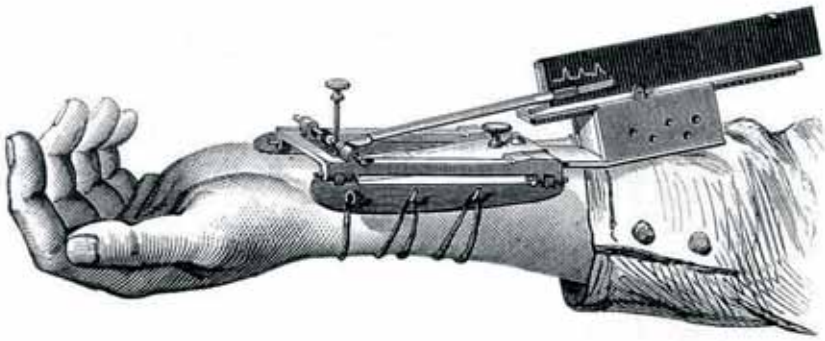

Teemu Niiranen

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HOME BLOOD PRESSURE MEASUREMENT − EPIDEMIOLOGY AND CLINICAL APPLICATION

A C A D E M I C D I S S E R T A T I O N

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 June 13th, 2008 at 12 noon.

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ABSTRACT

Hypertension, the leading global risk factor for early mortality, can not be detected or treated without accurate and practical methods of BP measurement. Although home blood pressure (BP) measurement enjoys considerable popularity among patients, the lack of evidence needed to assure its place in modern clinical practice has hindered its widespread acceptance among physicians. The objective of this study was to show that home BP measurement is more accurate than conventional clinic BP measurement and can be used effectively in clinical practice. We assessed the use of home BP for diagnosing hypertension and guiding antihypertensive treatment. The association between home BP and hypertensive end-organ damage was also examined.

The first study population consisted of a representative sample of the Finnish adult population (2 120 individuals aged 45–74 years). These subjects underwent a clinical interview, electrocardiography and measurement of clinic and home BP. Carotid intima-media thickness (an indicator of atherosclerosis) and arterial pulse wave velocity (an indicator of arterial stiffness) were also measured in two subsets of 758 and 237 subjects, respectively. In a second study cohort, consisting of 98 hypertensive patients, adjustment of antihypertensive treatment was randomized to either daytime ambulatory BP or home diastolic BP.

Clinic BP was significantly higher than home BP (mean systolic/diastolic difference was 8/3 mmHg), and the overall agreement between the two methods in diagnosing hypertension was moderate at best (75%). Of 593 subjects with elevated clinic BP, 38% had normal BP at home; so called white-coat hypertension. Hypertension could therefore be overdiagnosed in every third patient in a clinical screening situation. White-coat hypertension was associated with mildly elevated clinic BP, lower body mass index and non-smoking status, but not with psychiatric disease. However, the cardiovascular risk profile of white-coat hypertensives was between that of the normotensives and sustained hypertensives, indicating that white-coat hypertension is not a completely benign phenomenon, and may be a precursor of true hypertension. Home BP was more closely associated with hypertensive end-organ damage (intima-media thickness, pulse wave velocity, and electrocardiographic

evidence of left ventricular hypertrophy) than was clinic BP. The adjustment of antihypertensive treatment based on home BP measurement is effective as it led to equally good BP control as did ambulatory BP monitoring, which has been considered by many as the gold standard.

On the basis of these results and data from previous studies, it can be concluded that home BP measurement is an improvement over conventional clinic BP measurement. Home monitoring of BP is as a convenient, accurate, and widely available option and may become the method of choice when diagnosing and treating hypertension. A paradigm shift is needed in BP measurement as evidence-based medicine suggests that clinic BP measurement should only be used for screening purposes.

