 5y absolute benefit of 55 events per 1000 |
| MRC (53) | Diur. reduced risk of stroke by 31%, CV events by 44% and all CV events by 35% | BB showed no significant reductions in these endpoints |
| SYST-EUR (27) | Nitrendipine reduces the rate of cardiovascular complications | |
| VHAS (54) | Similar antihypertensive efficacies and cardiovascular event rates | More hyperuricemia and hypokalemia with chlorthalidone |
| HOT (28) | Intensive lowering of BP ↓ to 82.6mmHg associated with a low rate of CV events | ≤80 vs ≤90: 51% reduction in major CV events with diabetics |
| UKPDS 38 (36) | Tight BP control reduces risk of death and complications related to diabetes | |
| UKPDS 39 (8) | Similarly effective in reducing the incidence of diabetic complications | BP reduction in itself may be more important than the treatment used |
| CAPPP (55) | ACE as effective as conventional treatment (D/ BB or both) | Incidence of DM2 lower in captopril group |
| NORDIL (56) | CCB as effective as treatment based on Ds, BBs, or both in preventing CV events | In both arms drugs were equally tolerated |
| INSIGHT (57) | Both equally effective in preventing CV or cerebrovascular events | Choice of drug can be decided by tolerability and BP response |
| LIFE (58) | ARB prevents more CV morbidity and mortality, especially stroke and CV death | New-onset diabetes was less frequent with losartan |
| ALLHAT (59) | No difference in prim. outcomes; in secondary outcomes diur better than ACE | RRR of developing DM2 highest with lisinopril |
| ELSA (60) | No significant difference between treatments was found in any CV events | Clinic BP reductions were identical with both treatments |
| ANBP2 (61) | ACE-based therapy superior in older men | BP reduction similar in both arms |
| SCOPE (62) | Market reduction of non-fatal strokes with candesartan | No signific. difference in MI, CV mortality, MMSE or cognitive function |
| ALPINE (63) | Diuretic-based treatment was associated with an aggravated metabolic profile | ARB-based group had less adverse events but no metabol. adverse effects |
| VALUE (29) | No significant difference in main outcomes of cardiac disease | Emphasize the importance of prompt BP control |
| FEVER (30) | Felodipin group superior in preventing CV morbidity and mortality | SBP <140mmHg superior to that of >140mmHg in preventing CV outcomes |
| ASCOT (31) | CCB+ACE combination superior in reducing CV events | CCB+ACE combination induced less diabetes |
| CAFE (64) | BB±D-based therapy less effective than CCB±ACE at lowering central BP | For the same brachial BP, central BP may be higher with BBs |
| HYVET (65) | Active treatment reduced fatal or nonfatal strokes by 30% in elderly | |
| ACCOMPLISH (66) | ACE+CCB combination superior in reducing CV events | |
| ONTARGET (67) | ACEs and ARBs have similar outcome benefits | Combination had more adverse events without an increase in benefit |

Abbreviations of the trials are described on "Abbreviations". MI, myocardial infarction; BP, blood pressure; CV, cardiovascular; BB, beta-blocker; RRR, relative risk reduction; DM2, Type 2 diabetes mellitus; ACE, angiotensin convertin enzyme; D, diuretic; CCB, calcium channel blocker; MMSE, mini mental state examination; SBP, systolic BP.

**Table 3. Description of major clinical trials concerning hypertension and diabetes**

| Trial | Publ. | Population | Study design |
|---|---|---|---|
| Lewis et al. (68) | 1993 | IDDM+nephropathy | Captopril vs. placebo |
| SHEP (35) | 1996 | ISH+(NIDDM vs. non-DM ; ≥60y | Low-dose THZ (±BB or reserpine) vs. placebo(±other) |
| HOT (28) | 1998 | HBP (8% had DM) | DBP≤80 vs ≤85 vs ≤90 mmHg |
| UKPDS 38 (36) | 1998 | HBP+DM | DBP <85 vs. < 105 mmHg |
| UKPDS 39 (8) | 1998 | HBP+DM | Captopril vs. atenolol |
| ABCD-HT (37) | 1998 | HBP+NIDDM | (DBP ≤75 vs. 80-89); enalapril vs. nisoldipine |
| FACET (69) | 1998 | HBP+NIDDM | Fosinopril vs. amlodipine |
| SystEur (post hoc) (33) | 1999 | ISH+DM; ≥60y | SBP↓ ≥20 + ≤150mmHg (Active treatment vs. plasebo) |
| CAPPP (55) | 1999 | HBP; 25-66y | Captopril-based vs. conventional (D and/or BB) |
| STOP-2 (70) | 1999 | HBP+DM; 70-84y | Old vs. new anti-HT drugs |
| ABCD (38) | 2000 | HBP+NIDDM | DBP ≤75 vs. 80-89 mmHg; |
| micro-HOPE (40) | 2000 | DM+≥1RF (58%HBP) | Ramipril vs. placebo |
| NORDIL (56) | 2000 | DBP≥100; (7% DM); 50-74y | Diltiazem-based vs. D and/or BB |
| IDNT (71) | 2001 | HBP+DM+nephropathy | Irbesartan vs. amlodipine vs. placebo |
| RENAAL (72) | 2001 | DM+nephropathy | Losartan vs placebo |
| ABCD-NT (39) | 2002 | DM (normotensive) | DBP 10 below baseline vs. 80-89 mmHg |
| ALLHAT (59) | 2002 | HBP+≥1RF (36% had DM) | Amlodipin vs. lisinopril vs. chlorthalidone |
| LIFE (73) | 2002 | HBP+LVH; 55-80y | Losartan-based vs atenolol-based |
| LIFE (74) | 2002 | HBP+DM+LVH; 55-80y | Losartan-based vs atenolol-based |
| IRMA-2 (75) | 2003 | HBP+DM2+U-μAlb | Irbesartan 150mg/300mg vs. placebo |
| HOT (post hoc) (76) | 2003 | HBP+≥medium CV risk | DBP≤80 vs ≤85 vs ≤90 mmHg |
| BENEDICT (77) | 2004 | HBP+DM2 | Trandolapril+verapamil vs. both alone vs. placebo |
| FEVER (30) | 2005 | HBP+1-2RF (>10%DM) | HCTZ+felodipin vs. HCTZ+placebo |
| ASCOT (31) | 2005 | HBP+≥3RF (27% DM); 40-79y | CCB+ACE vs. BB+D |
| CAFE (64) | 2006 | HBP+≥3RF; 40-79y | BB±D-based vs. CCB±ACE-based |
| ADVANCE (78) | 2007 | DM2 (~17%HBP) | Perindopril and indapamide vs. placebo |
| ACCOMPLISH (66) | 2008 | HBP+high CV risk (27% had DM) | ACE+CCB vs. ACE+D |
| ONTARGET (67) | 2008 | CVD or high risk DM | Ramipril vs. telmisartan vs. both |
| TRANSCEND (79) | 2008 | High risk (75%CHD,36%DM) | Telmisartan vs. placebo (as add-on therapy) |
| ACCORD (43) | 2010 | DM2 | SBP<120 vs. <140 mmHg |

Abbreviations of the trials are described on "Abbreviations". MI, myocardial infarction; BP, blood pressure; CV, cardiovascular; IDDM, insulin dependent diabetes mellitus; NIDDM, non-insulin dependent diabetes mellitus; HBP, high blood pressure; DM, diabetes mellitus; ISH, isolated systolic hypertension; RF, risk factor; LVH, left ventricular hypertrophy; μAlb, mikroalbuminuria; CVD, cardiovascular disease; THZ, thiazide; DBP, diastolic blood pressure; HCTZ, hydrochlorthiazide; SBP, systolic blood pressure; BB, beta-blocker; DM2, Type 2 diabetes mellitus; ACE, angiotensin convertin enzyme; D, diuretic; CCB, calcium channel blocker;

**Table 3. (continued)**

| Trial | Primary message briefly | Secondary message briefly |
|---|---|---|
| Lewis et al. (68) | Captopril protects against deterioration in renal function | The protection is significantly more effective than BP control alone |
| SHEP (35) | Low-dose chlorthalidone effective in preventing major CV events | Absolute risk reduction with active treatment twice as great for DM than non-DM |
| HOT (28) | Intensive lowering of BP down to 82.6mmHg associated with a low rate of CV events | ≤80 vs ≤90: 51% reduction in major CV events with diabetics |
| UKPDS 38 (36) | Tight BP control reduces risk of death and complications related to diabetes | |
| UKPDS 39 (8) | Similarly effective in reducing the incidence of diabetic complications | BP reduction in itself may be more important than the treatment used |
| ABCD-HT (37) | ACE superior in preventing fatal and non-fatal MI | |
| FACET (69) | Fosinopril superior in preventing major vascular events | Both had similar effects on biochemical measures |
| SystEur (post hoc) (33) | Active treatment particularly beneficial in older patients with DM and ISH | Does not support that CCB harmful for diabetics |
| CAPPP (55) | ACE as effective as conventional treatment (D/ BB or both) | Incidence of DM2 lower in captopril group |
| STOP-2 (70) | Old and new: similar in prevention of cardiovascular mortality or major events | Decrease in BP is most important in preventing CV events |
| ABCD (38) | More intensive BP control decreased all-cause mortality | No difference on the incidence and progression of microalbuminuria |
| micro-HOPE (40) | Ramipril has beneficial vasculoprotective and renoprotective effects | The benefit exceeded that attributable to changes in BP |
| NORDIL (56) | Diltiazem as effective as treatment based on Ds, BBs, or both in preventing CV events | Both arms were equally well tolerated |
| IDNT (71) | Irbesartan superior in protecting the progression of diabetic nephropathy | This protection is independent of the reduction in BP |
| RENAAL (72) | Losartan conferred significant renal benefits (but no effect on the rate of death) | The benefit exceeded that attributable to changes in BP |
| ABCD-NT (39) | More intensive control decreased development and progression of nephropathy | More intensive: decreased incidence of stroke and the progression of retinopathy |
| ALLHAT (59) | No difference in prim. outcomes; in secondary outcomes diur better than ACE | RRR of developing DM2 highest with lisinopril |
| LIFE (73) | Losartan prevents more CV morbidity and death (for a similar BP reduction) | New-onset diabetes was less frequent with losartan which was better tolerated |
| LIFE (74) | Losartan superior in reducing CV morbidity and mortality and death for all cause | Losartan seems to have benefits beyond BP reduction |
| IRMA-2 (75) | Irbesartan significantly reduced proteinuria | Reduction was dose-dependent but independent of the reduction in BP |
| HOT (post hoc) (76) | Aggressive therapy most beneficial in diabetics | |
| BENEDICT (77) | ACE+verapamil as efective as ACE alone in preventing microalbuminuria | |
| FEVER (30) | Felodipin group superior in preventing CV morbidity and mortality | SBP <140mmHg superior to that of >140mmHg in preventing CV outcomes |
| ASCOT (31) | CCB+ACE combination superior in reducing CV events | CCB+ACE combination induced less diabetes |
| CAFE (64) | BB±D-based therapy less effective than CCB±ACE at lowering central BP | For the same brachial BP, central BP may be higher with BBs |
| ADVANCE (78) | Combination reduced the risks of major vascular events, including death | Benefit seen irrespective of initial BP level |
| ACCOMPLISH (66) | ACE+CCB combination superior in reducing CV events | |
| ONTARGET (67) | ACEs and ARBs have similar outcome benefits | Combination had more adverse events without an increase in benefit |
| TRANSCEND (79) | Telmisartan had no significant effect on primary outcome | ARB modestly reduced risk of composite outcome of CV death, MI, or stroke |
| ACCORD (43) | Tight BP control did not reduce fatal or non-fatal CV events | |

Abbreviations of the trials are described on "Abbreviations". HBP, high Blood pressure; ISH, isolated systolic hypertension; DM, diabetes mellitus; RRR, relative risk reduction; CV, cardiovascular; DBP, diastolic blood pressure; MI, myocardial infarction; BB, beta-blocker; D, diuretic; CCB, calcium channel blocker; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; SBP, systolic blood pressure

**Table 4. Description of major clinical trials concerning hypertension and CHD**

| Trial | Publ. | Population | Study design |
|---|---|---|---|
| HOPE (46) | 2000 | (CHD/CVD/DM) + RF | Ramipril vs. placebo |
| PART-2 (80) | 2000 | HCD/TIA/intermitt.claudication | Ramipril vs. placebo |
| DAVIT I+II,MDPIT (81) | 2001 | HBP+ post-MI | Diltiazem/Verapamil vs. placebo |
| QUIET (82) | 2001 | CHD+LVEF≥40% | Quinapril vs. placebo |
| ALLHAT (59) | 2002 | HBP+≥1RF | Amlodipin vs. lisinopril vs. chlothalidone |
| ELSA (60) | 2002 | HBP | Lacidipine vs. atenolol |
| OPTIMAAL (83) | 2002 | CHD+MI+CHF | Losartan vs. Captopril |
| INVEST (84) | 2003 | HBP+CHD; >50y | Verapamil+ACE-based vs. BB+HCTZ-based |
| EUROPA (47) | 2003 | CHD (27%HBP) | Perindopril vs. placebo (after wash-out) |
| VALIANT (85) | 2003 | MI+(LVEF<35%/CHF/both) | add-on: (valsart. vs. valsart.+captopr. vs. captopr.) |
| PEACE (50) | 2004 | CHD+LVEF>40% | (Trandolapril vs. placebo)+ other drugs |
| JMIC-B (86) | 2004 | HBP+ CHD;<75y | Nifedipine vs. ACE |
| CAMELOT (48) | 2004 | CHD+NBP | Amlodipin vs. enalapril vs. placebo |
| VALUE (29) | 2004 | HBP+high CV risk;>50y | Valsartan vs. amlodipin |
| ACTION (49) | 2005 | HBP+stable angina | Nifedipine vs. placebo in NT- vs. HT-patients |
| FEVER (30) | 2005 | HBP+1-2RF (>10%CHD) | HCTZ+felodipin vs. HCTZ+placebo |
| JIKEI Heart (87) | 2007 | HBP+CVD | (Valsartan vs. non-ARB therapy)+other drugs |
| ACCOMPLISH (66) | 2008 | HBP+high CV risk | ACE+CCB vs. ACE+D |
| ONTARGET (67) | 2008 | CVD or high risk DM | Ramipril vs. telmisartan vs. both |
| INVEST substudy (88) | 2008 | HBP+CHD+MI; >50y | Verapamil-sustained release vs. atenol-based |
| TRANSCEND (79) | 2008 | High risk (75%CHD,36%DM) | Telmisartan vs. placebo (as add-on therapy) |
| Cooper-DeHoff et al. (41) | 2010 | HBP+CHD+DM | SBP<130 vs. 130-139 vs. ≥140 mmHg |

Abbreviations of the trials are described on "Abbreviations". CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; RF, risk factor; HBP, high blood pressure; MI, myocardial infarction; BP, blood pressure; CV, cardiovascular; TIA, trans ischaemic attack; BB, beta-blocker; DM2, Type 2 diabetes mellitus; LVEF, left ventricular ejection fraction; CHF, chronic heart failure; NBP, normal blood pressure; HCTZ, hodrochlorthiazide; HT, hypertensive; NT, normotensive; ACE, angiotensin converting enzyme; D, diuretic; CCB, calcium channel blocker; SBP, systolic blood pressure;

**Table 4. (continued)**

| Trial | Primary message briefly | Secondary message briefly |
|---|---|---|
| HOPE (46) | Ramipril reduces rates of death, MI, and stroke | |
| PART-2 (80) | ACE inhibitor showed no benefits on major CV events | ACE reduced signific. more BP and LV mass in nonhypertensive patients |
| DAVIT I+II,MDPIT (81) | HR lowering CCB decrease event rates (without pulmonary congestion) | With pulmonary congestion, event rates were increased |
| QUIET (82) | NS difference in clin. outcomes or progression of coronary atheroscler. | ACE was well tolerated |
| ALLHAT (59) | NS difference in prim. outcomes; in sec. outcomes D better than ACE | RRR of developing DM2 highest with lisinopril |
| ELSA (60) | NS difference between treatments was found in any CV events | Clinic BP reductions were identical with both treatments |
| OPTIMAAL (83) | NS difference in total mortality | Losartan better tolerated, however, ACE should remain first-choice after MI |
| INVEST (84) | CCB+ACE-based as clinically efective as BB+HCTZ-based | BP control 71.7% and 70.7% |
| EUROPA (47) | Perindopril significantly improves outcome | On top of other prevent. medications, should be consid. to all CHD patients |
| VALIANT (85) | Valsartan as effective as captopril | Combination increased adverse events without improving survival |
| PEACE (50) | No CV benefit from the addition of ACE inhibitor | |
| JMIC-B (86) | No difference in reducing cardiac events and mortality | |
| CAMELOT (48) | Amlodipin reduced adverse CV events | For amlodipine, IVUS showed slowing of atherosclerosis progression |
| VALUE (29) | No significant difference in main outcomes of cardiac disease | Emphasize the importance of prompt BP control |
| ACTION (49) | Nifedip. effective in controlling high BP and reducing major vasc. events | Supports the emphasis of BP control |
| FEVER (30) | Felodipin group superior in preventing CV morbidity and mortality | SBP <140mmHg superior to that of >140mmHg in preventing CV outcomes |
| JIKEI Heart (87) | Valsartan+convent. therapy prevented more CV events than convent.therapy | Mortality and tolerability did not differ |
| ACCOMPLISH (66) | ACE+CCB combination superior in reducing CV events | |
| ONTARGET (67) | ACEs and ARBs have similar outcome benefits | Combination had more adverse events without an increase in benefit |
| INVEST substudy (88) | Verapamil-SR-based equival. to BB-based for BP control and prevent. CV events | Verapam. group had greated subj. feeling of well-being than BB-based group |
| TRANSCEND (79) | Telmisartan had no significant effect on primary outcome | ARB modestly reduced risk of composite outcome of cv death, MI, or stroke |
| Cooper-DeHoff (41) | Tight BP control not superior to usual control in preventing CV outcomes | Tight BP control superior to uncontrolled in preventing CV outcomes |

Abbreviations of the trials are described on "Abbreviations". CV, cardiovascular; DM2, Type 2 diabetes mellitus; BP, blood pressure; LV, left ventricular; RRR, relative risk reduction; CHD, coronary heart disease; MI, myocardial infarction; BP, blood pressure; SR, sustained release; IVUS, intravascular ultrasound; SBP, systolic blood pressure; BB, beta-blocker; HCTZ, hydrochlorthiazide; ACE, angiotensin convertin enzyme; D, diuretic; CCB, calcium channel blocker; ARB, angiotensin receptor blocker; HR, heart rate; NS, non significant

## 2.2 Target blood pressure according to guidelines

### 2.2.1 Patients with essential hypertension (including uncomplicated hypertensive patients)

In the early nineties, the FHA working group recommendation [32] set the overall target of BP below 160/90 mmHg. However, it stated that the desirable BP for all patients should be below 130/85 mmHg. Accordingly, the World Health Organization – International Society of Hypertension (WHO-ISH) guideline [45], which was the current international guideline during the Health 2000 Survey, recommended that the target BP be below 140/90 mmHg. However, for young and middle-aged patients, it was remarked that the desirable BP should remain below 130/85 mmHg.

The general BP target below 140/85 mmHg for all hypertensive subjects was set by the FCCH guidelines in 2002 [12]. The JNC7 [18], as well as the ESH/ESC retained the target BP below 140/90 mmHg for all hypertensive patients in their guidelines published in 2003 [16]. However, the guidelines recommended even lower values for all, if tolerated. The FCCH guidelines, updated in 2005 [13], retained the target BP of less than 140 mmHg for systolic BP and less than 85 mmHg for diastolic BP, which was at that time the evidence-based target. For uncomplicated hypertensive s, the FCCH guidelines in 2005 retained the same target BP.

Due to lack of trial evidence, especially for elderly patients, in 2009 the ESH guidelines [7] reappraised the target BP to 130-139/80-85 mmHg, even for those at high cardiovascular risk.

There have been several studies in the past 15-20 years, which have lead into above recommendations. Among these, Collins et al. 1990 [11], McMahon et al. [20], Lewington et al. [23], Vasan et al. [22], and a few randomized clinical trials (Table 2), of which especially Syst-Eur [27], the STOP trial [24], SHEP trial [26], HOT trial [28], VALUE trial [29], and FEVER trial [30] are the ones most important. For details, see Table 2. See also Table 5 (Target of clinical BP according to guidelines from 1994 to 2009, column “General population”).

### 2.2.2 Diabetic patients

According to the FHA working group, the recommendation (1994) for target BP for diabetic patients was as for the general population, below 160/90 mmHg. In 1997 the JNC6 [17] and in 1999 the WHO-ISH [45], both set the target BP below 130/85

mmHg for diabetic patients. Benefits of tight BP control were demonstrated in the HOT trial [28], UKPDS38 [36], UKPDS39 [8], and ABCD trials [38, 39]. Thereafter the FCCH guidelines [12] in 2002 determined a separate BP target, below 140/80 mmHg, although in case of renal disease or significant proteinuria, the target BP was set below 130/80 mmHg.
The JNC7 [18] and ESH guidelines [16] in 2003 lowered the target BP below 130/80 mmHg. An update of the FCCH guidelines [13] in 2005 kept their previous BP goal below 140/80 mmHg for diabetic patients, however, in case of diabetic nephropathy, microalbuminuria, non-diabetic kidney disease, or significant proteinuria, the target was set below 130/80 mmHg.

The ESH guidelines published in 2007 [19], retained the BP target set in 2003.Due to lack of trial evidence the ESH guideline [7] stated in 2009 that the target BP 130-139/80-85 mmHg for all, including high risk patients as diabetic patients, may be prudent. Although the reappraisal of the ESH guidelines raised heavy criticism due to controversial trial evidence, the target systolic BP for diabetic patients remained below 130 mmHg. Yet, it was stated clearly that SBP below 130 mmHg is not consistently supported by trial evidence. Despite that, during the same year, the Finnish national recommendation [14] lowered the target BP below 130/80 mmHg for diabetic patients and patients with renal disease to be in line with previously updated national guidelines [89] for management of diabetes.

In addition to trials mentioned above, there have also been several other studies which directly or indirectly have guided the development of these recommendations. Among many other studies, such as Collins et al. 1990 [11], Peterson et al. 1995 [34], the post hoc analyses of the Syst-Eur trial [33], and the post hoc subgroup analyses of the HOT trial [76] and FEVER trial [30] are the most important. For details, see Table 3. See also Table 5 (Target of clinical BP according to guidelines from 1994 to 2009, column “DM”). According to recent evidence, which has been published later than these guidelines, no benefit is gained, if the systolic BP is lowered further, below 130 mmHg [41] or below 120 mmHg [43], as compared with those with a target systolic BP <140 mmHg.