Keywords: Hypertension, blood pressure, blood pressure determination, home blood pressure monitoring, epidemiology

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TIIVISTELMÄ

Kohonnutta verenpainetta, maailmanlaajuisesti merkittävintä ennenaikaiselle kuolemalle altistavaa riskitekijää, ei voida tunnistaa tai hoitaa ilman tarkkoja ja käytännöllisiä verenpaineen mittausmenetelmiä. Verenpaineen kotimittaus on saavuttanut suuren suosion potilaiden keskuudessa. Lääkärit eivät ole kuitenkaan vielä täysin hyväksyneet verenpaineen kotimittausta, sillä riittävä todistusaineisto sen toimivuudesta ja eduista on puuttunut. Tämän tutkimuksen tarkoituksena oli osoittaa, että kotona mitattu verenpaine (kotipaine) on perinteistä vastaanotolla mitattua verenpainetta (vastaanottopaine) tarkempi, ja että se on tehokas myös kliinisessä käytössä. Tutkimme kotipaineen käyttöä verenpainetaudin diagnosoinnissa ja hoidossa. Lisäksi tarkastelimme kotipaineen yhteyttä verenpainetaudin aiheuttamiin kohde-elinvaurioihin.

Ensimmäinen aineisto, joka oli edustava otos Suomen aikuisväestöstä, koostui 2 120 45–74-vuotiaasta tutkimushenkilöstä. Tutkittavat mittasivat kotipainettaan viikon ajan ja osallistuivat terveystarkastukseen, johon sisältyi kliinisen tutkimuksen ja haastattelun lisäksi sydänfilmin otto ja vastaanottopaineen mittaus. 758 tutkittavalle suoritettiin lisäksi kaulavaltimon seinämän intima-mediakerroksen paksuuden (valtimonkovettumataudin mittari) mittaus ja 237:lle valtimon pulssiaallon nopeuden (valtimojäykkyyden mittari) mittaus. Toisessa aineistossa, joka koostui 98 verenpainetautia sairastavasta potilaasta, hoitoa ohjattiin satunnaistamisesta riippuen joko ambulatorisen eli vuorokausirekisteröinnillä mitatun verenpaineen tai kotipaineen perusteella.

Vastaanottopaine oli kotipainetta merkittävästi korkeampi (systolisen/diastolisen paineen keskiarvoero oli 8/3 mmHg) ja yksimielisyys verenpainetaudin diagnoosissa kahden menetelmän välillä oli korkeintaan kohtalainen (75 %). 593 tutkittavasta, joilla oli kohonnut verenpaine vastaanotolla, 38 %:lla oli normaali verenpaine kotona eli ns. valkotakkiverenpaine. Verenpainetauti voidaan siis ylidiagnosoida joka kolmannella potilaalla seulontatilanteessa. Valkotakkiverenpaine oli yhteydessä lievästi kohonneeseen verenpaineeseen, matalaan painoindeksiin ja tupakoimattomuuteen, muttei psykiatriseen sairastavuuteen. Valkotakkiverenpaine ei kuitenkaan vaikuttaisi olevan täysin vaaraton ilmiö ja voi ennustaa tulevaa verenpainetautia, sillä siitä kärsivien sydän- ja verisuonitautien riskitekijäprofiili oli

normaalipaineisten ja todellisten verenpainetautisten riskitekijäprofiilien välissä. Kotipaineella oli vastaanottopainetta vahvempi yhteys verenpainetaudin aiheuttamiin kohde-elinvaurioihin (intima-mediakerroksen paksuus, pulssiaallon nopeus ja sydänfilmistä todettu vasemman kammion suureneminen). Kotipaine oli tehokas verenpainetaudin hoidon ohjaaja, sillä kotipaineeseen ja ambulatoriseen paineeseen, jota on pidetty verenpainemittauksen ”kultaisena standardina”, perustuva lääkehoidon ohjaus johti yhtä hyvään verenpaineen hallintaan.

Tämän ja aikaisempien tutkimusten tulosten pohjalta voidaan todeta, että verenpaineen kotimittaus on selkeä parannus perinteiseen vastaanotolla tapahtuvaan verenpainemittaukseen verrattuna. Verenpaineen kotimittaus on käytännöllinen, tarkka ja laajasti saatavilla oleva menetelmä, josta voi tulla jopa ensisijainen vaihtoehto verenpainetautia diagnosoitaessa ja hoitaessa. Verenpaineen mittauskäytäntöön tarvitaan muutos, sillä näyttöön perustuvan lääketieteen perusteella vaikuttaa, että vastaanotolla tapahtuvaa verenpainemittausta tulisi käyttää vain seulontatarkoitukseen.

Avainsanat: Verenpainetauti, verenpaine, verenpaineen mittaus, verenpaineen kotimittaus, epidemiologia

CONTENTS

ABBREVIATIONS

ANOVA	Analysis Of Variance
ARIC	Atherosclerosis Risk in Communities
BDI	Beck Depression Inventory
BMI	Body Mass Index
BP	Blood Pressure
ECG	Electrocardiography/electrocardiogram
ECG-LVH	Electrocardiographic evidence of Left Ventricular Hypertrophy
ESH	European Society of Hypertension
GHQ-12	12-item General Health Questionnaire
HDL	High Density Lipoprotein
ICH	Isolated Clinic Hypertension
IMT	Intima-Media Thickness
LDL	Low Density Lipoprotein
PAMELA	Pressioni Arteriose Monitorate E Loro Associazioni
PWV	Pulse Wave Velocity
TAS-20	20-item Toronto Alexithymia Scale
Whiteley-7	7-item Whiteley index

LIST OF ORIGINAL PUBLICATIONS

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

I **Niiranen TJ, Jula AM, Kantola IM, Reunanen A.** Comparison of agreement between clinic and home-measured blood pressure in the Finnish population: the Finn-HOME Study. J Hypertens 2006; 24(8):1549−55.

II **Niiranen TJ, Jula AM, Kantola IM, Reunanen A.** Prevalence and determinants of isolated clinic hypertension in the Finnish population: the Finn-HOME Study. J Hypertens 2006; 24(3):463-70.

III **Niiranen T, Jula A, Kantola I, Moilanen L, Kähönen M, Kesäniemi YA, Nieminen MS, Reunanen A.** Home-measured blood pressure is more strongly associated with atherosclerosis than clinic blood pressure: the Finn-HOME Study. J Hypertens 2007; 25(6):1225-31.

IV **Niiranen TJ, Jula AM, Kantola IM, Kähönen M, Reunanen A.** Home-measured blood pressure is more strongly associated with arterial stiffness than is clinic blood pressure: the Finn-HOME Study. Submitted.

V **Niiranen TJ, Jula AM, Kantola IM, Karanko H, Reunanen A.** Home-measured blood pressure is more strongly associated with electrocardiographic left ventricular hypertrophy than is clinic blood pressure: the Finn-HOME Study. J Hum Hypertens. J Hum Hypertens 2007; 21(10):788-94.

VI **Niiranen TJ, Kantola IM, Vesalainen R, Johansson J, Ruuska MJ.** A comparison of home measurement and ambulatory monitoring of blood pressure in the adjustment of antihypertensive treatment. Am J Hypertens 2006; 19(5):468−74.

1 INTRODUCTION

A few risk factors account for a large contribution to global loss of healthy life. Overall, 26% of the worldwide adult population had high blood pressure (BP) i.e. hypertension (clinic BP ≥ 140 mmHg systolic and/or 90 mmHg diastolic) in 2000 and 29% are projected to have this condition in 2025 [1]. Hypertension has been identified as the third most important cause for global burden of disease and as the leading global risk factor for mortality, accounting for over 7 million deaths yearly [2]. The risks of high BP are not only limited to those with severe hypertension, as there is a continuous relationship with cardiovascular risk even throughout the normal range of usual BP (down at least as far as 115/75 mmHg). Lowering of the systolic BP by only 10 mmHg, or lowering the diastolic BP by only 5 mmHg would, in the long term, be associated with a lower risk (about 40%) of stroke death and a lower risk (about 30%) of death from ischemic heart disease or other vascular causes throughout middle age [3]. In Finland, mean BP has decreased significantly during the past 30 years, but hypertension care is still far from optimal as only 20 to 30% of treated hypertensives have adequately controlled BP [4, 5]. Hypertension is indeed an important public health challenge worldwide and prevention, detection, treatment, and control of this condition should receive high priority.

BP, however, can not be prevented, detected, treated nor controlled without accurate and practical methods of BP measurement. If proper methods are not used, inexact BP measurement can lead to poor diagnostic accuracy, unnecessary costs and therapy, and poor medical treatment. Despite several limitations, measurement of BP has until recently occurred primarily at the physician's office using a stethoscope and a conventional mercury sphygmomanometer. Only during the past decade have techonogical advances provided novel options for measuring BP, such as home monitoring, which is becoming increasingly popular world-wide [6].