### 2.2.3 Coronary heart disease patients

In 1994, the FHA working group [32] recommended a diastolic BP below 90 mmHg as target BP for CHD patients. However, diastolic BP consistently below 85 mmHg was not supported by this recommendation. In 1997, the JNC6 [17] set the target BP below 140/90 mmHg and even lower if angina pectoris was present. The target BP for CHD patients remained below 140/90 mmHg according to guidelines of WHO-

**Table 5. Target of clinical BP according to guidelines from 1994 to 2009**

| Guideline | Year | General population | DM | CHD | Remarks |
|---|---|---|---|---|---|
| **FHA w.g.** (32) | **1994** | **<160/90 *** | ***not specified*** | **DBP<90 †** | ***desirable BP in all <130/85**<br>**† not consistently DBP< 85** |
| **JNC6** (17) | 1997 | <140/90 | <130/85 | <140/90 * | *<140/90 and even lower if angina persists |
| **WHO-ISH** (45) | 1999 | <140/90 | <130/85 | *not specified* | <130/85 desirable in young, middle aged or diabetics |
| **BHS** (51) | 1999 | ≤140/85 | ≤140/80 * | *not specified* | *<140/80 (DM1 and DM2) or lower if proteinuria present (DM1) |
| **FCCH** (12) | 2002 | <140/85 * | <140/80 * | *not specified* | *<130/80 if renal disease or significant proteinuria |
| **ESH** (16) | 2003 | <140/90 * | <130/80 | *not specified* | *<140/90 and definitely lower values if tolerated, for all;<br>home BP 5/5 mmHg lower |
| **JNC7** (18) | 2003 | <140/90 | <130/80 * | *not specified* | *<130/80 also if HT and renal disease |
| **BHS** (52) | 2004 | <140/85 * | <130/80 * | *not specified* | *<140/80 minimum acceptable BP;<br>< 125/75 if proteinuria ≥ 1g/day |
| **FCCH** (13) | **2005** | **<140/85 *** | **<140/80 *** | ***not specified*** | ***<130/80 if diabetic nephropathy, microalbuminuria,**<br>**non-diabetic kidney disease, or significant proteinuria** |
| **ESH/ESC** (19) | 2007 | <140/90 * † | <130/80 † | <130/80 † | *<140/90 and to lower values if tolerated, for all;<br>† <130/80 in high or very high risk patients<br>(MI, renal dysfuntion, proteinuria, stroke) |
| **ESH** (7) | 2009 | 130-139/80-85* | SBP<130 † | SBP 130-139 † | * 130-139/80-85 (incl. high risk patients) may be prudent. Evidence missing in elderly;† SBP<130/80 in diabetics and SBP<130 in patients with high CV risk is not consistently supported by trial evidence |
| **FCCH** (14) | 2009 | <140/85 † ¥ | <130/80 * ¥ | <130/80 ‡ | *<130/80 if kidney disease; ¥ <125/75 if proteinuria<br>(diabetic or non-diabetic) >1g/day; † <150/85 if >80 years of age;<br>‡ only for those suffered from MI or stroke |

FHA w.g., Finnish Heart Association working group; JNC6, The Sixth Report of the Joint National Committee; WHO-ISH, World Health Organization - International Society of Hypertension; BHS, British Hypertension Society; FCCH, Finnish Current Care Hypertension; ESH, European Society of Hypertension; JNC7, The Seventh Report of the Joint National Committee; ESC, European Society of Cardiology; DM, diabetes mellitus; CHD, coronary heart disease; SBP, systolic blood pressure, HT, hypertension; MI, myocardial infarction; CV, cardiovascular; BP, blood pressure; DBP, diastolic blood pressure

ISH in 1999 [45], FCCH in 2002 [12], ESH in 2003 [16], JNC7 in 2003 [18], and FCCH in 2005 [13].

In 2007, for the first time, the ESH/ESC guidelines [19] set the target BP below 130/80 mmHg for patients at high or very high risk, especially for those having suffered MI or stroke.

Several studies have made an impact on the recommendation of tight BP control for CHD patients. The ACTION trial [49], but also the VALUE trial [29], EUROPA trial [47], CAMELOT trial [48], and FEVER trial [30] showed benefits of lowering BP to relatively low levels and are those most important. On the other hand, after the publication of the secondary analyses of data from the INVEST Study [90], the ONTARGET trial [91] and the TNT trial [92], which showed somewhat controversial trial evidence against previous recommendations due to the J-curve phenomenon, the reappraised ESH guidelines in 2009 [7] raised substantial criticism. Consequently, it took a more conservative opinion by stating that the target BP in the range 130-139/80-85 mmHg may be prudent for all, including high risk patients. In 2009, the FCCH guidelines [14] set the target BP below 130/80 mmHg only for those CHD patients who had a history of MI or stroke. For details, see Table 4. See also Table 5 (Target of clinical BP according to guidelines from 1994 to 2009, column "CHD").

After the publication of recent guidelines, there is evidence that no benefit is achieved if the systolic BP is further lowered below 130 mmHg [41] except for those at high risk for stroke, as compared with those with a target systolic BP of <140 mmHg.

## 2.3 Antihypertensive medication according to guidelines

### 2.3.1 Patients with essential hypertension

#### *2.3.1.1 Initial antihypertensive medication*

Initial antihypertensive medication for (essential or primary) hypertension recommended by 12 guidelines from 1994 to 2009, is described in Table 6.

The guidelines of the nineties (FHA working group [32] and JNC6 [17]) recommended initiating antihypertensive medication either with a diuretic or a BB unless contraindicated or there is a specific indication for another drug. In 2002, the FCCH guidelines [12] recommended the initiation of antihypertensive medication with low-dose hydrochloride thiazides, ACE inhibitors, or BBs. Also a CCB, in case of high systolic BP, was recommended as a first line agent. The ESH guidelines in 2003 [16] and the FCCH guidelines in 2005 [13] stated that the treatment of hypertension can be initiated with all major antihypertensive agents, although a low-dose was recommended. However, JNC7 [18], in 2003, recommended starting with a thiazide diuretic. The British Society of Hypertension (BHS) guidelines [52] in 2004 brought out the AB/CD algorithm, which was modified from the Cambridge AB/CD rule [93]. The original Cambridge AB/CD rule recommended initiating antihypertensive medication either with those drugs which inhibit (ACE inhibitors/ARBs or BBs) or with those which do not inhibit (CCBs or diuretics) the renin-angiotensin system. The modified AB/CD algorithm was different for elderly patients and for those younger than 55 years. Moreover, it placed BBs within brackets by not preferring them as first-line agents for the treatment of hypertension, especially for elderly patients.

Thereafter the ESH/ESC in 2007 [19] and ESH in 2009 [7] did not significantly depart from their earlier recommendations, although the role of thiazides was emphasized among diuretics. The ESH guidelines during the 2000s as well as the FCCH guidelines in 2009 [14] indicated initiation with a two-drug combination for a first choice approach as an alternative to monotherapy, especially if BP was markedly elevated. The WHO-ISH [45] and JNC7 [18] did not recommend a short-acting CCB, while the BHS guidelines in 1999 [51] and the ESH/ESC guidelines in 2007 [19] did not recommend high-dose thiazides for the initiation of antihypertensive medication. In addition, BBs, especially non-vasodilating ones, were not recommended as first-line agents by the ESH/ESC guidelines in 2007 [19] and the FCCH guidelines in 2009 [14], especially for patients with a metabolic syndrome or high risk for diabetes.

In the early nineties, three trials, the STOP trial [24], the SHEP trial [26], and the MRC trial [53], showed significant effects in preventing cardiovascular morbidity and mortality when using low-dose diuretics or BBs as initial treatment. The results of prospectively designed overviews of randomized trials of Turnbull et al. [94] and the meta-analysis of Law et al. in 2009 [95] have shown that treatment with any commonly used regimen reduces the risk of total major cardiovascular events. In addition, the Syst-Eur trial [27], CAPPP trial [55], and ONTARGET trial [67] showed the benefits of CCBs, ACE inhibitors, and ARBs as initial treatment of hypertension (Table 2).

On the contrary, 2 meta-analyses, Lindholm et al. [96] and Wiysonge et al. [97], have shown evidence against BBs as a first-line choice in the treatment of primary hypertension. Third meta-analysis, Khan et al. [98] which compared BBs with other drugs, showed that BBs had a similar reduction in endpoints among patients less than 60 years old, but among elderly patients, treatment with BBs was associated with a superior risk of strokes, as compared with other antihypertensive agents. The meta-analysis of Bangalore et al. [99] showed that BBs are associated with an increased risk for new-onset diabetes and with a 15% increased risk for stroke, as compared with other agents. According to Mancia et al. [100] thiazide diuretics seem to have dyslipidaemic and diabetogenic effects when used at high doses. The meta-analysis of Elliot et al. [101] showed that the association with incident diabetes is highest with diuretics, followed by BBs, CCBs, ACE inhibitors, and ARBs.

#### *2.3.1.2 Combination antihypertensive medication*

Combination antihypertensive medication for (essential or primary) hypertension, recommended by 12 guidelines from 1994 to 2009, is described in Table 6.

Since the late nineties, guidelines have emphasized that most hypertensive patients require a combination antihypertensive medication in order to reach the target BP. Most guidelines in the 2000s have emphasized the importance of a low-dose combination rather than increasing the dose of the initial regimen, in order to improve the efficacy and to reduce adverse effects. Practically in all of these guidelines, a diuretic- (or a thiazide)-based treatment has been the cornerstone of combination therapy. A clear trend towards preferring RAS blockers is seen in the guidelines of the late 2000s. Still, since 1999 until 2005, with an exception of the BHS guidelines 2004 [52], a BB plus a diuretic (thiazide in JNC7 [18]) was on the list of recommended 2-drug therapies for initiation of combination antihypertensive medication. On the contrary, BHS guidelines 2004 did not recommend BBs to be used as primary drugs for initiation of combination therapy. Besides, according to recently published ESH guidelines, a BB combined with a thiazide (in ESH/ESC 2007 [19]) or a diuretic (in ESH 2009 [7]) is no longer recommended, particularly in case of a metabolic syndrome or risk of incident diabetes because of higher diabetogenic potential. In the recent guidelines, a combination of an ACE inhibitor and an ARB has become a non-preferred combination. On the other hand, according to recent guidelines, other drugs, such as aliskiren, has become accepted for combination antihypertensive treatment, especially in a multiple approach.

There have been numerous studies in the course of the past couple of decades, which have lead to the combination medication recommended by these guidelines. The meta-analyses of Law et al. in 2003 [6], and of Lindholm et al. [96], the ASCOT [31], ACCOMPLISH [66], ONTARGET [67], LIFE [58], ALPINE [63], FEVER [30], and CAFE trials [64], the meta-analyses of Bangalore et al. [102], and of Wald et al. [103], Calhoun et al. [104], Chapman et al. [105], and Musini et al. [106] are the most important ones (Table 2).

**Table 6. Antihypertensive medication in essential hypertension, according to guidelines from 1994 to 2009**

| | | INITIAL MEDICATION | | | COMBINATION MEDICATION | | | |
|---|---|---|---|---|---|---|---|---|
| Guideline | Year | Recommended (compelling indic.) | Possible indication | Not recommended | Recommended | Possible indication | Not recommended | Remarks |
| **FHA w.g.** (32) | **1994** | **D*, BB†** | ***not specified*** | ***not specified*** | **D+ACE, D+BB<br>DHP-CCB+BB** | **ACE+BB‡** | ***not specified*** | ***low-dose THZ suitable for most patients<br>†not if bradycardia, incompensatory HF, or obstructive pulmonary disease, ‡sometimes** |
| **JNC6** (17) | 1997 | D*, BB* | *not specified* | *not specified* | D+BB * | addition of 2. agent<br>(D if not already used) | *not specified* | * unless no specific indication for other drug |
| **WHO-ISH** (45) | 1999 | D | *not specified* | short-acting CCB | D+BB, D+ACE, D+ARB<br>CCB+BB, alpha+BB | *not specified* | *not specified* | |
| **BHS** (51) | 1999 | low-dose THZ * | *not specified* | high-dose THZ,<br>high-dose HCTZ,<br>nifedipine † | D+BB, D+ACE, BB+CCB<br>CCB+ACE<br>D+ACE+CCB, D+BB+CCB | *not specified* | BB+verapamil or<br>DLZM, ACE+ARB,<br>potas.-spar. D+ACE | *unless there is compelling indication for another drug class<br>† in capsule form |
| **FCCH** (12) | 2002 | D,BB, CCB,<br>ACE | ARB | *not specified* | D+ACE/ARB *, D+BB/alpha†,<br>HCTZ+potassium-sp.D†<br>CCB+ACE/ARB† | BB+CCB§<br>BB+alpha<br>alpha/BB+ACE/ARB‡ | BB+DLZM/verapamil<br>ACE+ARB<br>alpha+CCB | * very good combin.; † good combin.;<br>‡ in specific conditions;<br>§not verapamil or diltiazem |
| **ESH** (16) | 2003 | D*, BB*, CCB*,<br>ACE*, ARB* | combination<br>of 2-drugs<br>at low-doses§ | *not specified* | D+BB, D+ACE/ARB,<br>DHP-CCB+BB, CCB+RAS, CCB+D,<br>alpha+BB, other combinations† | ACE+ARB | *not specified* | * start with low-dose; § if TOD and RF-s<br>†e.g with central agents, incl. a2-adr.rec. agonist and imidzoline $I_2$-2rec. Modulator |
| **JNC7** (18) | 2003 | THZ | ACE/ARB/BB/CCB | short-acting CCB | (THZ +<br>ACE/ARB/BB/CCB)* | *not specified* | *not specified* | *if RR ≥ 160/100<br>should be started<br>as initial therapy |
| **BHS** (52) | 2004 | $ACE_{(1)}$, $ARB_{(1)}$,<br>$CCB_{(2)}$, $THZ_{(2)}$ | $BB_{(1)}$ | potassium-<br>retaining D*,<br>loop-D† | step 2: ACE/ARB+CCB/THZ<br>step 3: ACE/ARB+CCB+THZ<br>step 4: add alpha/spironol./D | (step 2) BB+CCB/THZ<br>(step 3) BB+CCB+THZ<br>(step 4) add alpha/spironol./D | *not specified* | (1) <55y and non-black; (2) ≥55y or black;<br>*except with hyperaldosteronism;<br>†except with impaired renal function and/or HF |
| **FCCH** (13) | **2005** | **ACE*, ARB*, BB*,<br>D*, CCB*** | ***not specified*** | ***not specified*** | **ACE/ARB + D†,<br>ACE/ARB + CCB<br>BB+D†, BB+DHP-CCB** | **ACE/ARB + BB,<br>D† + CCB** | **BB +<br>verapamil/DTZM** | *** star with low-dose<br>†most often thiazide** |
| **ESH/ESC** (19) | 2007 | THZ*‡, CCB*‡, ACE*,<br>ARB*, BB* | initiate 2-drug<br>combination at<br>low-doses§ | non-vasodilating<br>BB†, high-dose<br>THZ | THZ+ACE/ARB/CCB<br>CCB+ACE/ARB<br>BB+DHP-CCB | ARB+ACE/BB, THZ and BB<br>alpha+BB/ACE/ARB/CCB/THZ<br>BB+ACE | THZ and BB† | † if metabolic syndrome or high risk of DM<br>* start with low-dose; ‡ preferred in blacks<br>§if grade 2 or 3 HT or ≥ high CV risk |
| **ESH** (7) | 2009 | THZ(also chlorthalid.<br>and indapamide),<br>BB, CCB or RAS | initiate combination<br>of 2-drugs<br>at low-doses* † | *not specified* | D+ACE/ARB/CCB †<br>ACE/ARB+CCB†,<br>ACE/ARB+CCB+THZ | ACE+ARB‡<br>D+BB §<br>alpha/ BB /aliskiren ¥ | ACE+ARB# | * if HT with high CV risk; †fixed-dose combin. favored; ‡if chronic renal disease or proteinuria; §unless required for other reason; ¥in a multiple approach; # at least in high CV risk |
| **FCCH** (14) | 2009 | ACE/ARB*, BB*†,<br>D*, CCB* | initiate<br>2-drug<br>combination§ | BB† | ACE/ARB+CCB‡,<br>ACE/ARB+THZ<br>ACE/ARB+D+CCB | D+CCB, DHP-CCB+BB | BB+D†<br>ACE+ARB‡<br>BB+DLZM/verapamil | † not recommended if metabolic syndrome or risk of DM; *start with low-dose; ‡ if high risk patient; §if BP markedly elevated or high risk patient |

FHA w.g., Finnish Heart Association working group; JNC6, The Sixth Report of the Joint National Committee; WHO-ISH, World Health Organization - International Society of Hypertension; BHS, British Hypertension Society; FCCH, Finnish Current Care Hypertension; ESH, European Society of Hypertension; JNC7, The Seventh Report of the Joint National Committee; ESC, European Society of Cardiology. BB, beta-blocker; CCB, calcium channel blocker; D, diuretic; ACE, Angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; DHP, Dihydropyridin; alpha, alpha-blocker; THZ, Thiazide diuretic; HCTZ, hydrochlorthiazide; DLZM, diltiazem; TOD, target organ damage; RF, risk factor; DM, diabetes mellitus; CV, cardiovascular; HT, hypertension

## 2.3.2 Diabetic patients

### *2.3.2.1 Initial antihypertensive medication*

Initial antihypertensive medication for diabetic patients, recommended by 12 guidelines from 1994 to 2009, is described in Table 7.

In 1994, the FHA working group guideline [32] recommended ACE inhibitors for initial antihypertensive medication, especially for diabetic nephropathy. With minor exceptions, since the late nineties, a blocker of renin-angiotensin system (whether an ACE inhibitor of an ARB), especially in case of diabetic nephropathy, has been the drug of choice for hypertensive diabetic patients. However, most of the trials before the early 2000s were carried out with ACE inhibitors, and therefore, due to lack of evidence supporting ARBs, ACE inhibitors were favored over ARBs in the JNC6 [17], WHO-ISH [45], and BHS (1999) [51] guidelines. However, probably due to the UKPDS39 trial [8] and the SHEP trial [35], low-dose diuretics and BBs were also classified as possible treatments of choice for initial therapy in the guidelines of the late nineties.  CCBs and alpha-blockers were also stated as possible treatments of choice by the FHA working group guideline in 1994 [32], and by the JNC6 [17] in 1999.

The FCCH guidelines (2002) [12] and (2005) [13], recommended all major antihypertensive agents, although RAS blockers were preferred in the case of diabetic nephropathy. The ESH guidelines (2003) [16] stated that all well tolerated and efficient agents can be used, although the ESH guidelines, also, favored ACE inhibitors for Type 1 diabetic nephropathy, and ARBs for Type 2 diabetic nephropathy. In fact, the ESH guidelines emphasized particularly the renoprotective effects of RAS blockers and stated that microalbuminuria in Type 1 or 2 diabetic patients is an indication for antihypertensive treatment, especially by RAS blockers, irrespective of the blood pressure values. The JNC7 [18], in 2003, recommended BBs only in the case of concomitant ischaemic heart disease, whereas FCCH guidelines, (2005), noted that thiazide diuretics and BBs [107] without intrinsic sympathomimetic activity may increase blood glucose level but improve the diabetic patients prognosis [8]. The BHS guidelines (2004) [52], besides favoring ACE inhibitors for Type 1 diabetic nephropathy and ARBs for Type 2 diabetic nephropathy, noted that BBs should be used with caution except with concomitant CHD.

Since 2007, the guidelines have recommended RAS blockers as a compelling indication for diabetic patients. Still, all major agents were also indicated as options except BBs and thiazides in the ESH/ESC guidelines in 2007 [19] and BBs (unless required for another reason) in the FCCH guidelines [14] in 2009.

Numerous studies have been leading the way for these recommendations during the past couple of decades. The meta-analysis of Pahor et al. [108], the STOP-2 trial [70], NORDIL [56], ABCD [38], ALLHAT [59] and CAPPP trials [55] have shown the benefits of different antihypertensive agents. The benefit of the ACE inhibitors and ARBs, as compared with placebo or other agents was shown in the ABCD [37], FACET [69], micro-HOPE [40], and LIFE trials [74]. The studies of Lewis et al. [68], the IDNT [71], RENAAL [72], and IRMA-II trials [75] concerning the development and/or progression of diabetic nephropathy deserve also mentioning. A description of major clinical trials concerning hypertension and diabetes is shown in Table 3.

### *2.3.2.2 Combination antihypertensive medication*

Combination antihypertensive medication for diabetic patients, recommended by 12 guidelines from 1994 to 2009, is described in detail in Table 7.

The FHA working group guidelines in 1994 [32] recommended diuretics at low doses as a second line drug after initial therapy. In the late nineties and early 2000s, an ACE inhibitor was favored over ARBs, as shown in the BHS guidelines (1999) [51] and JNC7 [18] (2003), although the ESH guidelines [16] (2003) stated that all well-tolerated and efficient agents are indicated. The FCCH guidelines (2002) [12] gave no specific recommendations separately for diabetic patients, concerning initial combination antihypertensive medication. Since the BHS guidelines [52] (2004), the golden standard and a compelling indication in the combination antihypertensive medication for diabetes is that a RAS blocker should be one of the partner drugs of antihypertensive treatment. However, the update of the FCCH guideline in 2005 [13] did not state RAS blockers as compelling indications for the initiation of combination antihypertensive medication for diabetic patients, although it noted the benefits of RAS blocker based medication. Similarly, for patients with essential hypertension, a combination of a diuretic and a BB was still one of the recommended two-drug combinations.

Since 2007, guidelines have not recommended any combination of a diuretic (especially thiazide) and a BB in the treatment of diabetes unless a specific indication (for example concomitant CHD) exists.

These recommendations favoring the use of RAS blockers are based on the LIFE [74], ADVANCE trial [78], and ACCOMPLISH trials [66]. Accordingly, the UKPDS [8], LIFE [74], and ASCOT trials [31] concerning the inferiority of BBs and diuretics, deserve to be pointed out. A description of major clinical trials concerning hypertension and diabetes is shown in Table 3.

After the publication of recent guidelines, there is evidence that no benefit is achieved if Aliskiren is added to standard therapy with renin-angiotensin system blockade for patients with Type 2 diabetes who are at high risk for cardiovascular and renal events [109].