One of the reasons why home BP measurement has not received widespread acceptance in the minds of physicians, despite its considerable popularity with patients, is a lack of evidence needed to assure its place in modern clinical practice. This thesis was planned to provide physicians with evidence that home BP measurement can be used effectively in clinical practice, and that it offers clear benefits compared with conventional clinic measurement.

2 REVIEW OF THE LITERATURE

2.1 History of home blood pressure measurement

The standard method of indirect measurement of BP is based on the principle of arterial occlusion and BP detection by various techniques, the first of which of was palpation, described by Scipione Riva-Rocci in 1896 [7]. In 1905, Nikolai Korotkoff improved Riva-Rocci's method when he recognized that by placing a stethoscope over the brachial artery at the cubital fossa, distal to a Riva-Rocci cuff, tapping sounds could be heard as the cuff was deflated, caused by blood flowing back into the artery. Korotkoff concluded correctly that the appearance of the tapping sounds coincided with systolic BP and the disappearance of the sounds with diastolic BP [8]. The method of BP measurement invented by Korotkoff quickly received wide recognition and became a standard medical procedure. His technique has truly stood the test of time as it has been used for more than a century with practically no alterations [9].

Brown was the first to report that BP measured in the home was lower than that recorded by a doctor [10]. Ayman and Goldshine proposed the concept of "self BP measurement" in 1940 and also concluded that BP measured at home was lower than clinic BP [11]. Ayman and Goldshine were also clearly ahead of their time, as they suggested that home BP monitoring was useful for (1) instructing the patients about their chronic disease, (2) teaching physicians about the natural course of the disease and about factors that affect the disease, (3) learning the prognosis of disease, and (4) increasing the precision of determining the effectiveness of treatment, as all of these hypotheses are slowly being proved correct [11]. However, self-measurement was initially performed using Korotkoff's auscultation method and remained a rarity for many decades due to its complex nature. In the mid-1970s, the first automated sphygmomanometers based on the auscultatory technique became available, but were not widely distributed because of high price and mechanical problems [12]. Development of the Dinamap, the first commercial oscillometric device for BP measurement begun in the early 1970s and it was first offered for sale in 1976 [13]. When simple and small automated devices based on the cuff-oscillometric method were presented in the 1980s, the popularity of home BP measurement exploded and has seen exponential growth ever since [6]. Currently home BP monitors are becoming ever smaller and are being embedded with additional features such as printers, PC connections, long-term tracking memories for morning and evening measurements, and the ability to detect an irregular heart beat.

In 1994 the American Heart Association estimated that $126 million was spent on home BP monitors in the United States alone [14]. By now, the world market for home-use digital BP monitors has grown to be worth almost $800 million [6]. The gradual ageing of the world population combined with the increasing prevalence of hypertension will probably provide an increasing potential market. The predicted rise of telehealth will add even greater value to the market, which is forecast to grow at 6.7% per year, taking it to over $1 billion by 2010 [6].

2.2 Measuring home blood pressure

2.2.1 Blood pressure as a physiological phenomenon

Unfortunately, BP is not a constant variable and significant spontaneous variation in BP occurs, which complicates its measurement. Intra-arterial beat-to-beat BP monitoring in ambulatory subjects has shown that BP values may vary by more than 50–60 mmHg over 24 hours [15]. These variations originate from short-lasting pressor and depressor episodes that give BP recording a typical unstable appearance even over short periods in immobilized patients. BP is a hemodynamic phenomenon that is affected by respiration, emotion, exercise, meals, tobacco, alcohol, temperature, bladder distension, and pain [16, 17].

BP variation also largely originates from the diurnal variation of BP characterized by a substantial reduction during sleep, which has been known for over a century [18]. A seminal study by Millar-Craig et al. showed by using continuous intra-arterial measurements that BP is highest mid-morning and then falls progressively throughout the rest of the day; in addition, BP is lowest at night (nocturnal dip), but rises before awakening (morning surge) [19]. These findings highlighted the importance of the circadian rhythm of BP with regard to management of hypertension. BP also seems to vary between months and seasons, as BP is lower during the summer period and higher in winter [20].