**Table 7. Antihypertensive medication in diabetes according to guidelines from 1994 to 2009**

| | | INITIAL MEDICATION | | | COMBINATION MEDICATION | | | |
|---|---|---|---|---|---|---|---|---|
| **Guideline** | **Year** | **Recommended (compelling indic.)** | **Possible indication** | **Not recommended** | **Recommended indication** | **Possible indication** | **Not recommended** | **Remarks** |
| **FHA w.g.** (32) | **1994** | **ACE*** | **CCB, alpha, BB†, ß1BB ‡** | ***not specified*** | **initial therapy and D (at low doses)** | ***not specified*** | ***not specified*** | *** especially if nephropathy † if concomitant CHD ‡ if IDDM** |
| **JNC6** (17) | 1997 | ACE‡, ARB* | CCB, D (low-dose), alpha | BB, D (high-dose) | *not specified* | *not specified* | *not specified* | * if ACE not tolerated ‡especially if nephropathy |
| **WHO-ISH** (45) | 1999 | ACE | D or BB | *not specified* | *not specified* | *not specified* | *not specified* | |
| **BHS** (51) | 1999 | ACE*, ARB*§ | †ACE, DHP-CCB†, low-dose THZ† or BB† | *not specified* | *ACE+THZ/CCB/BB/alpha | *not specified* | *not specified* | *DM1 § if ACE induced cough † DM2 (only ACE officially stated) |
| **FCCH** (12) | 2002 | ACE†, D, BB, CCB, ARB† | THZ* or BB(non-isa)* | *not specified* | *not specified* ‡ | *not specified* ‡ | *not specified* ‡ | *might increase glucose level †1-line agent in diabetic nephropathy because decrease proteinuria; ‡ see Table 6 |
| **ESH** (16) | 2003 | ACE*‡, ARB†‡ | all well tolerated and effective agents | *not specified* | all well tolerated and effective agents | *not specified* | *not specified* | * Type 1 diabetic nephropathy † Type 2 diabetic nephropathy or diabetic microalbuminuria; ‡ if microalbuminuria |
| **JNC7** (18) | 2003 | D†, BB*‡, ACE, ARB, CCB | *not specified* | *not specified* | ACE+D, initial therapy + BB/ CCB | *not specified* | *not specified* | *in ischaemic heart disease † notice: worsen hyperglycemia ‡ notice: worsen insulin sensitivity |
| **BHS** (52) | 2004 | ACE*, ARB†$ | ACE‡ | (BB)§ | ACE/ARB as as part of drug therapy | initial therapy + long acting-CCB/BB/alpha; low-dose THZ/CCB/BB/alpha¥* | | * DM1 nephropathy; † DM2 nepthropathy; $ in DM1 nephropathy if ACE not tolerated; ‡ DM2; §caution except with CHD;¥ add-on drugs |
| **FCCH** (13) | **2005** | **ACE*, ARB*, D†, BB†, CCB** | ***not specified*** | ***not specified*** | ***not specified* ‡** | ***not specified* ‡** | ***not specified* ‡** | *** initial drugs if diabetic nephropathy † Thiazide-diuretics and BBs (non-isa) might increase blood glucose level; ‡ see Table 6** |
| **ESH/ESC** (19) | 2007 | ACE, ARB | all major agents | BB or thiazide | ACE/ARB as part of drug therapy | initial therapy + all other major agents | THZ + BB | |
| **ESH** (7) | 2009 | ACE, ARB | all major agents | *not specified* | ACE/ARB as part of drug therapy | *not specified* | D + BB* | * unless required for other reason |
| **FCCH** (14) | 2009 | ACE, ARB† | all major agents‡ ( BB*) ‡ | BB* | ACE/ARB + D ACE + CCB loop-D as part of therapy§ | *not specified* ¥ | BB + D | † especially if diabetic nephropathy; * unless required for other reason; ‡ proven to improve prognosis; § if nephropathy; ¥ see Table 6 |

FHA w.g., Finnish Heart Association working group; JNC6, The Sixth Report of the Joint National Committee; WHO-ISH, Wortd Health Organization - International Society of Hypertension; BHS, British Hypertension Society; FCCH, Finnish Current Care Hypertension; ESH, European Society of Hypertension; JNC7, The Seventh Report of the Joint National Committee; ESC, European Society of Cardiology; BB, beta-blocker; CCB, calcium channel blocker; D, diuretic; ACE, Angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; DHP, Dihydropyridin; ß1, Beta-1-selectiv; THZ, Thiazide diuretic; alpha, alpha-blocker; IDDM, Insulin dependent diabetes mellitus; DM1, Type 1 diabetes mellitus; DM2, Type 2 diabetes mellitus; CHD, coronary heart disease

### 2.3.3 Coronary heart disease patients

#### *2.3.3.1 Initial antihypertensive medication*

Initial antihypertensive medication for CHD patients, recommended by 12 guidelines from 1994 to 2009, is described in Table 8.

According to the Finnish national guidelines, [12, 13, 32], BB has been a drug of choice for the hypertensive CHD patients. On the other hand, JNC6 [17], BHS guidelines (1999) [51], JNC7 [18], as well as the ESH guidelines (2003) [16], have recommended BBs to be used as primary drugs for hypertensive CHD patients in case of angina and/or after myocardial infarction. Their advantage was clearly shown in the meta-analysis of Freemantly et al. [110]. The status of CCB has varied since the nineties, depending on which type of CCB is concerned, as shown in Table 8. Since JNC6 [17], with an exception of BHS guidelines (1999) [51] and FCCH guidelines in 2002 [12] and 2005 [13], ACE inhibitors as antihypertensive drugs have been a compelling indication for CHD after MI. On the contrary, the FCCH guidelines in 2002 [12] and 2005 [13] did not recommend their use as compelling indications until in the most recent guidelines in 2009 [14]. ARBs have become competitive drugs to ACE inhibitors since the ESH/ESC guidelines in 2007, although the FCCH guidelines in 2009 [14] have recommended their use in case an ACE inhibitor is not tolerated.

There have been numerous studies in the course of the past couple of decades, which have been leading the development of these guidelines. Furberg et al. [111] showed the disadvantage of short-acting CCBs in moderate to high doses, while Messerli et al. [81] showed the benefit of verapamil and diltiazem. The JMIC-B showed no difference in the reduction of cardiac events and mortality with nifedipine as compared with ACE inhibitors. The meta-analysis of Al-Mallah et al. [112], which included 6 randomized clinical trials: The HOPE [46], EUROPA [47], PEACE [50], QUIET [82], PART-2 [80], and CAMELOT [48] trials showed a modestly favorable effect of ACE inhibitors as compared with placebo, for CHD patients with preserved left ventricular function. The OPTIMAAL [83], VALIANT [85], and ONTARGET trials [67] (40% of CHD patients) have shown more or less similar benefits with ARBs as compared with ACE inhibitors. Neither the ALLHAT trial [59] (in which more than 50% had a history or signs of atherosclerotic cardiovascular disease) showed any significant difference in primary outcomes between the treatment with chlorthalidone, amlodipine, and lisinopril, although treatment with a thiazide-type diuretic was superior to an ACE inhibitor at preventing secondary outcomes. A description of major clinical trials concerning hypertension and CHD is shown in Table 4.

### *2.3.3.2 Combination antihypertensive medication*

Combination antihypertensive medication for CHD patients, recommended by 12 guidelines from 1994 to 2009, is described in detail in Table 8.

A limited number of guidelines have specified recommendations for combination antihypertensive medication for CHD patients, as shown in Table 8. Typical to these few specified recommendations (including the Finnish national guidelines [12, 14, 32]) is that BB is the base of the treatment. Two of the most recent international guidelines [7, 19] have stated that all major antihypertensives are acceptable for initiation of drug therapy as for CHD patients, although drugs in combination therapy were not specified. On the other hand, the FCCH guidelines in 2002 [12] recommended a combination of a BB and a low-dose diuretic, whereas JNC7 [18] mentioned that long-acting dihydropyridine-CCBs are preferred for combination therapy with BBs.
In the INVEST trial [84], a verapamil together with an ACE inhibitor-based treatment was clinically efficient as a BB plus a hydrochlorthiazide-based treatment. A description of major clinical trials concerning hypertension and CHD patients is shown in Table 4.

**Table 8. Antihypertensive medication in coronary heart disease, according to guidelines from 1994 to 2009**

| | | INITIAL MEDICATION | | | COMBINATION MEDICATION | | | |
|---|---|---|---|---|---|---|---|---|
| **Guideline** | **Year** | **Recommended (compelling indic.)** | **Possible indication** | **Not recommended** | **Recommended (compelling indic.)** | **Possible indication** | **Not recommended** | **Remarks** |
| **FHA w.g.** (32) | **1994** | **BB** | **CCB*** | ***not specified*** | **BB+D, DHP-CCB+BB** | ***not specified*** | ***not specified*** | ***if BB contraindicated** |
| **JNC6** (17) | 1997 | BB (non-isa) †, ACE (with systolic dysfunction)† | BB‡, CCB‡, verapamil*/ diltiazem* | short-acting CCB | *not specified* | *not specified* | *not specified* | † after MI; * if BB contraindicated ‡ if angina |
| **WHO-ISH** (45) | 1999 | BB *, ACE†, CCB‡ | *not specified* | *not specified* | *not specified* | *not specified* | *not specified* | * after MI or if angina †after MI ‡ if angina |
| **BHS** (51) | 1999 | BB* CCB (rate-limiting)† | CCB (rate-limiting)‡, DPH-CCB† | *not specified* | *not specified* | *not specified* | CCB(rate-limiting) + BB | *after MI or if angina † if angina ‡after MI |
| **FCCH** (12) | 2002 | BB | ACE† | fast-acting CCB* | BB+low-dose D | *not specified* | *not specified* | *might increase ischaemia and risk of MI; † if diabetes or other CV risk factor |
| **ESH** (16) | 2003 | BB*‡, CCB*, ACE‡, D‡ | *not specified* | *not specified* | *not specified* | *not specified* | *not specified* | * if angina ‡after MI |
| **JNC7** (18) | 2003 | BB‡, ACE‡ aldo-ANT‡ | CCB(not short-acting)*, | short-acting CCB† | BB+long-acting DHP-CCB* | *not specified* | *not specified* | *in stable angina and silent ischaemia if BB contraindicated, †especially in acute MI; †especially in acute MI; ‡after MI |
| **BHS** (52) | 2004 | BB*, CCB†, ACE‡ | ARB§ or CCB‡ | *not specified* | *not specified* | *not specified* | *not specified* | *after MI or if angina † if angina; ‡after MI; § if LV dysfuction post MI |
| **FCCH** (13) | **2005** | **BB** | **ACE verapamil/diltiazem †** | **(fast-acting CCB)*** | ***not specified **** | ***not specified*** | ***not specified*** | ***caution: might increase ischaemia and risk of MI; †might decrease ischaemia and risk of MI** |
| **ESH/ESC** (19) | 2007 | BB*, ARB‡, ACE‡, CCB†, aldo-ANT‡ | all major anti-HT drugs | *not specified* | *not specified* | *not specified* | *not specified* | *after MI or if angina ‡after MI † if angina |
| **ESH** (7) | 2009 | BB*, ARB‡, ACE‡, CCB†, aldo-ANT‡ | all major anti-HT drugs | *not specified* | *not specified* | *not specified* | *not specified* | *after MI or if angina ‡after MI † if angina |
| **FCCH** (14) | 2009 | BB, ACE, ARB‡ | verapamil or diltiazem† | short acting nifedipin* | BB+DHP-CCB | *not specified* | *not specified* | * without BB; †unless systolic dysfunction or gr II-III AV-block; ‡ if ACE not tolerated |

FHA w.g., Finnish Heart Association working group; JNC6, The Sixth Report of the Joint National Committee; WHO-ISH, World Health Organization - International Society of Hypertension; BHS, British Hypertension Society; FCCH, Finnish Current Care Hypertension; ESH, European Society of Hypertension; JNC7, The Seventh Report of the Join National Committee; ESC, European Society of Cardiology. BB, beta-blocker; CCB, calcium channel blocker; D, diuretic; ACE, Angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; RAS, renin-angiotensin system inhibitor; DHP, Dihydropyridin; THZ, Thiazide diuretic; aldo-ANT, aldosteronantagonist; MI, myocardial infarction; CV, cardiovascular; LV, left ventricular; AV, atrioventricular;

## 2.3.4 Uncomplicated hypertensive patients

Antihypertensive medication for uncomplicated hypertensive patients, recommended by 12 guidelines from 1994 to 2009, is described in Table 9.

As shown in Table 9, practically only the FCCH guidelines [12-14] and JNC6 [17] have specified antihypertensive medication for uncomplicated hypertensive patients. In other guidelines, uncomplicated hypertensive patients have been included with patients with essential or primary hypertension, which is discussed in Chapter 2.3.1.

The FCCH guidelines in 2002 [12] recommended starting antihypertensive medication with low-dose thiazides, ACE inhibitors, or BBs. CCBs and ARBs were optional in specific cases. In 2005, the FCCH guidelines [13] stated that the treatment of uncomplicated hypertension can be initiated with RAS blockers, BBs, diuretics, and CCBs. However, they made a note on the poor evidence of benefits with BBs in the treatment of uncomplicated hypertension. In combination therapy, the FCCH guidelines in 2005 [13] noted that most drugs can be combined.

These recommendations are based on studies, most of which have been already mentioned in Chapter 2.3.1. In addition, the meta-analysis of Messerli et al. 1998 [113] concluded that BBs should no longer be considered appropriate first-line therapy of uncomplicated hypertension in elderly hypertensive patients whereas Messerli et al. 2008 [114] concluded that, in uncomplicated hypertension, neither diuretics nor BBs are acceptable for first-line treatment.

According to the recently-published study of De Caterina et al. [115] (2010 after above guidelines), BBs should not be used as first choice for uncomplicated hypertension.

**Table 9. Antihypertensive drug therapy in uncomplicated hypertension, according to guidelines from 1994 to 2009**

| | | INITIAL MEDICATION | | | COMBINATION MEDICATION | | | |
|---|---|---|---|---|---|---|---|---|
| Guideline | Year | Recommended (compelling indic.) | Possible indication | Not recommended | Recommended (compelling indication) | Possible indication | Not recommended | Remarks |
| **FHA w.g.** (32) | **1994** | ***not specified **** | ***not specified **** | ***not specified **** | ***not specified **** | ***not specified **** | ***not specified **** | **See Table 6** |
| **JNC6** (17) | 1997 | D, BB | *not specified* | *not specified* | *not specified* | *not specified* | *not specified* | |
| **WHO-ISH** (45) | 1999 | *not specified* | *not specified* | *not specified* | *not specified* | *not specified* | *not specified* | |
| **BHS** (51) | 1999 | *not specified* | *not specified* | *not specified* | *not specified* | *not specified* | *not specified* | |
| **FCCH** (12) | 2002 | low-dose HCTZ, ACE, BB, CCB* | ARB† | *not specified* | *See Table 6* | *See Table 6* | *See Table 6* | *if high SBP; † if others not tolerated; |
| **ESH** (16) | 2003 | *not specified* | *not specified* | *not specified* | *not specified* | *not specified* | *not specified* | |
| **JNC7** (18) | 2003 | *not specified* | *not specified* | *not specified* | *not specified* | *not specified* | *not specified* | |
| **BHS** (52) | 2004 | *not specified* | *not specified* | *not specified* | *not specified* | *not specified* | *not specified* | |
| **FCCH** (13) | **2005** | **ACE*, ARB*, BB*†, D*, CCB*** | ***not specified*** | ***not specified*** | **ACE/ARB+D‡, ACE/ARB + CCB BB+D‡, BB+DHP-CCB** | **ACE/ARB+BB, D‡+CCB** | ***BB* + verapamil/DLZM** | ***start with low-dose; † evidence of prognosis poor especially with atenolol and propranolol; ‡ most often THZ** |
| **ESH/ESC** (19) | 2007 | *not specified* | *not specified* | *not specified* | *not specified* | *not specified* | *not specified* | |
| **ESH** (7) | 2009 | *not specified* | *not specified* | *not specified* | *not specified* | *not specified* | *not specified* | |
| **FCCH** (14) | 2009 | *ACE, ARB,* CCB, D | *BB* | *not specified* | *not specified* | *not specified* | *not specified* | |

FHA w.g., Finnish Heart Association working group; JNC6, The Sixth Report of the Joint National Committee; WHO-ISH, World Health Organization - International Society of Hypertension; BHS, British Hypertension Society; FCCH, Finnish Current Care Hypertension; ESH, European Society of Hypertension; JNC7, The Seventh Report of the Joint National Committee; ESC, European Society of Cardiology; BB, beta-blocker; CCB, calcium channel blocker; D, diuretic; ACE, Angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; DHP, Dihydropyridin; SBP, systolic blood pressure; THZ, Thiazide diuretic; HCTZ, hydrochlorthiazide; DLZM, diltiazem

## 2.4 Prevalence of hypertension and control of BP in population-based studies

### 2.4.1 General population

Numerous population-based studies have evaluated the prevalence of hypertension in general populations [3, 5, 116, 117]. From the early eighties, the reported prevalence of hypertension has varied around the world, with the lowest prevalence in rural India (less than 10%) and the highest prevalence in Poland (approximately 70%) [3]. From the early 1980s to the early 2000s, in economically developed countries, the prevalence of hypertension has ranged between approximately 20% and 50% at the 140/90 mmHg threshold [3]. In the mid-nineties, the age-standardized prevalence of hypertension in most populations has been less than 30% at the 160/95 mmHg threshold and less than 50% at the 140/90 mmHg threshold [5].

The definition of hypertension has varied largely in epidemiological studies. Consequently, differences in hypertension criteria affect significantly the prevalence figures of hypertension, which requires to be taken into account. The definition of hypertension has commonly required a history of use of an antihypertensive agent and/or measurement of elevated BP, which most commonly has been ≥160/90 or ≥140/90 mmHg.

Control of BP has usually been reported among treated hypertensive patients. In numerous studies the control of hypertension has been reported among those who are aware of their hypertension and are being treated with antihypertensive medication. Levels of control among treated hypertensive patients have ranged from approximately 30% to 50% with a threshold value of 140/90 mmHg [3].

Surveys have in several countries been repeated over time, or different surveys have been conducted at different points of time. For example, in the US, hypertension control among all patients, (BP less than 140/90 mmHg) improved from 27.3% in the period 1988-1994 to 50.1% in the years 2007-2008 [117]. The Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) studies have been conducted in a number of European countries since the early 80s. In Finland as well as in most of the WHO MONICA populations, trends in prevalence, awareness, treatment, and control of hypertension has improved [5]. However, the results obtained have varied considerably between different countries and regions [3, 116]. There is evidence that, on the average, BP levels have been higher in European countries than in the US and Canada [116] (Figure 1). In the Finnish population, according to the FINRISK studies, BP values have decreased significantly during the past thirty years, some differences between sex and district of living, however, exists [2, 118]. Altogether, prevalence of hypertension and control of BP are still far from optimal [2, 118]. In 1982, with a threshold value of 140/90 mmHg, prevalence of hypertension in Finland was on the average 59-68% for men and 40-55% for women. Of the hypertensive patients, 11-17% of men and 21-25% of women received antihypertensive drugs, and of those 12-15% of men and 10-15% of women had their BP controlled below 140/90 mmHg. In 2002, the corresponding figures were 48-52%, 26-32%, and 30-35% for men, and 33-36%, 27-43%, and 22-36% for women, respectively [2, 118] (Figure 2). In 2006, among Finnish primary care patients, roughly three-quarters of the hypertensive patients failed to reach the BP target of 140/90 mmHg [119].

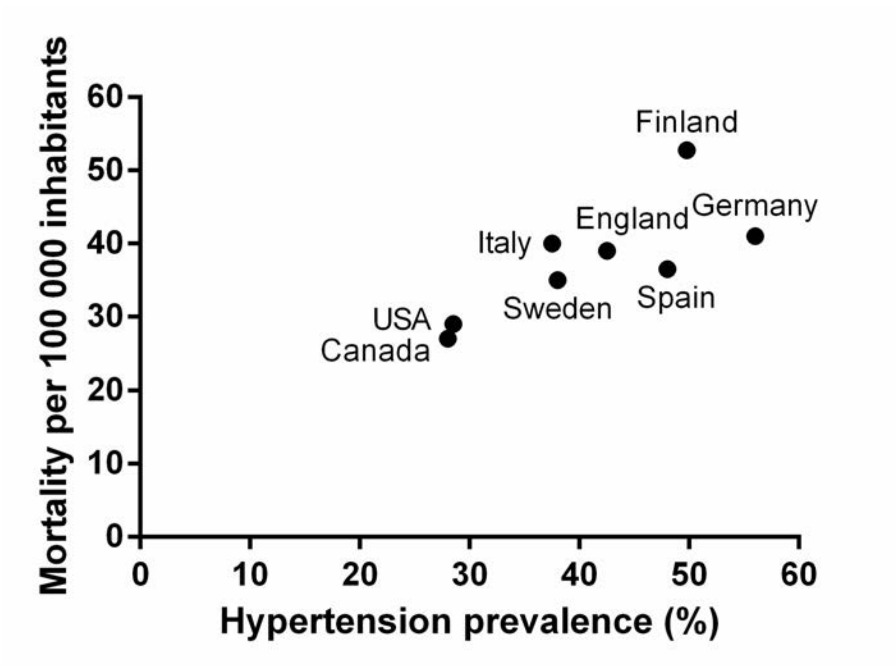


***Figure 1.*** *Hypertension Prevalence vs Stroke Mortality in 6 European and 2 North American Countries, Men and Women Combined (35-64 Years), Age-adjusted. Adapted from Wolf-Maier et al. 2003* [116].

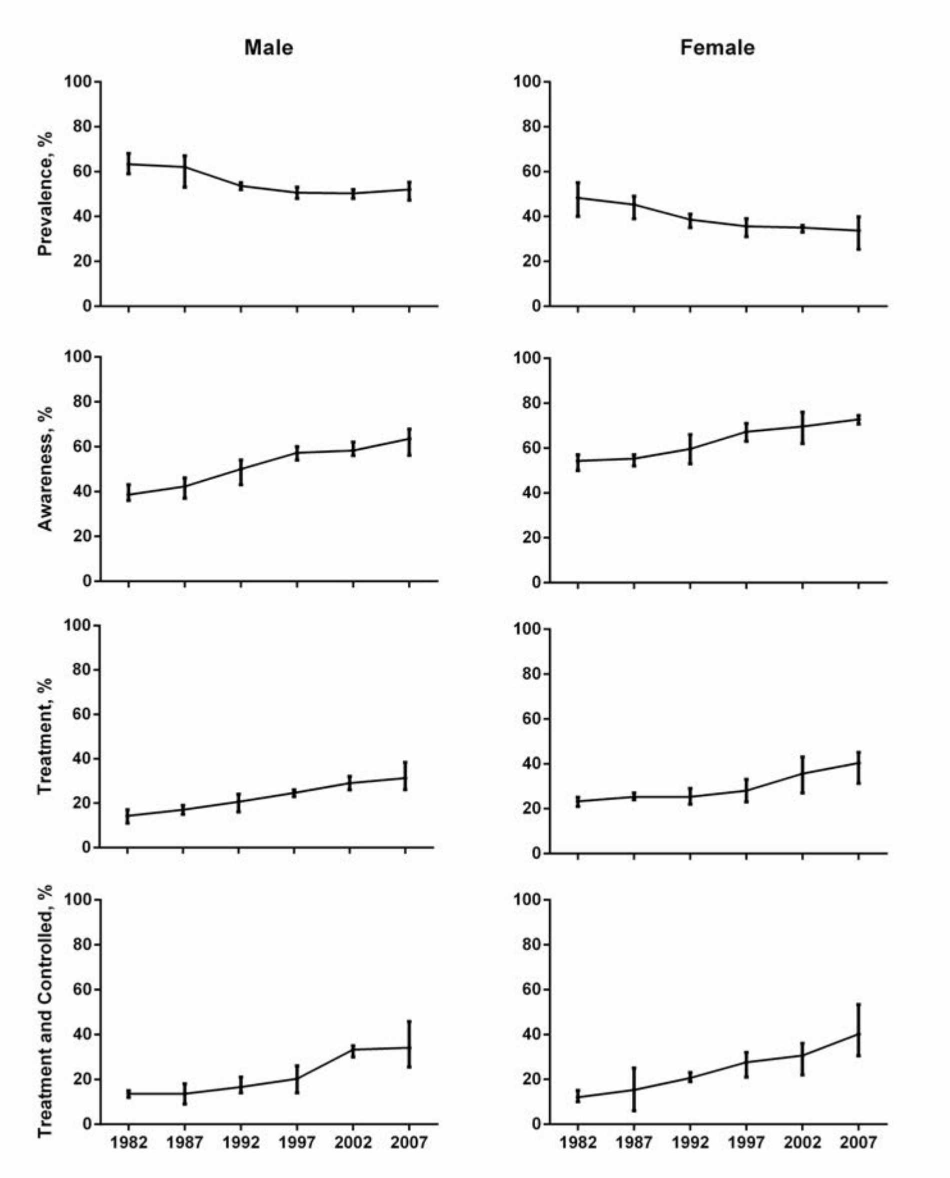


***Figure 2.*** *Prevalence, awareness, treatment and control of hypertension by sex in the national FINRISK study during 1982-2007. (Hypertension defined as systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg or antihypertensive drug treatment). Values of bars describe the mean, minimum, and maximum values. They are calculated from the average values from North Karelia, Northern Savo, and South-western Finland. Modified from Kastarinen et al. 2006* [118] *and Kastarinen e al. 2009* [2]*.*

### 2.4.2 Diabetic patients

Hypertension is an extremely common co morbid condition in diabetes, affecting approximately 20-60% of diabetic patients [120]. There is evidence that, control of hypertension is poorest for diabetic patients [121]. However, there is also evidence that awareness, treatment, and control of hypertension has improved among the diabetic patients, although prevalence of hypertension has increased [122]. Besides, Want et al. found no evidence of improvement for adults 20-44 years of age in US between 1988 and 2008 [122].

Several population-based studies and/or otherwise representative studies (for example large database studies) have evaluated the prevalence of hypertension and control of BP among diabetic patients (Table 10). Like in the studies carried out for general populations, the definition of hypertension has varied largely in epidemiological studies. Differences in hypertension criteria affect significantly the prevalence figures of hypertension, as stated in the previous chapter. In these studies, the definition of hypertension has commonly required a history of use of an antihypertensive agent and/or measurement of elevated BP, which in fact has varied greatly (being ≥130/80 mmHg at the lowest and ≥160/95 mmHg at the highest).

As was done in the studies for general populations, the control of BP for diabetic patients was commonly evaluated among treated hypertensive patients. There are numerous studies in which the control of hypertension has been evaluated among those who are aware of their hypertension and are being treated with antihypertensive medication.

As shown in Table 10, prevalence of hypertension and control of hypertension have varied greatly in different studies in the past 15-20 years. The great variation in these results can be partly explained by methodological differences. In Finland between 1972-1977, according to the framework of the North Karelia Project and the FINRISK study, the prevalence of hypertension (≥160/95 mmHg) in diabetic patients was 50.4% [123], while according to the FINRISK study in 1992, the prevalence of hypertension (≥140/90 mmHg) was 77% [124].

**Table 10. Hypertension and control of BP in earlier population-based studies of diabetic patients**

| Study | Year(s) | Country | n | Average age (y) | Male (%) | DM type | HT (raised BP) | CONTROL OF BLOOD PRESSURE <130/80 | <130/85 | <140/90 | Other limit | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **North Karelia Project/Finrisk** (123) | 72-77 | Finland | 2091 | NR | NR | NR | 50.44$^{4}$ | NR | NR | NR | NR | aged 25-64 |
| **NHANES III** (125) | 88-94 | US | 1 507 | NR | NR | NR | 71.0$^{2}$ | NR | 12.0* | 45.0¥(43.0#) | NR | ≥18 years old |
| **NHANESIII** (126) | 91-94 | US | 733 | NR | NR | Type 2 | 63$^{3}$ | NR | NR | 60.0¥ | NR | ≥25 years old |
| **Colhoun et al.** (127) | 91-94 | UK | 970 | NR | NR | Both | 74.0$^{3}$ | NR | NR | NR | 46.0#$^{7}$ | |
| **FINRISK** (124) | 1992 | Finland | 172 | NR | 55.8 | Type 2 | ~77$^{3}$ | NR | NR | NR | NR | 25-64 years old |
| **Gulliford et al.** (128) | 1993 | UK | 4519∆ | NR | NR | type 2 | 34.0 | NR | NR | NR | NR | ≥30 years old |
| — // — | 2001 | UK | | NR | NR | Type 2 | 58.0 | NR | NR | NR | NR | ≥30 years old |
| **Färnkvist et al.** (129) | 96-97 | Sweden | 5 143 | 68±12.1¶ | 54.0 | Both | 50.0 | NR | NR | NR | 66.06, 23.06# | ≥18 years old |
| **Smith et al.** (130) | 96-97 | US | 526 | 78.2 | 46 | Both | 78.0$^{3}$ | NR | 27.0# | 50.0# | NR | ≥65 years old |
| **Nilsson et al.** (131) | 96 | Sweden | 15 935 | 69.1±9.7¶ | 51.0¶ | Both | NR | NR | 5.8¶† | NR | 22.46¶† | >18 years old |
| — // — | 97 | Sweden | 22 605 | 68.4±10.0¶ | 53.0¶ | Both | NR | NR | 7.1¶† | NR | 27.56¶† | >18 years old |
| — // — | 98 | Sweden | 20 429 | 68.8±10.0¶ | 54.0¶ | Both | NR | NR | 7.9¶† | NR | 29.46¶† | >18 years old |
| — // — | 99 | Sweden | 19 613 | 68.4±10.0¶ | 55.0¶ | Both | NR | NR | 9.4¶† | NR | 33.36¶† | >18 years old |
| **de Pablos-Velasco et al.** (132) | 1999 | Spain | 136 | NR | NR | NR | 79.4$^{3}$ | NR | NR | 4.8† | (4.88, 50.49) † | ≥30 years old |
| **Aquilar-Salinas et al.** (133) | 2000 | Mexico | 3 597 | 55.2±13.5 | 30.3 | Type 2 | 49.9$^{3}$ | NR | NR | 30.0# | NR | ≥20 years old |
| **Hypertension Study Group** (134) | 99-00 | BAN & IND | 157 | NR | NR | Both | 82.0$^{2}$ | NR | 11.7¥,18.8† | NR | NR | ≥ 60 ears old |
| **AusDiab** (135) | 99-00 | Australia | 439 | NR | NR | Type 2 | NR | NR | NR | 32.2# | NR | ≥25 years old |
| **NHANES 1999-2000** (136) | 99-00 | US | 441 | 59.3±0.87 | 50.0 | NR | 51.4$^{A}$ | 35.8 | 36.6 | 59.6 | NR | ≥20 years old † |
| **Supina et al.** (137) | 2000 | Canada | 392 | 62.3±12.5 | 41.6 | Type 2 | 75.8$^{2}$ | NR | 25.3 (34.3#) | NR | NR | ≥20 years old |
| **Phenomen** (138) | 2001 | France | 2 346 | 64.6±10.4 | 57.8 | Type 2 | ALL | NR | 2.7† | NR | (6.5†, 3.0†*)$^{5}$ | ‡ |
| **Johnson et al.** (139) | 2001 | US | 9 975 | 61.2±11.5 | 97 | NR | ALL | NR | 25.2¥ | NR | NR | £ |
| **NHANES 1999-2002** (140) | 99-02 | US | 742 | NR | 46.0 | NR | 82.8$^{22}$ | NR | NR | NR | NR | ≥55 years old |
| **NHANES 1999-2002** (141) | 99-02 | US | 998 | 59.1±0.7 | 49.1 | NR | NR | 39.6 | NR | NR | NR | ≥18 years old |
| **NHANES 1999-2004** (142) | 99-00 | US | 415 | 59.1 | 49.8 | NR | 75.3$^{1}$ | 35.7 | NR | NR | NR | ≥ 60 ears old |
| — // — | 01-02 | US | 412 | 57.3 | 50.3 | NR | 75.8$^{1}$ | NR | NR | NR | NR | ≥ 60 ears old |
| — // — | 03-04 | US | 491 | 59.7 | 46.7 | NR | 75.0$^{1}$ | 48.3 | NR | NR | NR | ≥ 60 ears old |
| **Al-Maskari et al.** (143) | 03-04 | UAE | 513 | 53.3 | 52.0 | Both | 34.9$^{4}$ | NR | NR | NR | NR | |
| **Toti et al.** (144) | 04-05 | Albania | 7 259 | NR | 47.6 | Both | 38.5$^{1}$ | 31.9 | NR | 36.6 | NR | ≥18 years old |
| **Raum et al.** (145) | 00-02 | Germany | 1 375 | 64.0±6.4 | 53.3 | NR | 77.6$^{oo}$ | 8.7(7.5†) | 15.6(12.8†) | NR | NR | 50-74 years old |
| **NHANES 1999-2008** (146) | 99-00 | US | 149 | 55.4 | 52.7 | NR | 66.6$^{1}$ | 47.6 | NR | NR | NR | ≥20 years old |
| — // — | 01-02 | US | 220 | 57.0 | 58.4 | NR | 76.4$^{1}$ | 43.1 | NR | NR | NR | ≥20 years old |
| — // — | 03-04 | US | 209 | 59.1 | 56.3 | NR | 69.4$^{1}$ | 50.5 | NR | NR | NR | ≥20 years old |
| — // — | 05-06 | US | 240 | 59.2 | 45.0 | NR | 75.5$^{1}$ | 48.3 | NR | NR | NR | ≥20 years old |
| — // — | 07-08 | US | 396 | 60.0 | 52.2 | NR | 74.2$^{1}$ | 55.1 | NR | NR | NR | ≥20 years old |
| **CIRCLE study** (147) | 2007 | Canada | 885 | 54.9±14.2 | 63.3 | Type 2 | 92.0$^{1}$ | 34.4 | NR | NR | NR | ≥18 years old |

DM, diabetes mellitus; HT, hypertension; ‡ All treated for hypertension; ¶ DM2; NR, not reported; # of treated patients; ¥ of hypertensives; †of treated hypertensives; * of those on monotherapy; £ All hypertensives; Hypertension defined if antihypertensive agent were used and/or BP measured ≥130/80mmHg$^{1}$, ≥130/85mmHg$^{2}$, ≥140/90mmHg$^{3}$, ≥160/95mmHg$^{4}$, $^{A}$ ADA standard criteria; $^{22}$ prior physician-diagnosed HT or BP≥130/85mmHg. $^{oo}$ HT documented by primary physician and/or use of anti-HT drug, BP control limit <140/80mmHg $^{5}$, <140/85mmHg $^{6}$, <160/90mmHg$^{7}$, SBP<140mmHg$^{8}$, DBP<90mmHg$^{9}$. ∆ Total number of patients during the follow-up time 1993-2001; UAE, United Arab Emirates; US, United States; UK, United Kingdom

### 2.4.3 Coronary heart disease patients

There are only a few population-based studies and/or otherwise valuable studies representing the whole population, which have evaluated cardiovascular risk factors, such as prevalence of hypertension and control of BP among CHD patients, as described in Table 11. Also for patients with CHD, the definition of hypertension has varied in epidemiological studies. Consequently, the difference in hypertension criteria affects significantly the obtained prevalence of hypertension, which requires to be taken into consideration. In these studies, hypertension has commonly been defined as “raised BP” i.e., systolic BP ≥140 mmHg and diastolic BP ≥90 mmHg. Alternatively, in some studies, hypertension has been defined by using the ESH/ESC 2003 guidelines [16] i.e., systolic BP ≥140 mmHg (≥130 mmHg for diabetic patients) and diastolic BP ≥90 mmHg (≥80 mmHg for diabetic patients). Contrary to the studies made for general populations and for diabetic patients, control of BP of CHD patients has commonly been evaluated among all patients, not only among those with a history of hypertension. However, in the Euroaspire Surveys I-III [148, 149], the control of hypertension has been assessed also among treated patients. Yet, all BP lowering drugs have not always necessarily been used for the treatment of hypertension.

As shown in Table 11, prevalence of hypertension and control of hypertension have varied largely within different populations during the past 15 years. Despite a substantial increase in antihypertensive drug therapy in Euroaspire surveys I-III, control of BP remained unchanged at the level of 40% on the average in 8 European countries [148]. The prevalence of hypertension in Euroaspire II [148], carried out in 1999-2000, was slightly lower and therapeutic control of hypertension slightly higher in Finland than on the average in eight other European countries. In Euroaspire III [148], carried out in 2006-2007, the prevalence of hypertension was somewhat higher and control of hypertension somewhat lower in Finland than on the average in 8 European countries.

**Table 11. Hypertension and control of blood pressure in population studies of coronary heart disease patients**

| Study | Year(s) | Country | n | Average age (y) | Male (%) | HT (raised BP) | Control of blood pressure ESH/ESC-03 ¶ | Control of blood pressure <140/90 | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| PREVESE II (150) | 1998 | Spain | 2 054 | 64.3 | 74.9 | 47.5 | NR | NR | £ |
| Muntwyler et al. (151) | 2000 | Switzerland | 565 | 68±11 | 75.0 | 65.0[3] | NR | 51.0 (57.0*) | $ |
| **Euroaspire I** (152) | **95-96** | **9 European†** | **3 569** | **NR¥** | **78.6** | **55.4**[3] | **NR** | **44.6#** | **≤70years old, Δ** |
| **Euroaspire II** (152) | **99-00** | **9 European†** | **3 379** | **NR§** | **77.9** | **53.9**[3] | **NR** | **46.1#** | **≤70years old, Δ** |
| **Euroaspire I** (148) | **95-96** | **8 European‡** | **3 180** | **59.3** | **75.1** | **58.1**[1] | **41.0#** | **NR** | **≤70years old, Δ** |
| **Euroaspire II** (148) | **99-00** | **8 european‡** | **2 975** | **59.4** | **74.8** | **58.3**[1] | **41.2#** | **NR** | **≤70years old, Δ** |
| — // — | — // — | Czech Republic | 410 | NR | NR | 51.8[1] | 47.2# | NR | ≤70years old, Δ |
| — // — | — // — | Finland | 348 | NR | NR | 55.7[1] | 43.4# | NR | ≤70years old, Δ |
| — // — | — // — | France | 364 | NR | NR | 60.7[1] | 36.7# | NR | ≤70years old, Δ |
| — // — | — // — | Germany | 401 | NR | NR | 69.5[1] | 29.1# | NR | ≤70years old, Δ |
| — // — | — // — | Hungary | 389 | NR | NR | 45.5[1] | 55.0# | NR | ≤70years old, Δ |
| — // — | — // — | Italy | 258 | NR | NR | 54.7[1] | 45.7# | NR | ≤70years old, Δ |
| — // — | — // — | Netherlands | 357 | NR | NR | 56.9[1] | 43.5# | NR | ≤70years old, Δ |
| — // — | — // — | Slovenia | 446 | NR | NR | 68.4[1] | 31.1# | NR | ≤70years old, Δ |
| **Euroaspire III** (148) | **06-07** | **8 European‡** | **2 392** | **60.9** | **76.9** | **60.9**[1] | **38.7#** | **NR** | **≤70years old, Δ** |
| — // — | — // — | Czech Republic | 402 | NR | NR | 69.2[1] | 30.1# | NR | ≤70years old, Δ |
| — // — | — // — | Finland | 167 | NR | NR | 71.3[1] | 29.1# | NR | ≤70years old, Δ |
| — // — | — // — | France | 266 | NR | NR | 56.3[1] | 44.1# | NR | ≤70years old, Δ |
| — // — | — // — | Germany | 452 | NR | NR | 55.0[1] | 45.2# | NR | ≤70years old, Δ |
| — // — | — // — | Hungary | 382 | NR | NR | 55.5[1] | 44.1# | NR | ≤70years old, Δ |
| — // — | — // — | Italy | 299 | NR | NR | 63.9[1] | 34.8# | NR | ≤70years old, Δ |
| — // — | — // — | Netherlands | 185 | NR | NR | 63.4[1] | 35.3# | NR | ≤70years old, Δ |
| — // — | — // — | Slovenia | 223 | NR | NR | 58.7[1] | 41.4# | NR | ≤70years old, Δ |
| **Euroaspire III** (153) | **06-07** | **22 European** | **13 935** | **NR** | **73.0** | **56.0**[1] | **44.0 (43.9#)** | **NR** | **18-80 years old, Δ** |
| TASPIC-CRO II (154) | 1999 | Croatia | 2 627 | 62.7 | 65.9 | 57.0[3] | NR | NR | ≤70years old, Δ |
| TASPIC-CRO V (154) | 2003 | Croatia | 3 054 | 64.2 | 63.9 | 69.0[3] | NR | NR | ≤70years old, Δ |
| CINHTIA (155) | 2006 | Spain | 2 024 | 66.8 | 68.3 | NR | 40.5 | NR | ≥ 18years old, [a] |

HT, Hypertension; ESH/ESC, European Society of Hypertension/European Society of Cardiology; ¶ <140/90mmHg (<130/80mmHg for diabetics); NR, not reported; # of treated patients; * of under 70 years of age, ¥78.8% >60years; §77.7% >60years; Δ history of MI or coronary revascularisation or ischaemia; $ 53% had a history of MI; £ all had a history of MI; [a] all had ischaemic heart disease; [1] Systolic blood pressure ≥140mmHg and diastolic blood pressure ≥90mmHg (SBP≥130mmHg and DBP≥80mmHg in patients with diabetes; [3] Systolic blood pressure ≥140mmHg and diastolic blood pressure ≥90mmHg; † Czech Republic, Finland, France, Germany, Hungary, Italy, Netherlands, Slovenia and Spain; ‡ Czech Republic, Finland, France, Germany, Hungary, Italy, Netherlands and Slovenia.

### 2.4.4 Uncomplicated hypertensive patients

There are only a few population studies describing the prevalence and/or control of hypertension among uncomplicated hypertensive patients. However, practically all of these are limited to newly treated patients, patients of a certain age [156], or other subgroups, and do therefore not deserve further presentation in this context.

## 2.5 Utilization of antihypertensive drugs in population-based studies

### 2.5.1 General population

There is a huge number of studies dealing with representing antihypertensive treatment for general populations. The portion treated patients has commonly been reported as being hypertensive patients (i.e., treated hypertensive patients). However, the threshold BP for the classification of hypertension has been varying, which reflects to these percentages and requires to be taken into account.

According to the WHO MONICA project in the late eighties and early nineties, using 140/90 mmHg for threshold, less than 30% of the hypertensive individuals were on antihypertensive medication in 20 out of 24 male populations, while less than 40% of the hypertensive individuals were on antihypertensive medication in 18 out of 24 female populations [5]. In Finland, in 1982, 1997, 2002, and 2007, using a 140/90 mmHg threshold, 11-17%, 23-26%, 26-32%, and 26-38% of the hypertensive men were on antihypertensive drug treatment, respectively [2, 118]. The corresponding figures for females were 20-25%, 23-33%, 27-43%, and 31-45%, respectively [2, 118] (Figure 2). In 1995, among Finnish primary health care patients, BBs were the drugs most frequently used by all patients. For women, combination therapy included more frequently diuretics, whereas ACE inhibitors were favored by men [157].

The CardioMonitor 2004 Survey in 5 western European countries and in the United States has shown that the use of thiazides was quite similar across these countries (29-31%) [158]. In contrast, the use of other antihypertensive drug classes varied considerably from one country to another, especially for BBs (20-49%), ACE inhibitors (27-52%), and ARBs (18-36%). The use of combination drug therapy was highest in the US (64% vs. 44-59% across the European countries) [158]. The I-SEARCH study between 2005 and 2006 in 26 countries showed that, in the overall population, of those on antihypertensive medication, approximately 30% used one drug, approximately 40% used two drugs, and approximately 30% used 3 or more antihypertensive drugs [159]. According to the I-SEARCH study, in monotherapy, ACE inhibitors were most frequently used by men (29.8% vs. 26.3%), while BBs were most frequently used by women (27.6% vs. 24.2%) [159].

In a study of three similar population-based databases of dispensed drugs for newly treated hypertensive patients, carried out in 2006 in Italy, Sweden, and Netherlands, ACE inhibitors were used as first-line agent by 23%, 21%, and 13%, in above order. Corresponding figures concerning BBs were 18%, 33%, and 34%, respectively [160].

### 2.5.2 Diabetic patients

There are several population-based studies and/or otherwise representative national studies treating utilization of antihypertensive drugs for diabetic patients (Table 12). There are methodological differences in these studies and therefore the results are not equally comparable with each other. Despite the methodological differences, the distribution of major antihypertensive agents differs between the populations. Nevertheless, it seems that utilization of antihypertensive drugs for diabetic patients has increased during the past few decades. In addition, combination therapy seems to have increased. Yet there is still some way to go for better management of hypertension. On the other hand, longitudinal studies carried out 1993-2001 in UK [128], 1993-2001 in Canada [161], and 1997-2003 in Taiwan [162], demonstrate that the earlier the study was carried out, the less RAS blockers were used. It seems that both in cross-sectional and in longitudinal studies, BBs were clearly less frequently used than RAS blockers. This trend is very distinctly seen in longitudinal study in Taiwan, carried out from 1997 to 2003 [162].