It is not always possible to modify all the factors that affect BP variability, but it is possible to take them into account in reaching a decision as to the relevance of a single BP measurement often acquired at the clinic. Although clinic BP predicts increased cardiovascular risk to some extent on the population level, many patients with high clinic BP will not experience cardiovascular events [21]. This finding may be explained partly by the fact that isolated BP measurements made during clinic visits give only a very limited number of measurements, and no information of the diurnal variation of BP. These problems, however, can be addressed with more modern BP measurement methods, such as home and ambulatory BP measurement.

2.2.2 Devices and validation

Currently, nearly all the automated devices used for home BP measurement use the oscillometric technique. The fundamental concept underlying these devices is the same as that of other cuff-based BP measuring devices, in that compression of the brachial artery by an inflatable cuff allows indirect determination of the intra-arterial vascular pressure. However, the physiological differences among the various devices can be potentially quite large as the auscultatory method relies on the association between Korotkoff sounds and systolic and diastolic BP, whereas the oscillometric technique uses the small oscillations in cuff pressure to identify the systolic, mean, and diastolic pressures [22]. Another difference is that in oscillometric devices cuff inflation and deflation are automated and that BP determination is made by a microprocessor using information sent to it from a pressure transducer.

The precise technique of automated oscillometric BP measurement varies greatly from one device to another. In general, the BP cuff is inflated to between 160 and 180 mmHg for the first BP determination, or approximately 30 mmHg above the previously measured systolic BP. After a brief holding period, and if no oscillations are detected, the cuff pressure is reduced slowly in a discontinuous or continuous manner, depending upon the specific device. As the cuff pressure decreases, oscillations of the arterial wall increase in amplitude and reach a maximum when the cuff pressure is at mean arterial pressure. With further deflation the oscillations start to diminish. The mean BP is determined at the peak of the amplitude of the oscillations; the systolic BP, approximately 55% prior to the maximum; and the diastolic BP, approximately 85% after the maximum oscillations (Figure 1). The monitor then displays these BP values for the user [22]. However, the exact points of BP determinations and algorithms used by the devices are considered proprietary information by the manufacturers, making it impossible for investigators to verify the accuracy of their underlying physiological principle [23].

The sale and marketing of electronic BP monitors is currently not, nor has ever been, subject to any medical influence. Even in the early days of home BP measurement it was noticed that this freedom from medical control quickly resulted in the manufacture and marketing of a vast array of devices with poor accuracy, which few were validated in any way [24]. With this in mind, the Association for the Advancement of Medical Instrumentation (AAMI) published the first standard for electronic or aneroid sphygmomanometers in 1987 that included a protocol for evaluating the accuracy of devices [25]. Thereafter several other European, British, and North American protocols followed, but currently the European Society of Hypertension (ESH) International Protocol is most commonly used for validation of

BP measuring devices [26-28]. Hypertension guidelines and societies recommend the exclusive use of validated home monitors in clinical practice, although such validation is still not mandatory [29, 30]. Home-monitoring devices should also be checked for accuracy every 1–2 years.