In the primary care setting in Finland from 1992 to 1994, ACE inhibitors, BBs, CCBs, and diuretics were used by 46%, 39%, 31%, and 31%, of the hypertensive patients, respectively. Sixty-one percent of the hypertensive diabetic patients were on monotherapy and 8% had three or more antihypertensive drugs [163].

#### *2.5.2.1 Monotherapy*

There are not many studies describing the utilization of antihypertensive agents in monotherapy (Table 13). Some methodological differences exist in these studies, and the results are therefore not equally comparable with each other. ARBs were used on the average by 22-60%, while BBs were used, respectively, by 8-35%. There seems to be an increasing trend in the use of ARBs also in monotherapy (Table 13).

### *2.5.2.2 Combination therapy*

Only a few representative studies concern combination antihypertensive treatment for diabetic patients. The most frequent combination therapy in Alberta (province of Canada) in 2000 was an ACE inhibitor plus a CCB (26% of 2-drug combinations) followed by an ACE plus a loop diuretic (14% of 2-drug combinations) [137]. In the UK, from 1993 to 2001, (within the first year entering the study) the most frequently used 2-drug combination was a RAS blocker plus a CCB (23% of 2-drug combinations) while the most frequently used 3-drug combination was a combination of a RAS blocker, a CCB, and a diuretic (38% of 3-drug combinations) [128]. In Taiwan, from 1997 to 2000, the most frequently used 2-drug combination was a RAS blocker plus a CCB (23%, 31%, and 38% of 2-drug combinations in 1997, 2000, and 2003, respectively) while the 3-drug combination most frequently used was a combination of RAS blocker(s), BB(s), and CCB(s) (17%, 29%, and 33% of triple therapies in 1997, 2000, and 2003, respectively) [162].

**Table 12. Utilization of antihypertensive drugs in earlier population-based studies of diabetic patients**

| Study | Year(s) | Country | n | Average age (y) | Male (%) | DM type | Anti-HT drugs (%) | BB (%) | CCB (%) | Diur (%) | ACE (%) | ARB (%) | ACE/ARB (%) | 1-drug | 2-drug | 3-drug | ≥4-drug | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **North Karelia Project/Finrisk** (123) | 72-77 | Finland | 2091 | NR | NR | NR | 38.3¥ | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | 25-64 years old |
| **NHANES III** (125) | 88-94 | US | 1 507 | NR | NR | NR | 57.0 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | ≥18 years old |
| **NHANESIII** (126) | 91-94 | US | 733 | NR | Nr | Type 2 | 81.6¥ | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | ≥25 years old |
| **Gulliford et al.** (128) | 1993 | UK | 4519∆ | NR | NR | Type 2 | 81.9¥ | 30¥ | 33¥ | 20¥ § | 35¥ | 0¥ | NR | NR | NR | NR | NR | ≥30 years old, ¶ |
| —//— | 2001 | UK | | NR | NR | Type 2 | 83.4¥ | 31¥ | 33¥ | 30¥ § | 45¥ | 8¥ | NR | NR | NR | NR | NR | ≥30 years old |
| **Eurich et al. 2008** (161) | 1993 | Canada | 27 014 | NR | NR | Both | 34.6 | 8.0 | 11.9 | NR | 16.7 | NR | NR | NR | NR | NR | NR | all ages |
| —//— | 2001 | Canada | 40 098 | NR | NR | Both | 48.7 | 11.3 | 12.9 | NR | 32.9 | NR | NR | NR | NR | NR | NR | all ages |
| **McAlister et al.** (164) | 1995 | Canada | 27 822∆ | 72±5.4 | 51.0 | NR | All | 7.0† | 16.0† | 22.0† | 54.0† | NR | NR | 73.0£ | 22.0£ | 5.0£[a] | NR | >65years old, ‡ |
| —//— | 2001 | Canada | | | | NR | All | 7.0† | 6.0† | 10.0† | 76.0† | NR | NR | NR | NR | NR | NR | >65years old |
| **Färnkvist et al.** (129) | 96-97 | Sweden | 5 143 | 68±12.1¶ | 54.0 | Both | 50.0 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | ≥18 years old |
| **Smith et al.** (130) | 96-97 | US | 526 | 78.2 | 46.0 | Both | 89.0¥ | NR | 44.0† | 55.0† | 41.0† | NR | NR | NR | NR | NR | NR | ≥65 years old |
| **Chiang et al.** (162) | 1997 | Taiwan | 2 437 | 64.5±9.9 | 43.4 | Both | All | 19.8† | 38.6† | 11.2† | NR | NR | 19.6† | 58.2† | 32.0† | 8.3† | 1.6† | ‡ |
| —//— | 2000 | Taiwan | 4 086 | 64.7±10.4 | 43.7 | Both | All | 18.7† | 33.4† | 11.5† | NR | NR | 29.8† | 48.6† | 35.4† | 13.1† | 3.0† | |
| —//— | 2003 | Taiwan | 4 816 | 64.7±11.0 | 43.3 | Both | All | 16.9† | 33.9† | 11.1† | NR | NR | 33.4† | 47.1† | 36.7† | 13.1† | 3.2† | |
| **de Pablos-Velasco et al.** (132) | 1999 | Spain | 136 | NR | NR | Type 2 | 52.0 | 5.2† | 17.4† | 12.2† | 33.0† | NR | NR | 37.6 | 11.2 | 3.2[a] | NR | ≥30 years old |
| **Aquilar-Salinas et al.** (133) | 2000 | Mexico | 3 597 | 55.2±13.5 | 30.3 | Type 2 | 23.5, 47.1¥ | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | ≥20 years old |
| **Hypertension Study Group** (134) | 99-00 | 3AN & INI | 157 | 70 | NR | Both | 51.0, 62.5¥ | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | ≥ 60 ears old |
| **NHANES 1999-2000** (136) | 99-00 | US | 441 | 59.3±0.87 | 50.0 | NR | 85.2¥ | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | ≥20 years old |
| **Supina et al.** (137) | 2000 | Canada | 392 | 62.3±12.5 | 41.6 | Type 2 | 59.9 | 8.4* | 13* | 6.0* | NR | NR | 74.0* | 47.0# | 34.8# | 12.3# | 5.5# | ≥20 years old |
| **Phenomen** (138) | 2001 | France | 2346 | 64.6±10.4 | 57.8 | NR | All | 25.0† | 24.0† | 17.4† | NR | NR | 81.8† | 37.1† | 34.5† | 18.0† | 10.3† | ‡ |
| **Johnson et al.** (139) | 98-01 | US | 9 975 | 61.2±11.5 | 97.0 | NR | 80.9¥ | 28.5¥ | 35.3¥ | 38.1¥ | NR | NR | 62.2¥ | 23.7¥ | 24.0¥ | 18.0¥ | 15.2¥ | £ |
| **NHANES 1999-2002** (140) | 99-02 | US | 742 | NR | 46.0 | NR | NR | NR | NR | NR | NR | NR | 43.0 | NR | NR | NR | NR | ≥55 years old |
| **Toti et al.** (144) | 04-05 | Albania | 7 259 | NR | 47.6 | Both | 58.8 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | ≥18 years old |
| **Raum et al.** (145) | 00-02 | Germany | 1 375 | 64.0±6.4 | 53.3 | NR | 86.0¥ | 39.6 | 27.3 | NR | 51.5 | NR | NR | NR | NR | NR | NR | 50-74 years old |
| **NHANES 1999-2008** (146) | 99-00 | US | 149 | 55.4 | 52.7 | NR | 35.4 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | ≥20 years old |
| —//— | 01-02 | US | 220 | 57.0 | 58.4 | NR | 46.2 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | ≥20 years old |
| —//— | 03-04 | US | 209 | 59.1 | 56.3 | NR | 49.6 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | ≥20 years old |
| —//— | 05-06 | US | 240 | 59.2 | 45.0 | NR | 59.7 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | ≥20 years old |
| —//— | 07-08 | US | 396 | 60.0 | 52.2 | NR | 58.9 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | ≥20 years old |
| **CIRCLE study** (147) | 2007 | Canada | 885 | 54.9±14.2 | 63.3 | Type 2 | 90.1 | NR | NR | NR | NR | NR | 72.1 | 36.6 | 24.4 | 15.8 | 7.4 | ≥18 years old |

DM, diabetes mellitus; HT, hypertension; BB, beta-blocker; CCB, calcium channel blocker; D, diuretic; ACE, angiotensin convertin enzyme inhibitor; ARB, angiotension receptor blocker
‡ All treated for hypertension; £ All hypertensives; ¥ of hypertensives; # of treated; †of treated hypertensives;* of those on monotherapy; § thiazides; £ hypertension management within the first 2 years from diagnosis; [a] ≥3 drugs; ¶ Antihypertensive therapy recorded within 12 months from initiation of oral hypoglycemic therapy. ∆ Total number of patients during the follow-up time; NR, not reported; UK, United Kingdom; US, United States; NHANES, National Health and Nutrition Examination Survey

**Table 13. Monotherapy according to earlier population-based studies of diabetic patients**

| Monotherapy | Year(s) | BB(%) | CCB(%) | D(%) | ACE(%) | ARB(%) | ACE/ARB(%) | Alpha | Other |
|---|---|---|---|---|---|---|---|---|---|
| **Gulliford et al.** (128) | 93-01 | 34.7 | 13.0 | 17.4 | NR | NR | 34.7 | NR | NR |
| **Johnson et al.** (139) | 98-01 | 11.5 | 11.2 | 9.4 | NR | NR | 59.5 | 6.6 | 1.7 |
| **Supina et al.** (137) | 2000 | 8 | 13 | 6 | NR | NR | 74 | NR | NR |
| **Chiang et al.** (162) | 1997 | 18.2 | 44.4 | 6.6 | NR | NR | 22.0 | NR | 8.9 |
| —//— | 2000 | 14.5 | 36.3 | 4.8 | NR | NR | 39.0 | NR | 5.4 |
| —//— | 2003 | 11.7 | 36.6 | 3.7 | NR | NR | 44.8 | NR | 3.2 |

BB, beta-blocker; CCB, calcium channel blocker; D, diuretic; ACE, Angiotensin converting enzyme inhibitor; NR, not reported; ARB, angiotensin receptor blocker; alpha, alpha-blocker.

### 2.5.3 Coronary heart disease patients

There are several papers treating the utilization of antihypertensive drugs in population-based studies and/or otherwise representative national studies of CHD patients (Table 14). Because of methodological differences in these studies, the results are not equally comparable with each other.
On the other hand, the longitudinal Euroaspire Surveys I,II, and III, [148, 149, 152, 153], carried out in several European countries (including Finland), give an opportunity to compare the results with each other. In addition, trends in antihypertensive medication among CHD patients since mid-nineties will be uncovered. In studies concerning CHD patients, such as the Euroaspire Surveys, BP-lowering drugs (for instance BBs and ACE inhibitors) may not have always been prescribed for the treatment of hypertension. Nevertheless, it seems that utilization of BP lowering drugs for CHD patients has increased during the past 15-20 years. Utilization of BBs and diuretics and, particularly, RAS blockers, has increased widely. However, there are differences between the countries (Table 14). According to Euroaspire Surveys I-III, BBs are used more and diuretics and RAS blockers less in Finland than in the Czech Republic, France, Germany, Hungary, Italy, Netherlands, and Slovenia [149].

### 2.5.4 Uncomplicated hypertensive patients

Some studies describe the utilization of antihypertensive drugs in population-based studies of uncomplicated hypertensive patients. Practically all of these are limited to newly treated patients, elderly patients or other subgroups, and therefore only a retrospective prescription-based survey in Bahrain in 1998-2000 deserves mentioning [167]. Therein, in 1998, BBs were used by 65%, ACE inhibitors by 21%, CCBs by 20%, and diuretics by 27% while the corresponding figures in 2000 were 60%, 27%, 24%, and 27%, respectively [167].

**Table 14. Utilization of antihypertensive drugs in population studies of coronary heart disease patients**

| Study | Year(s) | Country | n | Average age (y) | Male (%) | Anti-HT drugs (%) | BB(%) | CCB(%) | D(%) | ACE(%) | ARB(%) | ACE/ARB(%) | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Usik 1995 (165) | 1995 | France | 2 563 | 67.0 | 67.0 | NR | 64 | NR | NR | 46 | NR | NR | £ |
| Prevenir 1 (165) | 1998 | France | 1 394 | (57%≥65) | 71.0 | NR | 68 | NR | NR | 41 | NR | NR | ¶ |
| Prevenir 2 (165) | 1999 | France | 2 527 | (51%≥65) | 74.0 | NR | 75 | NR | NR | 41 | NR | NR | ¶ |
| Usic 2000 (165) | 2000 | France | 2 320 | 65.0 | 73.0 | NR | 76 | NR | NR | 50 | NR | NR | £ |
| PREVESE I (166) | 1994 | Spain | 1 242 | 62.8 | 78,5 | NR | 33.5 | 26.5 | 12.9 | 32.5 | 0 | NR | £ |
| PREVESE II (150) | 1998 | Spain | 2 054 | 64.3 | 74.9 | NR | 45.1 | 17.7 | 15.9 | 46.4 | 4.0 | 50.4 | £ |
| Muntwyler et al. (151) | 2000 | Switzerland | 565 | 68±11 | 75.0 | NR | 58.0 (71)* | NR | NR | 35.0* | NR | 50 | $ |
| **Euroaspire I** (152) | **95-96** | **9 European†** | **3 569** | **NR¥** | **78.6** | **84.1** | **53.7** | **NR** | **NR** | **29.5** | **NR** | **NR** | **≤70 years old, Δ** |
| **Euroaspire II** (152) | **99-00** | **9 European†** | **3 379** | **NR§** | **77.9** | **89.9** | **66.4** | **NR** | **NR** | **42.7** | **NR** | **NR** | **≤70 years old, Δ** |
| **Euroaspire I** (148) | **95-96** | **8 European‡** | **3 180** | **59.3** | **75.1** | **84.5** | **56.0** | **NR** | **15.3** | **NR** | **NR** | **31.0** | **≤70 years old, Δ** |
| **Euroaspire II** (148) | **99-00** | **8 European‡** | **2 975** | **59.4** | **74.8** | **90.6** | **69.0** | **NR** | **18.8** | **NR** | **NR** | **49.2** | **≤70 years old, Δ** |
| —//— | —//— | Czech Republic | 410 | NR | NR | 90.2 | 73.7 | NR | 22.7 | NR | NR | 47.1 | ≤70 years old, Δ |
| —//— | —//— | Finland | 348 | NR | NR | 93.4 | 87.9 | NR | 12.4 | NR | NR | 31.0 | ≤70 years old, Δ |
| —//— | —//— | France | 364 | NR | NR | 90.7 | 60.4 | NR | 13.2 | NR | NR | 43.7 | ≤70 years old, Δ |
| —//— | —//— | Germany | 401 | NR | NR | 88.5 | 68.1 | NR | 32.7 | NR | NR | 50.6 | ≤70 years old, Δ |
| —//— | —//— | Hungary | 389 | NR | NR | 97.2 | 84.3 | NR | 23.9 | NR | NR | 58.6 | ≤70 years old, Δ |
| —//— | —//— | Italy | 258 | NR | NR | 94.2 | 61.2 | NR | 16.3 | NR | NR | 53.5 | ≤70 years old, Δ |
| —//— | —//— | Netherlands | 357 | NR | NR | 77.9 | 48.2 | NR | 12.6 | NR | NR | 42.9 | ≤70 years old, Δ |
| —//— | —//— | Slovenia | 446 | NR | NR | 93.0 | 65.7 | NR | 14.3 | NR | NR | 63.0 | ≤70 years old, Δ |
| **Euroaspire III** (148) | **06-07** | **8 European‡** | **2 392** | **60.9** | **76.9** | **96.8** | **85.5** | **NR** | **31.1** | **NR** | **NR** | **74.6** | **≤70 years old, Δ** |
| —//— | —//— | Czech Republic | 402 | NR | NR | 97.8 | 91.3 | NR | 36.3 | NR | NR | 76.1 | ≤70 years old, Δ |
| —//— | —//— | Finland | 167 | NR | NR | 98.8 | 95.8 | NR | 10.8 | NR | NR | 59.3 | ≤70 years old, Δ |
| —//— | —//— | France | 266 | NR | NR | 98.1 | 74.4 | NR | 19.2 | NR | NR | 78.9 | ≤70 years old, Δ |
| —//— | —//— | Germany | 452 | NR | NR | 94.2 | 85.0 | NR | 33.8 | NR | NR | 72.8 | ≤70 years old, Δ |
| —//— | —//— | Hungary | 382 | NR | NR | 97.1 | 85.9 | NR | 52.6 | NR | NR | 80.6 | ≤70 years old, Δ |
| —//— | —//— | Italy | 299 | NR | NR | 97.3 | 87.6 | NR | 20.4 | NR | NR | 70.9 | ≤70 years old, Δ |
| —//— | —//— | Netherlands | 185 | NR | NR | 94.1 | 74.6 | NR | 23.2 | NR | NR | 66.5 | ≤70 years old, Δ |
| —//— | —//— | Slovenia | 223 | NR | NR | 98.7 | 87.0 | NR | 29.1 | NR | NR | 83.0 | ≤70 years old, Δ |
| **Euroaspire III** (153) | **06-07** | **22 european** | **13 935** | **NR** | **73.0** | **NR** | **79.8** | **24.5** | **30.2** | **NR** | **NR** | **70.9** | **18-80 years old, Δ** |
| TASPIC-CRO II (154) | 1999 | Croatia | 2 627 | 62.7 | 65.9 | NR | 25* | 18* | 22* | 30* | NR | NR | ≤70 years old, Δ |
| TASPIC-CRO V (154) | 2003 | Croatia | 3 054 | 64.2 | 63.9 | NR | 29* | 18* | 20* | 35* | NR | NR | ≤70 years old, Δ |
| CINHTIA (155) | 2006 | Spain | 2 024 | 66.8 | 68.3 | 99.7 | 67.1 | 44.4 | 35.1 | 43.5 | 32.8 | 76.3 | ≥18 years old, [a] |

NR, not reported; Anti-HT, antihypertensive; BB, beta-blocker; CCB, calcium channel blocker; D, diuretic; ACE, Angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ¥78.8% >60years; §77.7% >60years; *of under 70y; Δ History of MI or coronary revascularisation or ischaemia; $ 53% had a history of MI; £ all had a history of MI; [a] All had ishaemic heart disease; ¶ All had acute coronary syndrome; † Czech Republic, Finland, France, Germany, Hungary, Italy, Netherlands, Slovenia, and Spain; ‡ Czech Republic, Finland, France, Germany, Hungary, Italy, Netherlands and Slovenia.

# 3 Aims of the Study

The purpose of this study was to evaluate the rationality of antihypertensive drug treatment in Finland between 2000 and 2006 in accordance with treatment guidelines. The specific aims were:

1. To assess utilization of antihypertensive drug therapy and control of hypertension among Finnish adult diabetic patients (I).

2. To assess utilization of antihypertensive drug therapy and control of hypertension among Finnish adult coronary heart disease (CHD) patients (II).

3. To assess utilization of antihypertensive drug therapy and control of hypertension among Finnish adult uncomplicated hypertensive patients (III).

4. To calculate the expected improvements in the control of hypertension and the expected reductions in cardiovascular morbidity, with intensified antihypertensive treatment (III).

5. To assess changes in the utilization of antihypertensive medication for subjects treated for moderate to severe hypertension and uncomplicated mild hypertension, in relation with changes in concomitant disease profiles (IV).

6. To assess whether utilization of antihypertensive drugs in late 2006 differs between recently treated and formerly treated moderately to severely hypertensive patients (IV).

# 4 Materials and Methods

## 4.1 Study designs and populations

*Studies I-III*

Two different data, the data of the Health 2000 Survey (H2000)) and the database of the Social Insurance Institution (SII), partly in parallel and partly complementary to each other, were used to assess changes in the utilization of antihypertensive drugs from 2000 to 2006 among Finnish adult patients with diabetes (I), CHD (II), and uncomplicated hypertension (III), and to evaluate the treatment and control of hypertension in these 3 subgroups. In addition, data of the Health 2000 survey were used to crossvalidate drug utilization data obtained from the database of the SII, and vice versa.

*Study III*

Among uncomplicated hypertensive patients, data of the Health 2000 survey and the database of the SII were used to calculate the achievable reduction in BP and cardiovascular morbidity, with intensified antihypertensive treatment.

*Study IV*

The database of SII was used to disclose changes in the utilization of antihypertensive drugs in subjects treated for moderate to severe hypertension and mild uncomplicated hypertension, in relation with changes in concomitant disease profiles between 2000 and 2006, and to assess whether utilization of antihypertensive drugs in late 2006 differs between recently treated and formerly treated moderately to severely hypertensive patients (IV).

### 4.1.1 The Health 2000 Survey

The Health 2000 Survey was carried out in Finland from late 2000 to early 2001. The population of the study was a two-stage stratified cluster sample representing the whole Finnish population aged 30 years or over. The frame was regionally stratified according to the five university hospital districts, each containing approximately one million inhabitants. From these, 16 health care districts were sampled as clusters. Firstly, the 15 largest cities were included with the probability of one. Secondly, the remaining 65 health care districts were selected by applying the systematic probability proportional to size method. Finally, from these 80 clusters, a sample of 8028 persons was selected by systematic sampling (Figure 3).

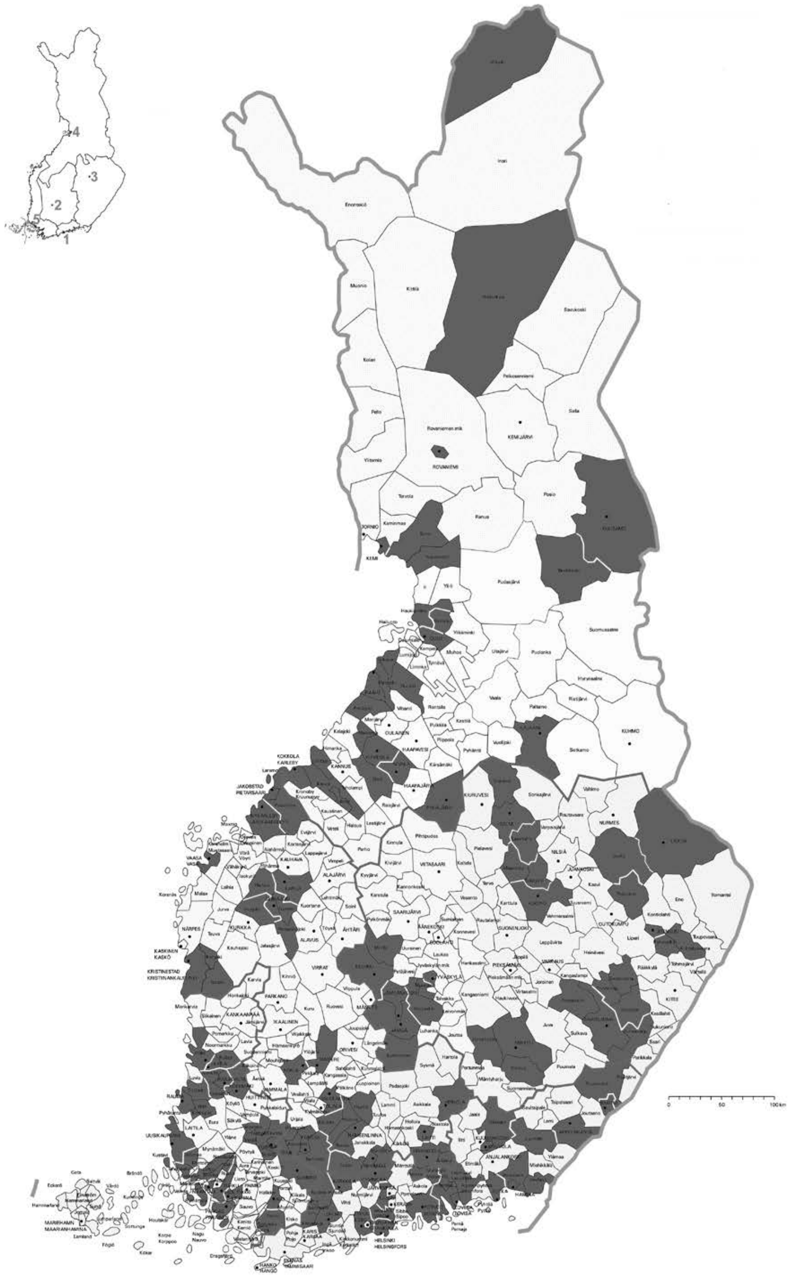

***Figure 3.*** *Study areas of the Health 2000 Survey. Study locations of the Health 2000 Survey are marked in dark grey on the map of Finland.*

The Health 2000 Survey included a structured health interview. The health interview elicited information about the participants' health, illnesses, medication, and functional ability as well as sociodemographic and health behavioral factors. In addition, during the health interview, the participant was given a questionnaire, which was to be returned on arrival at the health examination. If the person did not participate in the main interview, a supplementary interview was conducted later or eventually a questionnaire was sent. The participation rate in the health interview was 87% (n = 6 986). The participants took part at a comprehensive health examination in a health center (n= 6 354, 79% of the sample). The examination included measurement of anthropometry, functional capacity, and laboratory tests. In addition, a physical examination performed by centrally trained physicians and nurses was completed. The participants' height, weight, waist, and clinic BP were measured. Fasting blood samples for serum glucose and lipids were taken. In addition, a 12-lead resting ECG was recorded. An abbreviated health examination was conducted at home or in an institution for those who did not participate in the study center examination (n = 417, 5% of the sample). A detailed description of the study design, data collection methods, and health and functional status of population of the study have been published elsewhere [168, 169].

The study protocol of the Health 2000 Survey was approved by the Epidemiology Ethics Committee of the Helsinki and Uusimaa hospital region, and all participants gave a signed informed consent.

The study cohort from the initial Health 2000 Survey for studies I-III was selected as follows.
Persons who had not participated in the health examination (n=1257), had incomplete laboratory data (n=81), had not completed questionnaires properly (n=360), or had not participated in two measurements of BP (n=121), were excluded from the study. Altogether 6209 subjects were included for further analyses.

### *Study I*
Of those 6209 subjects, 388 patients with diabetes were included to Study I. Of these 324 were hypertensives, and 227 of the hypertensive diabetic patients used antihypertensive drugs. See Article I, Figure 1.

### *Study II*
Of those 6209 subjects, 527 coronary heart disease patients were included to Study II. Of these 396 were hypertensives, and 345 of the hypertensive CHD patients used antihypertensive drugs. See Article II, Figure 1.

*Study III*

Of those 6209 subjects, 1416 were using antihypertensive medication. Of those using antihypertensive medication, 687 subjects with diabetes, CHD, cardiac arrhythmias, or chronic heart failure were excluded. The remaining 729 uncomplicated hypertensive patients were included to Study III. See Article III, Figure 1.

### 4.1.2 Database of the Social Insurance Institution

*Studies I-II*

From the database of SII of Finland, comprehensive information on all prescribed antihypertensive and lipid-lowering drugs purchased in Finland between September 1st and November 30th in 2000, and in 2006, respectively, was gathered. Thereby prescribed drugs purchased by 722 405 individuals in 2000, and 993 680 in 2006, respectively, were included. Patients under 30 years were not included.

*Study I*

The data including antihypertensive- and lipid-lowering drug prescriptions were linked to the records concerning the patients entitled to reimbursed antidiabetic medication costs during the same year or one year after, respectively. Thereby, all Finnish adult diabetic patients aged 30 years or more, with entitlement to reimbursements for diabetes medication costs, were identified and included to the study (143 366 subjects in 2000-2001 and 187 099 subjects in 2006-2007). In addition, the entitlement to reimbursements for hypertension and/or CHD medication costs was also taken into account when applicable. See Article I, Figure 1.

*Study II*

The data including antihypertensive and lipid-lowering drug prescriptions, accordingly, were linked to the records concerning the patients entitled to reimbursement for CHD medication costs during the respective year. Consequently, all Finnish adult subjects aged 30 years or more with entitlement to reimbursement for CHD medication costs were identified and included to the study (192 440 subjects in 2000 and 206 394 subjects in 2006). In addition, the entitlement to reimbursements for hypertension and/or diabetes medication costs was also taken into account when applicable. See Article II, Figure 1.

*Study III*

From the database of SII of Finland, 100% of the prescribed antihypertensive drugs purchased in Finland between September 1st and November 30th in 2000, and in 2006, respectively, were collected. Patients under 30 years of age were excluded.

Thereby 699 936 individuals aged 30 years or over in 2000, and 880 654 in 2006, who used antihypertensive drugs, were identified and included to the study. From these 240 950 subjects with diabetes, CHD, cardiac arrhythmias, or CHF in 2000, and 289 448 in 2006, were excluded, and from the remaining subjects 428 986 treated uncomplicated hypertensive subjects were identified in 2000 and 591 206 in 2006. Of these, 264 313 moderately to severely hypertensive patients in 2000 and 288 352 in 2006 were identified. Accordingly, 164 673 mildly hypertensive patients in 2000, and 302 854 in 2006, respectively, were identified. See Article III, Figure 1.

*Study IV*

From the database of SII of Finland, 100% of the prescribed antihypertensive drugs purchased in Finland between September 1st and November 30th in 2000, and in 2006, respectively, were collected. These data were linked to the records of the subjects who were entitled to reimbursement of the medication costs of hypertension, diabetes, coronary heart disease (CHD), chronic heart failure (CHF), and cardiac arrhytmias, in 2000 and in 2006, respectively. In addition, records concerning reimbursements of antidiabetic medication costs, also one year after (i.e., 2001 and 2007, respectively), were included to the study. Patients under 30 years were not included. Consequently, from these data 274 791 formerly diagnosed moderately to severely hypertensives, 70 185 patients with uncomplicated mild hypertension, and 91 843 recently diagnosed moderately to severely hypertensives were identified.

## 4.2 Drug therapy

In the Health 2000 Survey, information on medication was elicited from a home interview and questionnaires were completed by centrally trained interviewers, described in detail elsewhere [168, 169]. The database of SII, included practically 100% of the prescriptions on antihypertensive and lipid-lowering drugs purchased by the Finnish population between 1st September and 30th November in 2000, and in 2006, respectively. All purchased drugs have been considered as a drugs used regularly. If a combination drug product was taken, the drug was accounted for in both drug classes.

## 4.3 Blood pressure measurement

BP measurements were available only in the Health 2000 Survey. BP was measured with the patient in a sitting position, from the right arm after a minimum of 10 minutes rest, with a conventional, calibrated sphygmomanometer (Mercuro 300, Speidel & Keller, Jungingen, Germany), by centrally trained professionals. The subjects were given instructions on how to prepare for the measurement. The measurement was done using a pressure cuff of appropriate size and methods in accordance with current guidelines [170]. The width of the rubber cuff was 12 cm and its length, 35 cm. If the proximal circumference of the upper arm measured at a height of 5 cm from the crook of the arm was in excess of 35 cm, a larger cuff (width 15, length 43 cm) was used. Systolic BP and diastolic BP were defined according to Korotkoff sounds I and V. The mean values of two measurements taken with a two-minute interval determined the systolic and diastolic BP.

## 4.4 Laboratory analyses

Laboratory analyses were available only in the Health 2000 Survey. Venous blood samples were taken from the antecubital vein after a minimum of four hours fasting. Total cholesterol, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, as well as the triglyceride and glucose concentrations were determined enzymatically (Roche Diagnostic, Mannheim, Germany, for HDL and LDL-cholesterol; Olympus System Reagent, Hamburg, for total cholesterol, triglyceride, and glucose) with a clinical chemistry analyzer (Olympus, AU4000, Hamburg, Germany).

## 4.5 Electrocardiography

ECGs, which were utilized in the diagnosis of MI and CHD, were available only in the Health 2000 Survey. Standard resting 12-lead ECG recordings were carried out in accordance with general clinical recommendations [170, 171]. ECGs were digitally recorded with a Marquette MAC 5000 device. The speed of paper during the recordings was 50mm per second. The ECGs were stored as digital data on a Marquette MUSE CV 5B system (Marquette Hellige, Milwaukee, WI, USA). All ECGs were overread by a single physician experienced with electrocardiography.

## 4.6 Medical history

In the Health 2000 survey, information concerning the subjects' medical history was elicited from health interviews, questionnaires, comprehensive health examinations (including clinical examination and laboratory analyses) of the initial Health 2000 Survey (I-III). In the database of SII, the information concerning medical history was simply based on subjects' entitlement to drug reimbursements for the medication costs of hypertension, diabetes, CHD, CHF, and cardiac arrhythmias (I-IV).

## 4.7 Definitions

### 4.7.1 The Health 2000 Survey

*Studies I-III*

A hypertensive patient was defined as being subject to at least one of four conditions: 1. documented definite hypertension diagnosis made by a physician at the health examination; 2. entitlement to reimbursements of hypertension medication costs; 3. a BP of 140/90 mmHg or over as measured at the health examination of the Health 2000 Survey; 4. a self-reported history of physician-diagnosed hypertension together with a regular use of antihypertensive medication (in Study II) or if he or she was taking antihypertensive medication (in Study I). All oral BBs, diuretics, antiadrenergic drugs, CCBs, ACE inhibitors, and ARBs were defined as antihypertensive regimens.

Diabetes mellitus was defined as a fasting serum glucose level of at least 7.0 mmol/l and/or a history of the use of antidiabetic drugs. The definition of CHD required at least one of the following: diagnosis of myocardial infarction (MI) and/or angina pectoris during the field examination; large Q-waves in ECG (including Minnesota codes 1.1 or 1.2 together with 5.1-2); hospitalization for CHD, a history of a coronary revascularization procedure; or having the entitlement to reimbursement for CHD medication costs. Chronic heart failure was defined by a documented history of congestive heart failure or a positive response to the medication for CHF. Cardiac arrhythmias were defined by a documented history of undeniable cardiac arrhythmia, existence of a cardiac pacemaker, or entitlement to reimbursement of cardiac arrhythmias medication costs conceded by SII. Definition of MI required either a clinical diagnosis of MI by the examining physician, large Q-waves indicating probable earlier MI (including Minnesota codes 1.1 or 1.2 together with 5.1-2), or an earlier hospital discharge with a diagnosis of MI (ICD-8 or ICD-9 code 410 or ICD-10 codes I21-I22). Peripheral arterial disease was defined by a documented history of arteriosclerosis of lower extremities or typical symptoms of claudication. Cerebrovascular disease was defined by a documented history of ischaemic or hemorrhagic stroke, transient ischaemic attack (TIA), or an anamnestically reliable stroke confirmed by a physician at the health examination. Retinopathy was defined as an earlier physician-made diagnosis of diabetic retinopathy, and nephropathy, as an earlier diagnosed renal failure, albuminuria, or changes in renal function caused by diabetes.

The definition of dyslipidemia was based on the Finnish dyslipidemia guidelines and required at least one of the following: A serum LDL-cholesterol value over 3.0 mmol/l; a serum triglyceride value over 2.0 mmol/l; serum HDL-cholesterol value less than 1.0 mmol/l; or the individual was already under lipid-lowering medication. As lipid-lowering drugs we included all drugs lowering serum cholesterol and triglycerides (fibrates also included). Smoking was defined as daily use of tobacco.

*Study III*

The definition of uncomplicated hypertension required a regular use of antihypertensive medication without presence of diabetes, CHD, cardiac arrhythmias, or CHF. The definition of mild hypertension required regular use of antihypertensive medication without entitlement to reimbursement for hypertension medication costs conceded by SII. The definition of moderate to severe hypertension required regular use of antihypertensive medication with entitlement to reimbursement for hypertension medication costs conceded by SII.

### 4.7.2 Database of the Social Insurance Institution

*Studies I-IV*

Hypertension, CHD, cardiac arrhythmias, and CHF, were defined as cases entitling to reimbursement for the medication costs of these specific illnesses as conceded by SII in 2000 and 2006, respectively. In case of diabetes, until 2010, the entitlement to reimbursement for diabetes medication costs may not have been conceded earlier than 6 months from the diagnosis of diabetes. Therefore, diabetic patients were defined as those entitled to reimbursement for antidiabetic medication costs during 2000 or 2001, and 2006 or 2007, respectively. Subjects using antihypertensive medication were defined as those who had purchased prescribed BP-lowering medication (oral BBs, diuretics, antiadrenergic drugs, CCBs, ACE inhibitors, or ARBs) between September 1$^{st}$ and November 30$^{th}$ in 2000, or 2006, respectively.

*Study III*

Those who had purchased BP-lowering drugs and were not entitled to reimbursement for medication costs of CHD, cardiac arrhythmias, CHF, or diabetes, were determined as uncomplicated hypertensive subjects. Accordingly, of those uncomplicated hypertensives, subjects were defined as moderately to severely hypertensive patients if they were entitled to reimbursement for hypertension medication costs, and, as mildly hypertensive patients, if they were not entitled to such reimbursement.

*Study IV*

Those using antihypertensive drugs without reimbursement for medication costs of hypertension, diabetes, CHD, CHF, or cardiac arrhythmias, were determined as uncomplicated mild hypertensives. As moderately to severely hypertensive subjects were defined those who were entitled to reimbursement for hypertension medication costs and who had purchased antihypertensive drugs. Though, subjects who were entitled to reimbursement for hypertension medication costs in 2006 but not in 2000 and who had purchased antihypertensive drugs in 2006 but not in 2000 were determined as recently diagnosed moderately to severely hypertensive subjects. On the other hand, those subjects who were entitled to reimbursement for hypertension medication costs in both 2000 and 2006 and who had purchased antihypertensive drug both in 2000 and 2006, were determined as formerly diagnosed moderately to severely hypertensive subjects.

## 4.8 Control of hypertension and estimated reduction of BP and cardiovascular morbidity

BP levels were measured only at the Health 2000 Survey in the beginning of the 2000s. BP levels and control of hypertension in 2006 were calculated by linking the data of the Health 2000 Survey and the database data of SII together and taking into account changes in age, sex, and drug utilization (mean number of antihypertensive drugs per treated subject) of the target population between late 2000 and late 2006. In addition, BP reductions as well as relative risks of stroke and ischaemic heart disease (IHD) events were calculated in resemblance with Law's meta-analyses [95], taking into account pre-treatment systolic and diastolic BP, age, number of drugs, and dose. The treatment was intensified, in theory, by adding one to two half standard doses (or one to two standard doses accordingly) only for those with a BP ≥140/90 mmHg. No drugs were added if a BP was already below 140/90 mmHg. The second drug was added only if the control of hypertension (BP<140/90 mmHg) was not achieved with the first drug add-on therapy.

## 4.9 Statistical analyses

Statistical analyses were performed with a SAS software version 9.1, (SAS Institute, Cary, North Carolina, USA). In studies I-III concerning data of the Health 2000 Survey, population weighting was taken into account. In studies I-III, comparisons between the Health 2000 Survey and the database of SII were made using a one-group t-test where the database mean value was taken as a constant. Categorical variables were compared with a chi-squared test where the database data was used to calculate the expected frequencies. The data from the databases of SII represent the whole population. Therefore, no statistical methods were used when comparing the database data. Data in tables are reported as mean values (SD) and/or percentages (I-IV). A P value of less than 0.05 was considered statistically significant.

*Study I*

A logistic regression analysis was used to calculate univariate odd ratios for a potential determinant of better controlled hypertension (BP less than 140/90 mmHg). Multivariate logistic regression with backward selection was used to identify independent determinants of a BP less than 140/90 mmHg. The variables included in the multivariate analyses were those reaching statistical significance in the univariate analyses. Only significant variables were retained in the model.

*Study III*

BP reductions as well as relative risks of stroke and ischaemic heart disease (IHD) events were calculated in resemblance with Law's meta-analyses, recently published and described in detail elsewhere [95], taking into account pre-treatment systolic and diastolic BP, age, number of drugs, and dose. The estimated effect of one drug at standard dosage at lowering BP from a pre-treatment blood pressure P is therefore (9.1 + 0.10 (P-154)) for systolic BP and (5.5 + 0.11 (P-97)) for diastolic BP. So, for example, the reduction in systolic BP was 8.7 mmHg from a pre-treatment value of 150 mmHg, and 4.7 mmHg in diastolic BP, from a pretreatment value of 90 mmHg. The higher the pre-treatment BP value was, the higher was the decrease in BP, and vice versa. The estimated BP reduction for two or three drugs at standard dosages was calculated by applying these equations to each drug in turn, allowing for the effect of the first in lowering pre-treatment BP for the second, and the second for the third.

In addition, the BP reductions obtained from one, two, and three drugs at half standard dose were [R + n x 0.078(P-150)] for systolic BP and [R + n x 0.088(P-90)] for diastolic BP, whereas P is the pre-treatment BP. R for systolic BP is 6.7 for the first drug, 13.3 for the second drug, and 19.9 for the third. For diastolic BP, accordingly, R is 3.7 for the first drug, 7.3 for the second drug, and 10.7 for the third drug. Thereby the first half standard dose decreases BP 6.7/3.7 mmHg, the second, 13.3/7.3 mmHg, and the third, 19.9/10.7 mmHg, when the pre-treatment BP is 150/90 mmHg. The higher the pre-treatment BP value is, the higher is the decrease in BP, and vice versa.

The associations between systolic and diastolic BP and CHD events and stroke were taken, as in Law's meta-analysis [95], from the largest published meta-analysis of 61 cohort studies [23]. Age-specific slopes of the lines (regression coefficients) were published, permitting the calculation of the predicted proportional reduction in disease events for any age and BP difference. For an age-specific regression slope S, and decrease in BP d, the relative risk was calculated using the formula

$S^{d/20}$ for systolic BP and $S^{d/10}$ for diastolic BP. Of these, the average value was used for relative risk.

### *Study IV*

Also two separate groups of patients were compared. Because of their differences in the mean values of their age, distribution of gender, and the geographical district of living, the prevalence of clinical diagnosis and the utilization of drugs were adjusted for age, gender, and district of living.

# 5 Results

## 5.1 Characteristics of study population

### 5.1.1 Study I (Diabetic patients)

The mean age of the diabetic patients in the Health 2000 Survey was 63 years, and 56% of them were males. Eighty-five percent of the diabetic patients had Type 2 diabetes. The mean BP was 147/83 mmHg, and 83% were receiving antihypertensive drugs. Twenty-one percent had CHD, 9% had suffered myocardial infarction, and 19% were current smokers. Diabetic patients in the database of SII, were on the average 2 years older, and the prevalence of females was somewhat higher than in the Health 2000 Survey. However, among the diabetic patients receiving antihypertensive drugs, there were neither age nor sex differences between the results of the Health 2000 Survey and the database of SII. Characteristics of the Finnish adult diabetic patients are shown in detail in Article I, Table 1.

### 5.1.2 Study II (CHD patients)

The mean age of the CHD patients in the Health 2000 Survey was 70 years, and 55% of them were males. The mean BP was 145/80 mmHg, and 82% were receiving BP-lowering drugs. Twenty-seven percent of the patients had gone through a coronary revascularization (PCTA or CABG). Seventeen percent of the patients had diabetes, 37% of the patients had suffered myocardial infarction, and 11% were currently smokers. There were no statistically significant differences in characteristics of the CHD patients between the Health 2000 Survey and the database of SII. Characteristics of the Finnish adult CHD patients are shown in detail in Article II, Table 1.

### 5.1.3 Study III (Uncomplicated hypertensive patients)

The mean age of the uncomplicated hypertensive patients in the Health 2000 Survey was 60 years, and 63% of them were females. The mean BP was 146/87 mmHg, and the mean duration of hypertension had been 12 years. Fifteen percent of the patients were currently smokers. Uncomplicated hypertensive patients in the database of SII were on the average 2 years older, and they used slightly more diuretics than their counterparts in the Health 2000 Survey.

Characteristics of the Finnish adult uncomplicated hypertensive patients are shown in detail in Article III, Table 1.

### 5.1.4 Study IV

#### *5.1.4.1 Subjects with uncomplicated mild hypertension*

The mean age of the subjects with uncomplicated mild hypertension in the database of SII in 2000 was 60 years (66 years in 2006), and 70% of them were females.

#### *5.1.4.2 Subjects with moderate to severe hypertension*

The mean age of the subjects with moderate to severe hypertension in the database of SII in 2000 was 63 years (69 years in 2006), and 58% of them were females. Thirteen percent of the patients had diabetes, 13% had CHD, 4% had CHF, and 2.5% had cardiac arrhythmias.

#### *5.1.4.3 Formerly diagnosed moderately to severely hypertensive subjects*

The mean age of the subjects with formerly diagnosed moderate to severe hypertension in the database of SII in 2006 was 69 years, and 58% of them were females. Twenty-one percent of the patients had diabetes, 17% had CHD, 5% had CHF, and 2.8% had cardiac arrhythmias.

#### *5.1.4.4 Recently diagnosed moderately to severely hypertensive subjects*

The mean age of the subjects with recently diagnosed moderate to severe hypertension in the database of SII in 2006 was 65.3 years, and 53% of them were females. Twenty-one percent of the patients had diabetes, 17% had CHD, 5% had CHF, and 3.5% had cardiac arrhythmias.

## 5.2 Prevalence, treatment, and control of hypertension (I-III)

### 5.2.1 The Health 2000 Survey

In the beginning of the 2000s, 83% of the diabetic patients were hypertensive and 69% of them were using BP-lowering medication. Accordingly, 75% of the CHD patients were hypertensives and 88% of them were using BP-lowering medication.