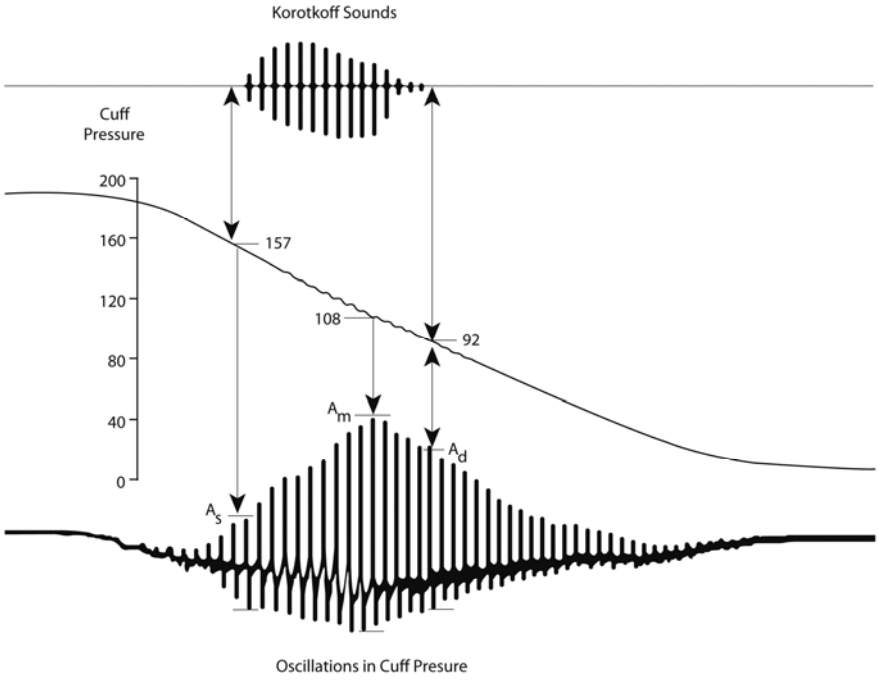

Figure 1. ***Oscillomteric technique compared with the auscultatory technique for measurement of blood pressure. A_s indicated auscultatory systolic blood pressure; A_m auscultatory mean blood pressure; and A_d auscultatory diastolic blood pressure. Reproduced with permission from Biomedical Instrumentation and Technology [23] .***

After the development of accuracy standards, a report assessed compliance with the guidelines. In 1989, of 23 monitors that underwent validation, only 12 (52%) met AAMI standards for diastolic accuracy and 39% of the devices met both systolic and diastolic standards [31]. Afterwards, validated BP measuring devices have been assessed in the literature from time to time, but as such surveys soon become outdated, up-to-date information can currently be easily found from the Internet site

of a non-profit organization [32]. Although validation protocols for home BP monitors have existed already for two decades and information of validated devices can be easily found, the state of the market is still poor. In 2003 only 53% of the Internet sites selling home BP monitors offered validated devices and only 9% of these sites mentioned device validation [33].

Different types of home BP monitors are also available. Upper arm devices are currently recommended, while the use of finger and wrist devices is discouraged [29, 30]. Devices that measure BP from a finger are not recommended, because of the inaccuracies caused by measurement distortion from peripheral vasoconstriction, the greater alteration in BP at more distal the sites of recording, and the effect of limb position on BP [26]. Although quite popular, wrist monitors are subject to the same latter two problems as the finger devices [34, 35]. Most of the wrist devices have not passed independent validation, [36, 37] although some newer monitors have been recommended [38-40]. Measurements are affected by anatomical factors, such as wrist anatomy and dorsal or ulnar flexion of the wrist [36]. Furthermore, if the wrist is not held at heart level, inaccurate measurements will be obtained [36]. Recently, to overcome this problem, wrist home BP devices with position sensors have been developed, but their performance still needs further analysis until wrist monitors can be recommended [38-40]. In the future, home telemonitoring of hypertension could also be a promising patient management approach, but more studies are needed to accummulate evidence related to its clinical effects and cost effectiveness [41].

2.2.3 Optimal scheme for home blood pressure measurement

The recommendations for performing home BP measurement do not vary in principle from those that apply to BP measurement in general: there should be a short period of rest before measurement, the arm should be supported with the cuff at the level of the heart, and a cuff of proper size should be used [30, 42, 43].

However, perfect consensus still does not exist on how many daily measurements and for how many days should be performed when measuring BP at home to obtain the best assessment of the actual BP levels in a given subject. The current ESH guidelines recommend two measurements in the morning and two measurements in the evening for one week with the exclusion of measurements from the first day [42]. However, the North American guidelines advise taking three readings on one occasion every morning and evening, but do not mention for how many days [30]. These conflicting guidelines only demonstrate that agreement on this matter has not yet been reached. Two methods have been used to define the most suitable schedule for home BP measurement, a statistical and a clinical approach [44].

In the statistical method, the criteria for defining the best frequency of home BP measurements should be based on (1) the reproducibility of home BP values obtained, (2) their stability over time, and (3) their relation to the average ambulatory BP values, the latter being considered the gold standard references [42, 45]. Chatellier et al. concluded that the maximal reduction in the standard deviation in the difference between two mean BP values was obtained when each mean was defined by 30 measurements (three measurements for ten consecutive days). However, 80% of this maximal reduction was already obtained with mean values defined by 15 measurements (three measurements collected over five days) [46]. This conclusion was supported by the results of the SMART study, which also showed that only a small decrease in the standard deviation of the mean difference in average home BP values between two sessions is achieved after six home BP measurements [47]. Two studies by Stergiou et al. also concluded that at least 12 measurements taken on three days are needed for the reproducibility of home BP to be superior to that of office measurements [48, 49]. On the other hand, Brook reported that if the accuracy of the average home BP was determined by agreement with average ambulatory BP values, the total number of measurements and the total duration of monitoring were not important and that most benefits could be achieved by obtaining as few as two home BP measurements on one day [50].