Of all hypertensive diabetic patients receiving BP-lowering drugs, 31% had a BP less than 140/90 mmHg, and 14%, less than 130/80 mmHg. Of all hypertensive CHD patients receiving BP-lowering drugs, the respective figures were 25% and 9%. Among uncomplicated hypertensive patients, 30% of those treated for hypertension had their BP controlled down below 140/90 mmHg. The control of BP according to the number of BP-lowering drugs among hypertensive diabetic patients receiving BP-lowering drugs is shown in Figure 2.  Among diabetic patients, better control of hypertension was associated with lower pulse pressure and lower mean arterial pressure. If pulse pressure and mean arterial pressure were excluded from the analysis, only CHF was independently associated with better control of hypertension. Among the CHD patients, a BP level of less than 140/90 mmHg tended to be reached more often in younger (≤ 70 years of age) than in older patients (30 vs. 21%, P= 0.06).

**POOR CONTROL OF BLOOD PRESSURE**
(independent of the number of antihypertensive drugs used)

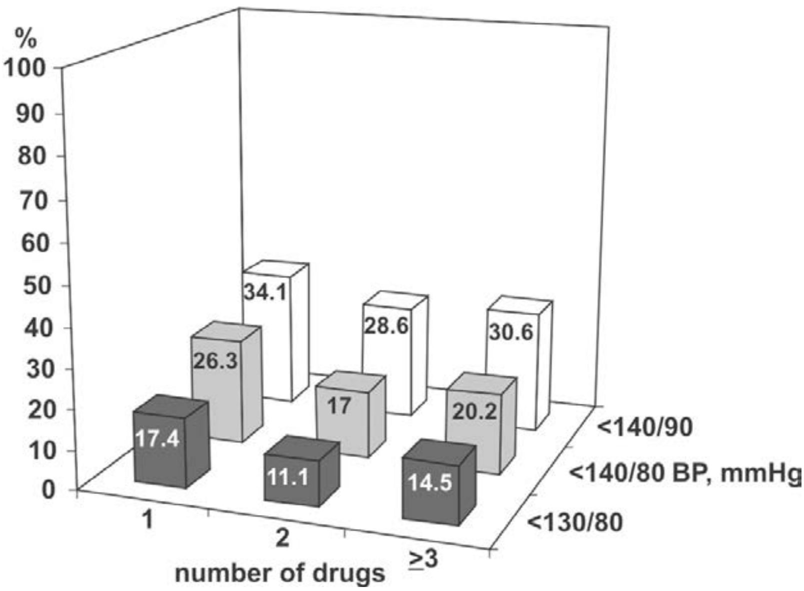


***Figure 4.*** *Association between control of blood pressure and number of antihypertensive drugs with different blood pressure cut of point. Only hypertensive diabetic patients (n=227) receiving antihypertensive drugs included. Results between patients using 1, 2, or ≥3 drugs are not comparable with each other because the characteristics of these patients are not equal. Adapted from Ahola et al. J Hypertens 2009, 27:2283-2293 (I).*

### 5.2.2 Database of the Social Insurance Institution

The number of diabetic patients receiving antihypertensive drugs increased by 53% (from 80 478 to 123 176) from 2000 to 2006. Accordingly, the number of CHD patients receiving BP-lowering drugs increased by 13% (from 141 454 to 160 262). The number of uncomplicated hypertensive patients receiving antihypertensive drugs increased by 38% (from 428 986 to 591 206), although the number of treated mildly hypertensives increased by 84% (from 164 673 to 302 854), respectively, from 2000 and 2006.

## 5.3 Estimated control of hypertension and reduction of BP and cardiovascular morbidity, with intensified antihypertensive treatment, among uncomplicated hypertensive subjects (III)

Taking into account changes in age, sex, and the mean number of antihypertensive drugs of the target population between 2000 and 2006, 34% of the treated uncomplicated hypertensive patients were assessed to have their BP controlled to below 140/90 mmHg in 2006. By adding one ordinary BP-lowering drug with a half standard dose for those with a systolic BP of 140 mmHg or more or diastolic BP or 90 mmHg or more would improve the control of hypertension (BP < 140/90 mmH) from 34% to 48%. This would reduce strokes by 18% and IHD events by 13%. In case one to two half standard doses of an ordinary BP-lowering drug were added for those with uncontrolled BP, when needed, the control of hypertension would increase up to a level of 67%. This would reduce strokes by 28% and IHD events by 21%.

The impact on BP control after intensifying the treatment, when needed, with one to two half standard/standard doses of ordinary antihypertensive regimen in 2006 is shown in Figure 5.

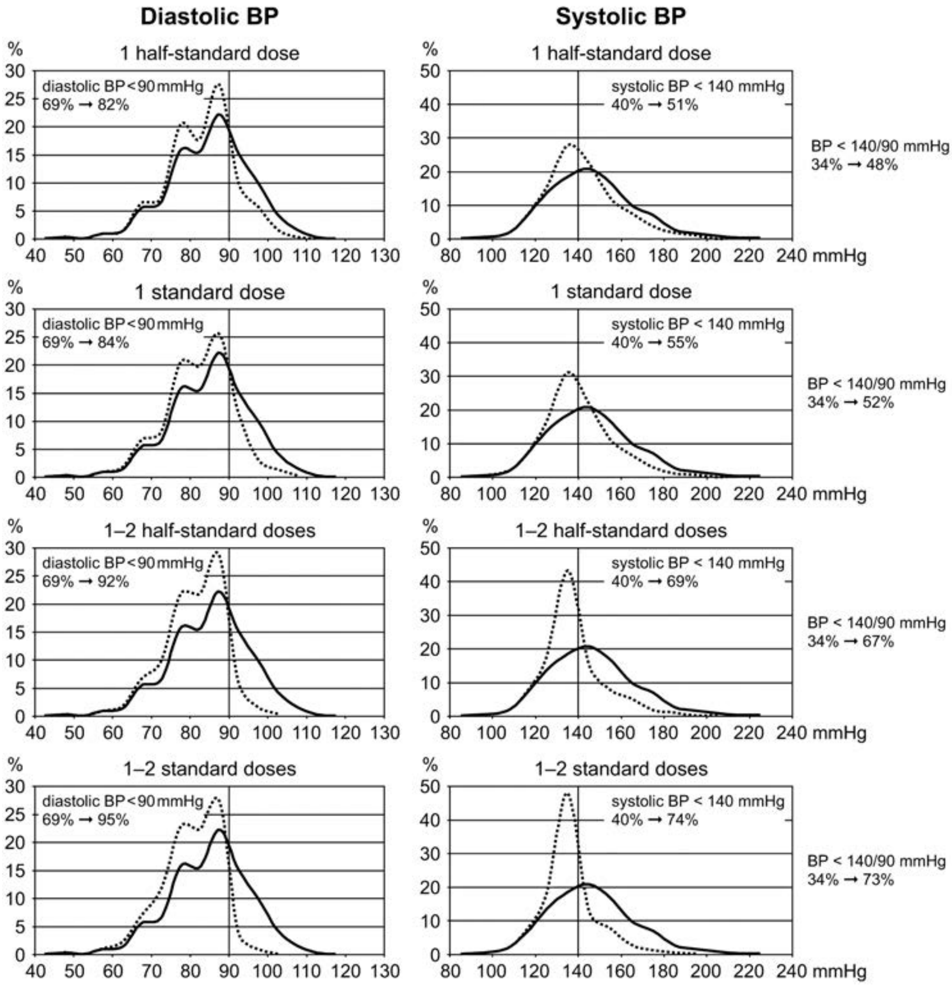


***Figure 5.*** *Impact on blood pressure (BP) control after intensifying treatment, when needed, with one to two half standard/standard doses of ordinary antihypertensive regimen in 2006. Distribution of primary BP is shown with full lines. Theoretical distribution of BP after intensification of treatment with one half standard dose, one standard dose, one to two half standard doses, and one to two standard doses, when needed, is shown with dashed lines. No drugs were added if a BP was already below 140/90 mmHg. The second drug was added only if the control target of hypertension (BP<140/90 mmHg) was not achieved with the first drug add-on therapy. Percentages on the left shows control of BP before intensification the drug therapy; percentages on the right shows data thereafter. Modified from Ahola et al. Eur J Prev Cardiol 2012, 19:712-722 (III).*

## 5.4 Antihypertensive drug therapy in Finland between 2000 and 2006

### 5.4.1 Diabetic patients (I)

The average number of BP-lowering drugs increased from 1.15 to 1.5 among all diabetic patients, and from 2.05 to 2.3, among those using antihypertensive drugs. Monotherapy decreased and combination therapy, especially the use of at least three BP-lowering drugs, increased significantly. During both years observed, the agent most frequently used in monotherapy was a BB or an ACE-inhibitor, whereas the drugs most frequently used in combination therapy were diuretics combined with BBs or ACE-inhibitors. The most often prescribed combination of at least three antihypertensive drugs, on the average, was a combination of diuretics, BBs and ACE inhibitors. Use of ARBs on the average tripled in monotherapy and in combination therapy. Utilization of either an ARB or an ACE-inhibitor was increased by 25-46%. Prescriptions of BBs, CCBs, and diuretics increased to a lesser degree. Utilization of BP-lowering drugs among diabetic patients receiving antihypertensive drugs in 2000 and in 2006 is shown in detail in Article I, Tables 3 and 4.

### 5.4.2 CHD patients (II)

Monotherapy decreased and combination therapy, especially the use of at least three BP-lowering drugs, increased. The average number of BP-lowering drugs increased from 1.3 to 1.5 among all CHD patients, and from 1.8 to 2.0 among those using antihypertensive drugs. During both years observed, the agents most frequently used in monotherapy were BBs (approximately three-quarters), while the drugs most frequently used in combination therapy were BBs combined with diuretics or ACE-inhibitors. The combination of at least three drugs most often prescribed was a combination of diuretics, BBs, and ACE-inhibitors. Use of ARBs on an average quadrupled in monotherapy and tripled in combination therapy. Utilization of BP-lowering drugs among CHD patients receiving antihypertensive drugs in 2000 and in 2006 are shown in detail in Article II, Tables 3 and 4. Recent CHD patients, as compared with those with a longer history of CHD, used more BBs and RAS blockers, although recent CHD patients had less comorbidities than their counterparts. Yet, the total number of antihypertensive drugs was essentially similar among these two groups of patients (Article II, Table 5).

### 5.4.3 Uncomplicated hypertensive patients (III)

The average number of BP-lowering drugs increased from 1.75 to 1.82 among treated uncomplicated hypertensive patients (from 1.95 to 2.14 among treated moderately to severely hypertensives and from 1.42 to 1.51 among treated mildly hypertensives).
The prescribing pattern for monotherapy regimen decreased while combination antihypertensive medication increased. The use of RAS blockers was increased more than 40%. The use of ARBs was more than doubled in monotherapy and increased two- to three-fold in combination therapy. Thereby, ARBs became the thirdly popular drugs after BBs and diuretics while ACE-inhibitors dropped from third to fifth place after CCBs. Use of BBs decreased, although they still remained most frequently used drugs among uncomplicated hypertensive patients. Utilization of diuretics increased, while utilization of ACE-inhibitors and CCBs decreased. The two-drug combination most frequently used became an ARB combined with a diuretic. The combination of at least three drugs most often prescribed became a combination of diuretics, BBs, and ARBs. Utilization of BP-lowering drugs among uncomplicated hypertensive patients receiving antihypertensive drugs in 2000 and in 2006 are shown in detail in Article III, Tables 1 and 2.

## 5.5 Changes in the utilization of antihypertensive drugs and concomitant diseases on the individual level between 2000 and 2006 (IV)

### 5.5.1 Subjects with moderate to severe hypertension

Among 274 791 moderately to severely hypertensive individuals the prevalence of diabetes increased 57%, to a level of 20%, and CHD increased 39%, to a level of 18%. The prevalence of CHF and cardiac arrhythmias increased to a lesser degree (see Article IV, Table 1, Group 1).
The mean number of antihypertensive drugs increased from 2.0 to 2.3. Monotherapy decreased from 36% to 24%, and combination therapy with at least 3 or more antihypertensive drugs increased from 30% to 42%. BBs remained the most frequently used antihypertensive drugs in monotherapy and in combination therapies, although the use of ARBs increased by 146%. The 2-drug combination used most frequently in 2000 and 2006 was a BB combined with a CCB (26% and 22%). However, for a 2-drug combination in 2006, 29% used a combination of a RAS blocker (ACE inhibitor or ARB) and a diuretic, while 19% used a combination of a RAS blocker and a BB. The most frequently used combination of at least 3 drugs, in 2006, became a combination of BBs, diuretics, and CCBs (27% of those using more

than 2 drugs), while 50% used a combination including RAS blocker(s), diuretic(s), and BB(s) and 34% used a combination including RAS blockers(s), diuretic(s), and CCB(s) (Article IV, Table 2, Group 1).

### 5.5.2 Subjects with uncomplicated mild hypertension

Among 70 185 uncomplicated mild hypertensive individuals, who did not develop diabetes or cardiac diseases during the follow-up time, the mean number of antihypertensive drugs increased from 1.4 to 1.7 (Article IV, Table 1, Group 2).
Monotherapy decreased from 67% to 51% and combination therapy with at least 3 or more antihypertensive drugs increased from 8% to 17%. BBs clearly remained the most frequently used drugs in monotherapy and in combination therapies, although the use of ARBs increased by 140%. The 2-drug combination used most frequently in 2000 and 2006 remained another 2-drug combination (mostly a combination of two different diuretics; a thiazide diuretic combined with a potassium-sparing diuretic). However, for 2-drug combinations in 2006, 27% used a combination of a RAS blocker and a diuretic, while 16% used a combination of a BB and a diuretic. In combination therapy with at least three BP-lowering drugs, a combination including BB(s), diuretic(s), and ARB(s) became the most common (19%). 36% used a combination including RAS blocker(s), BB(s), and diuretic(s) whereas 16% used a combination including RAS blocker(s), CCB(s), and diuretic(s) (Article IV, Table 2, Group 2).

## 5.6 Differences in utilization of antihypertensive medication in 2006 between recently and formerly diagnosed subjects with moderate to severe hypertension (IV)

Recently diagnosed moderately to severely (RDMS) hypertensive subjects used on the average 2.1 antihypertensive drugs, which was 10% less than that used by formerly diagnosed moderately to severely (FDMS) hypertensive subjects. Thus, the prevalence of diabetes, CHD, and CHF were essentially similar among these two patient groups. RDMS hypertensives were more often on monotherapy (+25%) and on 2-drug combination therapy (+7%) and less (-23%) on combination therapy with three or more BP-lowering drugs than were the FDMS hypertensive subjects. Among RDMS hypertensives, the most frequently used antihypertensive drugs were the diuretics, followed by BBs, CCBs, ARBs, and ACE-inhibitors. Among FDMS hypertensives, the most frequently used antihypertensive drugs were the BBs, followed by diuretics, CCBs, ACE-inhibitors, and ARBs. Thus, the RDMS hypertensives used 14% less BBs, 8% less diuretics, 16% less CCBs, and 14% less

ACE-inhibitors but 27% more ARBs than the FDMS hypertensive subjects. (Article IV, Table 3).

In monotherapy, the BBs, followed by ACE-inhibitors and CCBs, were the most frequently used BP-lowering drugs among RDMS hypertensives as well as among FDMS hypertensives. Still, the RDMS hypertensives used 130% more ARBs on monotherapy and 67% more 2-drug combination of ARBs and diuretics than the FDMS hypertensives. The most frequently used 2-drug combination among the RDMS hypertensives was a diuretic combined with an ARB (23%), while among the FDMS hypertensives that was a combination of a CCB and a BB. However, a combination including a RAS blocker and a diuretic was used by 37% and 31% of the RDMS and FDMS hypertensives, respectively. In combination therapy with at least three BP-lowering drugs, a combination including diuretic(s), BB(s), and ARB(s) became the most common (27%) among the RDMS hypertensives while among the FDMS hypertensives that was a combination including diuretic(s), BB(s) and CCB(s) (27%). However, a combination including RAS blocker(s), diuretic(s), and BB(s) was used by 48% and 49% and a combination including RAS blocker(s), diuretic(s), and CCB(s) by 34% and 35% of the RDMS and FDMS hypertensives, respectively (Article IV, Table 4).

# 6 Discussion

## 6.1 Utilization of antihypertensive drugs and control of hypertension among diabetic patients in Finland between 2000 and 2006 (I)

In 1994 the FHA working group guidelines [32] recommended ACE inhibitors for initial antihypertensive medication for diabetic patients, especially if nephropathy was related. The FCCH guidelines published in 2002 [12] and updated in 2005 [13] recommended all major antihypertensive agents, although RAS blockers were preferred in case of diabetic nephropathy. The ESH guidelines published in 2003 [16], stated that all well tolerated and effective agents can be used, although it also favored ACE inhibitors for Type 1 diabetic nephropathy and ARBs for Type 2 diabetic nephropathy. The JNC7 [18], published in 2003, recommended BBs only in case of concomitant ischaemic heart disease whereas the FCCH guidelines, updated in 2005, noted that thiazide diuretics and BBs [107] without intrinsic sympathomimetic activity may increase blood glucose level but improve diabetic patients prognosis [8].

RAS blockers may offer additional vasculoprotective benefits to high-risk diabetic patients beyond BP control [31, 40, 74]. There is evidence that RAS blockers retard the development and/or progression of diabetic nephropathy [40, 71, 72, 172]. Since 2007, guidelines have recommended RAS blockers as a compelling indication for diabetic patients. On the other hand, many studies support the view that the reduction of BP *per se* is more important than the individual properties of the specific drug, for decreasing cardiovascular risk among most hypertensive diabetic patients [8, 9]. According to recent evidence, however, no benefit is achieved except for those at a high risk of stroke, if the systolic BP is lowered intensively below 130 mmHg [41, 42], or below 120 mmHg [43], as compared with those with target systolic BP <140 mmHg. The FCCH guidelines [12] lowered the target BP for diabetic patients from 140/90 mmHg to 140/80 mmHg not earlier than 2002, although the WHO-ISH ESH guidelines [45] published already in 1999 stated that the desirable BP goal for diabetic patients is below 130/85 mmHg. Beyond that in 2003 the JNC7 [18] and the ESH guidelines [16] lowered the target BP below 130/80 mmHg, which was still the current international recommendation during the year 2006. However, the national recommendation in 2006 was to lower the BP below 140/85 mmHg according to the FCCH guidelines [13] updated in 2005.

According to the present study (I), during the early 2000s, 80% of the Finnish adult diabetic patients were hypertensive. Two-thirds of them were receiving antihypertensive medication and 31% of the treated hypertensive diabetic patients had their BP reduced to below 140/90 mmHg and only 14% below 130/80 mmHg. CHF was independently associated with better control of hypertension. This is quite understandable considering the impaired left ventricular ejection fraction and reduced cardiac output and/or antihypertensive polypharmacy of patients with CHF. However, age, gender, BMI, smoking, alcohol consumption, BP-lowering or lipid-lowering drug therapy, number of antihypertensive drugs, or any other comorbidities were not associated with better control of BP.

Between 2000 and 2006, monotherapy as well as utilization of exactly two antihypertensive drugs decreased relatively because combination therapy, especially the use of three or more antihypertensive drugs, increased significantly. Use of ARBs on the average tripled while the use of RAS blockers increased from 59% to 74%. In the early 2000s, according to the Health 2000 Survey, three-quarters of the hypertensive diabetic patients with nephropathy used either ACE-inhibitors or ARBs. During both observed years the agent most frequently used in monotherapy was a BB or an ACE-inhibitor, whereas the drugs most frequently used in combination therapy were diuretics combined with BBs or ACE-inhibitors. The use of renin-angiotensin system blockers was increased by 25-46% due to a three-fold increase in the utilization of ARBs. Combination therapy with RAS blockers together with diuretics increased by approximately 40% to a level of 40%, and the combination of RAS blockers with CCBs increased by 60% to a level of 22%. This increasing trend in the combination therapy with RAS blockers and diuretics or CCBs is favorable and in accordance with evidence-based data from trials [31, 74] and national and international guidelines [13, 19]. The most frequently used combination of at least three antihypertensive drugs in 2000 and in 2006 was a combination of diuretics, BBs, and ACE-inhibitors, although the use of this combination decreased relatively between 2000 and 2006 because in many cases ACE-inhibitors seemed to be replaced by ARBs. It is speculative but possible that the skills of the physicians in the management of hypertension, as a consequence of the treatment guidelines, have improved. On the other hand, increased production and vigorous marketing of well tolerated ARBs could largely explain the change observed in combination therapy.

According to the results of this study, the prevalence of hypertension among Finnish adult diabetic patients in the early 2000s was higher and the control of hypertension lower than those observed in other population studies in US, Mexico, and Sweden [133, 136 146, 173]. Moreover, in the beginning of the last decade, hypertensive diabetic patients in Finland were prescribed more BBs and diuretics and as much or less RAS blockers than was prescribed in UK [128] and US [139]. The results of this study are in line with several previous studies demonstrating underutilization of RAS blockers [128, 174, 175]. However, there is evidence that the use of RAS blockers has increased from the 1990s to 2000s [128, 162, 164]. Despite the fact that evidence-based drug therapies have increased among Finnish diabetic patients, there is a still need for more rational antihypertensive medication. For example, of the diabetic patients using BBs, only 40% in 2000 and 36% in 2006 had CHD. Furthermore, of those receiving antihypertensive drugs, without CHD, still 43% in 2000 and 47% in 2006 used BBs, which indicates relative overutilization of BBs among hypertensive diabetic patients. These findings highlight that physicians should take into account more precisely the individual characteristics and comorbidities when selecting antihypertensive agents for diabetic patients. The significance of the high utilization rate of BBs in the development of new-onset diabetes in Finland requires further investigation.

## 6.2 Utilization of antihypertensive drugs and control of hypertension among CHD patients in Finland between 2000 and 2006 (II)

A BB has been the drug of choice for hypertensive CHD patients, and Finnish national guidelines [12, 13, 32] have recommended their primary use in each guideline. Since JNC6 [17], with minor exceptions, ACE inhibitors, as antihypertensive drugs, have been a compelling indication for CHD after MI. However, FCCH guidelines in 2002 [12], and in 2005 [13], recommended ACE inhibitors as a possible indication but not as a compelling indication until in most recent guidelines published in 2009 [14]. ARBs have become competitive drugs for the ACE inhibitors since the ESH/ESC guidelines, published in 2007, although the FCCH guidelines in 2009 [14] have recommended their use in case the ACE inhibitor is not tolerated.