Prognostic clinical data is, of course, a more suitable method than statistical methods for defining the best amount of BP measurements needed. Recent follow-up studies have shown that even two home BP measurements are able to predict the risk of cardiovascular events [51, 52]. However, only Ohkubo et al. have tried to identify the best frequency of home BP measurements based on prognostic data from the community-based Ohasama study [53]. They reported that the predictive value for the risk of stroke increases progressively without any threshold if the number of measurements was increased from 1 to 14. In any case, whether the statistical or clinical approach is used for determining an optimal BP measurement schedule, it appears that the advantages of home BP measurement depend not only on the statistical advantages associated with the availability of repeated measurements, but also in obtaining information out of the clinical setting with even a few home BP measurements [53, 54].

The differences in morning and evening home BP in the general population appear to be quite small, under 2 mmHg [55, 56]. However, in treated hypertensives, trough morning home BP measurements and evening measurements can be used effectively for assessing the duration of antihypertensive drug action in patients [57, 58]. Measuring home BP in the morning and evening is therefore sensible, and also recommended by the guidelines [30, 42].

Higher and unstable values are usually obtained during the first home BP measurements and current ESH guidelines therefore recommend discarding home BP measurements from the first day [49, 53, 59]. Two or three measurements on each occasion are also recommended, although the two largest epidemiological studies have been performed with just one BP measurement on each occasion [30, 42, 52, 60]. However, no clear prognostic evidence yet exists to support either of these recommendations.

2.3 Diagnosing hypertension with home blood pressure

2.3.1 Reference values for home blood pressure measurement

All major epidemiological studies are primarily based on clinic BP measurements, which therefore is still the criterion standard for determining hypertension-related morbidity and mortality. Therefore it is extremely important to know whether differences between home and clinic BP exist. In untreated subjects, home BP is, on average, 7–8/5–6 mmHg lower than clinic BP and in treated subjects 5/3 mmHg lower than clinic BP [61, 62]. The difference between systolic home and clinic BP also appears to slightly increase with higher BP [61]. As a result, home and clinic BP are not directly comparable and separate diagnostic thresholds are needed for both. Data from ambulatory BP measurement are often reported as 24-hour daytime and night-time averages. Since home BP is usually measured at daytime, the daytime ambulatory average should be used for comparisons. In a meta-analysis with over 4000 subjects, the difference between daytime ambulatory BP and home BP was only -1.2/1.2 mmHg, which is clinically insignificant [62]. The reproducibility of home and ambulatory BP values is also better than that of clinic BP [63].

Home BP measurement should be distinguished from self-measurement of BP, which can occur in places other than home, such as at the worksite or in the community (e.g. the local health center or pharmacy), as different settings may give different readings. Self-measurement at the clinic has not been shown to eliminate the white-coat effect as two studies have reported no significant difference between self- and physician-measured BP in the clinic [64, 65]. Home readings taken by self versus a relative also appear to be almost identical [64].

The classification of BP is still mainly based on clinic BP values in all current major guidelines [29, 43, 66]. In addition to defining hypertension, most guidelines also give several subcategories for normotensives and hypertensives (Table 1) [29, 43, 66]. The problem with classifying BP is that it is a continuous variable, and risks of

various associated adverse outcomes rise as BP rises, without any clear threshold [3]. However, despite these problems, thresholds are needed for everyday clinical practice. One must still remember that the diagnostic thresholds are arbitrary and subjective, and also vary from one recommendation to another [29, 43, 66].

Table 1. ***Definitions and classification of clinic blood pressure levels***

	Classification according to guideline		
BP Level (mmHg)	Europe	United States	Finland
< 120/80	Optimal	Normal	Optimal
120–129/80–84	Normal	Prehypertension	Normal
130–139/85–89	High Normal	Prehypertension	Satisfactory
140–159/90–99	Grade 1 HT	Stage 1 HT	Mildly elevated
160–179/100–109	Grade 2 HT	Stage 2 HT	Moderately elevated
≥ 180/≥ 110	Grade 3 HT	Stage 2 HT	Markedly elevated

BP, blood pressure; HT, hypertension.