According to meta-analyses of six randomized placebo-controlled trials, treatment with ACE-inhibitors reduces all-cause mortality, cardiovascular mortality, and nonfatal MI, among CHD patients with preserved left ventricular function [112]. According to the HOPE study, the ACE-inhibitor Ramipril reduced the rate of cardiac death and MI by 20% among high-risk patients [46]. ARBs have proven to be non-inferior when compared with ACE-inhibitors in the prevention of CV events [67, 83, 85]. Still, for patients with hypertension and stable angina pectoris, the first drug of choice is a BB [176]. However, the benefit can also be obtained with different drugs and drug combinations, including CCBs, and it appears to be related to the degree of BP reduction [66].

According to the present study (II), during the early 2000s, three-quarters of the CHD patients were hypertensive and nearly 90% of them used antihypertensive medication. Of those receiving antihypertensive drugs, one quarter had the BP reduced below 140/90 mmHg and 9% had a BP less than 130/80 mmHg. According to Finnish national guidelines [12, 32] the target BP for CHD patients (as with the general population) was below 160/90 mmHg in 2000 and below 140/85 mmHg in

2006. On the other hand, according to international guidelines (JNC6 [17]), the target BP below 140/90 mmHg was the current recommendation among CHD patients before and during the follow-up time 2000-2006. This target, because of inconsistent evidence, still seems essentially reasonable as reappraised in recent guidelines [7].

Between 2000 and 2006, the use of RAS blockers increased markedly, mostly because of the more than three-fold increase in the use of ARBs. Owing to the increased use of ACE-inhibitors and ARBs, combination therapy with RAS blockers together with diuretics, BBs, and CCBs increased, which is in accordance with evidence-based data from trials and national and international guidelines [13, 19, 66, 176, 177]. Still, RAS blockers seemed to be underused among hypertensive CHD patients. BBs, instead, were already comparatively frequently used in 2000 and increased only by 5%, to a level of 77-79%, by the late 2006.

Earlier national studies in Europe have shown inadequate risk factor management for patients with CHD: PREVESE I and II studies in Spain [150, 166], Usik and PREVENIR in France [178], TASPIC-CRO study in Croatia [154], a national survey in Switzerland [151], and Euroaspire surveys I-III in eight European countries [148] (Finland being one of the participating countries). The results of the present study (III) are in line with the Euroaspire surveys [148], national surveys in Switzerland [151] and France [178], showing high prevalence of BBs and underutilization of RAS blockers. However, in this study, BBs were used more frequently but ACE-inhibitors less frequently than in earlier studies in Spain [150], France [178], Croatia [154], and Switzerland [151], in the beginning of the 2000s. On the other hand, results of this study are in line with the Euroaspire surveys by showing an increase in the use of BBs, RAS blockers, and diuretics, although all major antihypertensive agents were used less frequently than on the average in the recent Euroaspire survey [148, 149]. However, the utilization of diuretics in Finland, according to Euroaspire II, was exceptionally low (12%), and contrary to the other European countries, the use of diuretics even decreased in Finland, to a level of 11%, between 1999-2000 and 2006-2007 [149]. The results of the present study are not in line with these figures concerning the utilization of diuretics among CHD patients in Finland. Quite on the contrary, utilization of diuretics among Finnish CHD patients also increased but not as much as in many other European countries. It is worth noting that the studies in the Euroaspire surveys [148] were limited to outpatients ≤ 70 years of age who had a history of MI or acute coronary syndromes or coronary revascularization.

It seems that evidence-based drug therapies have increased among Finnish CHD patients between 2000 and 2006. As an example, recent CHD patients were prescribed BP-lowering drugs in 2006 more rationally (i.e., more BBs and more RAS blockers were used) than were those with longer history of CHD. It is speculative but possible that the skills of the physicians in the management of hypertension, as a consequence of the recent guidelines, have improved. This is supported by the findings, which show that even among same individuals the utilization of RAS blockers has increased from late 2000 to late 2006. Though, aging and increased prevalence of diabetes, hypertension, and other comorbidities might have also increased their usage. On the other hand, increased marketing of well tolerated ARBs, alone or in combination with diuretics, could largely explain the changes in combination therapy.

## 6.3 Utilization of antihypertensive drugs, control of hypertension and achievable reduction in BP and cardiovascular morbidity among uncomplicated hypertensive patients in Finland between 2000 and 2006 (III)

The FCCH guidelines [12-14] and JNC6 [17] have specified antihypertensive medication for uncomplicated hypertensive patients. In other guidelines, uncomplicated hypertensive patients have been included with patients with essential or primary hypertension. The FCCH guidelines published in 2002 [12] recommended starting antihypertensive medication with low-dose thiazides, ACE inhibitors, or BBs, for uncomplicated hypertensive patients. CCBs and ARBs were optimal in specific cases. In 2005, FCCH guidelines [13] stated that the treatment of uncomplicated hypertension can be initiated with RAS blockers, BBs, diuretics, and CCBs. However, it noted the poor evidence of benefits with BBs in the treatment of uncomplicated hypertension. In combination therapy, the FCCH guidelines in 2005 [13] noted that most drugs can be combined.

Between 2000 and 2006, the number of treated adult uncomplicated hypertensive patients increased from nearly 430 000 to more than 590 000 while the mean number of antihypertensive drugs increased from 1.7 to 1.8. At the same time monotherapy decreased and combination therapy increased. The proportion of mildly hypertensives nearly doubled while moderately to severely hypertensives increased only slightly. The increase of subjects treated for milder forms of hypertension suggests that clinicians have complied with national and international guidelines in that respect. On the other hand, the increase of subjects treated for milder forms of hypertension can also be interpreted that the criteria for the reimbursement of hypertension medication costs conceded by the SII meets the criteria of clinical hypertension set by international and national guidelines even less than before [13, 16].

According to the results of this study (III), the use of RAS blockers increased more than 40% because the use of ARBs more than doubled in monotherapy and increased two-fold to three-fold in combination therapy. Thereby, ARBs became the thirdly popular drugs after BBs and diuretics while ACE-inhibitors dropped from third to fifth place after CCBs. Use of BBs decreased, although they remained the most frequently used drugs among uncomplicated hypertensive patients without specific indications for their use. Utilization of diuretics, especially thiazide diuretics, increased due to their frequent use in combination therapy with ARBs. In fact, by the end of 2006, the two-drug combination most frequently used was an ARB combined with a diuretic, which is in line with the findings from RCT trials [73] and guidelines [7, 16]. The combination of at least three drugs most often prescribed became a combination of diuretics, BBs, and ARBs. British Hypertension Society Guidelines, published two years earlier, in 2004, recommended a blocker of renin-angiotensin system, a CCB, and a thiazide-diuretic, as a three-drug combination, which is still in line with the recommendations of recent European Guidelines on Hypertension Management published in 2009 [7].

It seems that, as first-line agents, BBs (especially among mildly hypertensives) were chosen more frequently than other antihypertensive agents. The status of BBs as first-line agents has been impugned. British Hypertension Society Guidelines for hypertension management, for instance, placed BBs within brackets in the AB/CD algorithm in 2004 [177]. However, recently published hypertension guidelines [7] have stated that BBs can initiate the treatment of hypertension, even in monotherapy. Still, recent guidelines have acknowledged, and there is evidence, that BBs decrease the risk of stroke less than other antihypertensive agents, especially among elderly patients [98]. Accordingly, BBs and especially combinations of BBs and diuretics should be avoided as primary treatment among individuals with a metabolic syndrome or increased risk for new-onset diabetes [99-101]. Worth considering is the fact that a combination of a BB and a diuretic was still on the list of efficient and well tolerated two-drug combinations in the hypertension guidelines published in 2003 [16]. In Finland in 2000-2006, fortunately, concerning two-drug combinations, a combination of a BB and a diuretic retreated from third to fourth place during the follow-up time.

Studies published earlier, concerning treated uncomplicated hypertensive patients have either involved a relatively small number of patients or have been made in special clinics or have included hypertensive patients only with a certain stage, and are therefore not comparable with this study. To date, this is the first longitudinal study prescribing in detail the use of different antihypertensive drug combinations (including three or more antihypertensive drugs) among adult treated uncomplicated hypertensive patients at a population based level.

It is well known that a combination therapy is usually required to achieve a proper control of BP whereas a low-dose combination therapy increases the efficacy and reduces adverse effects of the treatment [6, 7, 103]. According to the results of the present study, only one-third of the treated uncomplicated hypertensive patients were assessed to have their BP controlled to below 140/90 mmHg in 2006. By applying Law's meta-analyses to the results of the present study, an addition of only one-half standard dose, when needed, for subjects with a BP ≥ 140/90 mmHg, would improve the control of hypertension from one-third to 48%. This, accordingly, would reduce the incidence of strokes by 18% and ischaemic heart disease events by 13%. Therefore, more abundant antihypertensive treatment is evidently needed in order to improve the control of hypertension and to decrease cardiovascular morbidity among uncomplicated hypertensive patients.

The threshold for the reimbursement for hypertension medication costs in Finland is much higher than the thresholds for antihypertensive drug treatment presented in national [13] and international [19] guidelines. On the other hand, treatment of cardiovascular complications is a significant burden for the Finnish health care also from the financial point of view. Quite on the contrary, intensified antihypertensive treatment would substantially reduce cardiovascular morbidity among uncomplicated hypertensive patients. Beyond that, the entitlement to reimbursement for hypertension medication costs by lowering the patient's expenses would probably increase the treatment compliance. Under these circumstances it seems reasonable to recommend lowering the threshold for the reimbursement of hypertension medication costs in Finland. To what level precisely, from the public economic point of view, however, requires further clarification.

## 6.4 Beta-blockers are relatively overused in Finland (IV)

The guidelines of the nineties (FHA working group [32] and JNC6 [17]) recommended the initiation of antihypertensive medication with a diuretic or a BB unless contraindicated or specifically indicated for another drug. In 2002, the FCCH guidelines [12] recommended the initiation of antihypertensive medication with low-dose hydrochlorothiazides, ACE inhibitors, or BBs. According to national and international guidelines since the early 2000s, each agent can be preferentially prescribed under specific conditions [13, 14, 16]. The FCCH guidelines, published in 2002 [12] (updated in 2005 [13]), and the ESH and ESC guidelines for the management of arterial hypertension, published in 2003 [16], demonstrated evidence that specific drug classes may differ in some effect or with special groups of patients. However, the ESH guidelines stated that the main benefit of antihypertensive therapy is due to lowering BP *per se* [16]. Nevertheless, guidelines have emphasized that physicians should tailor the drug treatment for the individual patient after taking into account the patient's cardiovascular risk profile, target organ damage, and other coexisting disorders, as well as the indications and contraindications of the specific drug classes [13, 16]. Beyond that the ESH guidelines [16] emphasized the importance of low-dose combination therapy and established the renoprotective effects of RAS blockers [16]. However, since then the status of BBs as first line agents has been impugned. The AB/CD algorithm, for example, was brought out in 2004 [177]. According to meta-analyses of Lindholm et al, BBs should not be used as first choice in the treatment of primary hypertension. Furthermore, there is evidence that BBs decrease the risk of stroke less than other antihypertensive agents, especially among elderly patients. Besides, the ESH/ESC guidelines [19] suggested that BBs and, especially, combinations of BBs and diuretics should be avoided as primary treatment among individuals with a metabolic syndrome or increased risk for new-onset diabetes.

This study (IV) is the first study providing longitudinal nationwide data of the utilization of antihypertensive medication for subjects treated for moderate to severe hypertension and mild uncomplicated hypertension, in relation with changes in concomitant disease profiles at the individual level. According to the results of this study, among moderately to severely hypertensives (Group 1) as well as among uncomplicated mild hypertensives (Group 2), the mean number of antihypertensive drugs increased on the average by 0.3. Accordingly, monotherapy decreased while combination therapy increased. There are some possible explanations for these changes. Firstly, combinations of two drugs in a single tablet, which improve medication compliance [102], have become widely available during the last decade. Secondly, the majority of clinicians might have been influenced by the guidelines emphasizing the importance of combination therapy [13, 16]. Thirdly, in this study, patients in groups 1 and 2 became 6 years older, which probably increased the need for additional drugs, because higher age increases systolic BP. Fourthly, moderately to severely hypertensives (Group 1) developed more concomitant diseases, especially diabetes and CHD, which very likely called for more frequent and more effective drug therapy. Among uncomplicated mild hypertensives (Group 2), new-onset of diseases can not explain the increase in drug therapy, because existence of diabetes and cardiac diseases were excluded during the whole period of observation.

Utilization of BBs increased between 2000 and 2006, and they remained clearly the most frequently used antihypertensive drugs in both groups. This relative overuse of BBs was more outstanding among uncomplicated mild hypertensives (Group 2), although the patients had no compelling indication for the use of BBs. It is possible that vigorous marketing of BBs, particularly methoprolol, in the 1990s and early 2000s, is one probable reason for the high utilization of BBs.

The utilization of ARBs increased remarkably. There are several reasons for this: Firstly, the beneficial effects of ARBs, which go beyond the BP-lowering effect, has been proven at several trials and presented widely in the preceding guidelines [16, 19]. Secondly, fixed combinations of two drugs, particularly those of a RAS blocker combined with a thiazide diuretic, has increased during the recent years. On the other hand, among moderately to severely hypertensives, the prevalence of ACE inhibitors even decreased slightly during the follow-up time. Obviously quite often ACE inhibitors have been replaced by increasingly marketed ARBs, which are better tolerated.

The RDMS hypertensives used slightly less antihypertensive drugs than the FDMS hypertensives (2.1 vs. 2.3 per day) despite having essentially a similar burden of concomitant diseases. Diuretics, followed by BBs, were the most frequently used drugs for RDMS hypertensives, while for FDMS hypertensives, they appeared in reverse order. As expected, in monotherapy and in 2-drug combinations, ARBs and RAS blockers were clearly used more frequently for RDMS hypertensives than for FDMS hypertensives. However, concerning at least 3-drug combinations, a RAS blocker combined with a diuretic and a CCB was used less frequently for RDMS hypertensives than for FDMS hypertensives. It seems that, even for RDMS hypertensives, RAS blockers are prescribed as second-line or third-line drugs after BBs. Beyond that, monotherapy was more common for RDMS hypertensives than for FDMS hypertensives, which indicates that the RDMS hypertensives must have had milder hypertension and thereby less need for antihypertensive medication than the FDMS hypertensives. This, however, on the ground of missing BP measurements, is disputable. Anyhow, shorter history of hypertension could indicate milder hypertension. Beyond that it is possible that non-pharmacologic treatment of the RDMS hypertensives is more powerful than the treatment of those with a longer history of antihypertensive pharmacotherapy. Another explanation could be that, due to a recent diagnosis, the RDMS hypertensives have not had time to acquire the intensification of pharmacotherapy. Nevertheless, quite surprisingly, also for the RDMS hypertensives, BBs were clearly the most frequently used drugs in monotherapy. Besides, in monotherapy, the RDMS hypertensives used relatively 11 percent more BBs than did the FDMS hypertensives. Only approximately one fifth of the RDMS hypertensives had a compelling indication for BBs. Still, approximately one-half of all RDMS hypertensives and one-third of those on monotherapy used BBs.

However, despite the substantial differences in methodology, earlier studies share some similarities with our recent study. Results of this study are in line with earlier studies demonstrating a significantly increasing trend in the use of antihypertensive agents [179]. A relatively high prevalence of BBs, on the average 62%, has been reported in four European countries: Belgium, Germany, Switzerland, and Sweden [180]. In monotherapy, BBs in the present study, in 2006, were used more frequently than in Portugal, Canada, and England [181-183]. However, among newly treated hypertensive patients, BBs were used as first-line agents in Sweden and in the Netherlands even more frequently than for the recently diagnosed moderately to severely hypertensives in the present study [160]. It seems that BBs are more frequently used in the Northern European countries. Accordingly, RAS blockers were prescribed in Finland, in monotherapy and in 2-drug combinations, less than in Portugal, Canada, and England [181-183]. According to the results of this study, a preferred 3-drug combination (a RAS blocker plus a CCB plus a diuretic) was used by 11-22% of the subjects in 2006. However, the corresponding figure was 31% in England [183] and 45% in Portugal [181]. The European Society of Hypertension guidelines [7] and Finnish Current Care Hypertension guidelines [14] did not state clearly the preferred 3-drug combinations until in 2009, although a blocker of renin-angiotensin system and a CCB and a thiazide-diuretic was already stated as a recommended 3-drug combination in the British Hypertension Society Guidelines in 2004 [52].

Treatment guidelines of hypertension are insufficiently followed, particularly among those with a longer history of antihypertensive pharmacotherapy, which indicate that physicians do not easily change their drug prescribing routines.

## 6.5 Limitations

Firstly, BP was measured only in the population-based H2000 survey in 2000-2001. BP levels in 2006 instead are less reliable because they were not clinically measured but calculated by linking the H2000 survey and the database data of SII together and taking into account changes in age, sex, and drug utilization (mean number of BP-lowering drugs) of the target population between late 2000 and late 2006.

Secondly, BP was determined as a mean of two measurements made on a single occasion. However, there is evidence that multiple reading prevents overestimation of hypertension [184, 185] and therefore only two measurements made on a single occasion most obviously leads to an overestimation of hypertension and an underestimation of the control of hypertension.

Thirdly, the expected reductions in BP levels and cardiovascular morbidity with add-on therapy is only theoretical. The formulae used in these calculations are based on the meta-analysis of 147 randomized trials in the context of expectations from prospective epidemiological studies [95], which, eventually, can only give a sophisticated estimation.

Fourthly, all prescribed drugs purchased during the three months' period in 2000, and in 2006, respectively, have been considered as regular use of these drugs. However, it is obvious that some of the patients interrupted their medication and/or in some of the cases the medication was changed during the three months' period of gathering. Thereby utilization of antihypertensive actually may have been even somewhat less than that shown by the database data of the SII. On the other hand, taking into account the fact that, on the average, the compliance of drugs is less than 100%, it is possible that there have been some unidentified subjects who have purchased their drugs in the end of August and again in the beginning of December, but not during the 3 month period of data gathering, and thereby have not been accounted for in the database data of the SII.

Furthermore, dosages of the antihypertensive drugs used were not available. In relation to the recommendations of use of the low-dose antihypertensive agents, especially in case of thiazides, quantitative analyses of specific drugs would have been beneficial.

Finally, these studies may include some unidentifiable subjects using BP-lowering drugs not only for the treatment of hypertension but also for the treatment of other diseases, such as migraine and essential tremor. However, their proportion is estimated to be extremely low and would therefore not have any influence on the findings. However, the real utilization of antihypertensive drugs, especially BBs, has probable been a bit lower than described.

# 7 Summary and Conclusions

The database of the SII included practically 100% of the prescriptions on antihypertensive and lipid-lowering drugs for the Finnish population during late 2000 and late 2006. The drug utilization data from the database of SII proved to be basically in line with the data observed in the population-based Health 2000 Survey, and vice versa. Therefore, the results presented in this thesis can be considered accurate and reliable.

Taking into account the target BP during these studies, this thesis indicates that the control of BP in the beginning of the 2000s has been alarmingly poor. Then again, between 2000 and 2006, utilization of antihypertensive regimens, especially in combination therapy, increased significantly. It seems that, among moderately to severely hypertensives, use of antihypertensive drugs became more frequent, probably because of aging and new-onset of diseases, especially diabetes and CHD. However, among uncomplicated mild hypertensives, utilization of antihypertensive drugs increased without changes in patients' disease profiles, which suggests that clinicians have complied with guidelines in that respect. Furthermore, utilization of evidence-based drug therapies among adult hypertensive patients had increased significantly by the end of 2006, predicting benefits in cardiovascular morbidity and mortality in the future.

In spite of positive trends in the utilization of antihypertensive drugs, especially in the case of RAS blockers, underutilization of antihypertensive drugs together with somewhat irrational drug selection, especially in monotherapy but also in combination therapies, remain matters of concern. For instance, even among recently diagnosed hypertensives, RAS blockers seem to be prescribed as second-line or third-line drugs after BBs. In fact, there seems to be an unceasing relative overuse of BBs in the treatment of hypertension, especially among diabetic patients and uncomplicated hypertensive patients. Moreover, quite surprisingly, BBs seem to be chosen as first line agents far more often than other antihypertensive agents, even among recently treated hypertensives without compelling indication for their use. It seems that clinicians do not easily change their prescribing patterns.

Retrospectively, referring to contemporary guidelines, antihypertensive drug therapy between 2000 and 2006 can be assessed to be poor in Finland. On the other hand, taking into account both recent and previous guidelines for hypertension management, antihypertensive drug therapy has nonetheless improved in Finland. However, treatment recommendations are still insufficiently followed. The reasons for this must be patient-related, physician-related and medical/healthcare system -

related. Yet, the reasons are complex; clinical inertia is probably one of the major factors behind the lag.

Briefly, more substantial antihypertensive treatment for high-risk and low-risk hypertensive adult patients in Finland is obviously needed. Furthermore, more rational selections of antihypertensive drugs are also called for. Physicians should take into account with greater precision related or absent comorbidities, cardiovascular risk factors, and other individual characteristics when choosing antihypertensive agents for hypertensive patients in clinical practice.

However, as shown in this thesis, intensifying treatment of uncomplicated hypertensive patients whose BP is uncontrolled (≥140/90 mmHg), by only one- half standard dose of ordinary BP-lowering regimen, would increase the control of hypertension from 34% to 48%, reduce strokes by 18%, and reduce ischaemic heart disease events by 13%.

Finally, the threshold for the reimbursement of hypertension medication costs does not meet with the BP threshold for drug therapy presented in national and international guidelines. However, the entitlement to reimbursement for hypertension medication costs by lowering the patient's expenses would probably increase the treatment compliance. Better compliance would probably improve the control of hypertension which could decrease cardiovascular complications and their burden for the Finnish health care also from the financial point of view. Consequently, it seems reasonable to recommend lowering the threshold for the reimbursement of hypertension medication costs in Finland by taking into account also the fact that, during the past few years, the appearance of low-priced generic antihypertensive drugs has relatively lowered the expenses for the Social Insurance Institution of Finland as caused by patients entitled to reimbursement for hypertension medication costs. On the other hand, low-priced generic antihypertensive drugs have relatively lowered also patients' expenses and thereby the role of the entitlement to reimbursement for hypertension medication costs has become less significant, especially from the patients' financial point of view. Further investigation in the field of cost-effectiveness from the public health point of view is required in order to evaluate the optimal threshold and criteria for the reimbursement of hypertension medication cost. Yet, some of the results of Study III may be valuable for these evaluations. Anyway, the major findings of this thesis can be utilized in daily clinical practices, for the benefit of Finnish physicians and hypertensive patients in the long run.

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