Widespread clinical use of home BP measurement was first limited by the lack of a generally accepted reference frame and operational thresholds for initiating treatment. Before prognostic data were available, home BP thresholds were defined from cross-sectional observations using different statistical criteria, such as the normal distribution criterion, percentile criterion, or regression criterion. In 1998, a meta-analysis of 17 population-based studies with 5422 untreated subjects suggested that a home BP ≥ 135/85 mmHg should be considered hypertensive (equivalent to a clinic BP ≥ 140/90 mmHg) which was quickly adopted by the guidelines [29, 30, 43, 67]. However, normal BP should be preferably defined in terms of cardiovascular risk. So far, only one study has suggested threshold values for home BP based on outcome data. The Ohasama investigators proposed a reference value of 137/84 mmHg for hypertension, which luckily was in line with the reference values obtained from the cross-sectional studies [68]. At the moment, all major guidelines concur with the idea that home BP levels < 135 mmHg systolic and 85 mmHg diastolic are normal, although even with these thresholds the agreement between clinic and home BP in diagnosing hypertension is moderate at best [29, 30, 42, 66, 69, 70]. Further prospective studies are therefore needed to establish with more certainty the normal range of the self-measured home BP.

2.3.2 Isolated clinic ("white coat") hypertension

In 1983, Mancia used a continuous intra-arterial recorder to measure BP in the periods during which a doctor repeatedly measured BP by the cuff method [71]. He observed that in almost all normotensive and hypertensive subjects tested the doctor's arrival at the bedside induced immediate rises in systolic and diastolic BP peaking within 1–4 minutes (mean 27/15 mmHg above pre-visit values). After the peak response BP declined and at the end of the visit was only slightly above the pre-visit level. This was the first recognition of the phenomenon known as the "white-coat effect", a transient elevation in BP due to an alerting reaction characterized by a behaviour of the adrenergic nervous system that causes muscle sympathoinhibition and skin sympathoexcitation [72]. Mancia also demonstrated that the white-coat effect cannot be avoided by repeated measurements by a physician over a short time span, but can be reduced by over 40 %, however, if BP measurements are performed by a nurse [73]. The white-coat effect leads to poor diagnostic accuracy and is one of the main shortcomings of clinic BP measurement.

Some patients have a persistently elevated clinic BP while their ambulatory or home BP is within normal range. This condition is widely known as "white-coat hypertension" [74], although the ESH guidelines suggest a more descriptive term "isolated clinic hypertension" (ICH) be used. This is because at least the difference between ambulatory and clinic BP does not seem to be strongly associated with the clinic BP elevation induced by the alerting reaction to a doctor or a nurse, which is the true white coat effect [75]. Instead, the white-coat effect appears to be associated with greater BP reactivity to psycho-social stimuli, such as public speaking [76].

ICH should be diagnosed whenever clinic BP is repeatedly ≥ 140/90 mmHg, while home BP is within normal range (< 135/85 mmHg). Its diagnosis can also be based on 24-hour mean and daytime BP, bearing in mind that subjects with ICH diagnosed with home BP may not be entirely the same group identified by ambulatory BP measurements [77, 78]. Automated serial BP measurement in a clinic setting has also been successfully used to identify patients with ICH, but no reference values exist yet for this method of measurement [79]. Depending on the definition of ICH and the characteristics of the study cohort, its prevalence can range from 11–17% in the general population [78, 80, 81] to 10–60% of the patients with elevated clinic BP [74, 82-88].

Data allowing an estimate of the probability of ICH are very scarce [74, 80, 84, 86], and nearly all of the previous studies have been performed using ambulatory BP monitoring in hypertension clinics or academic settings, and used selected patient materials. Furthermore, the findings have often been conflicting or non-significant. Overall, the previous data indicate that, in untreated hypertensive subjects, the

probability of ICH might increase with female sex, non-smoking status, a low body mass index (BMI) and mildly elevated clinic BP levels [74, 80, 84, 86]. Very little attention has been focused on the possible psychological determinants of ICH, although ICH is considered to be a consequence of the white-coat effect. There is some evidence that ICH might be associated with suppression of emotion [89], but not necessarily with anxiety or depression [89-91]. However, the findings of these studies with a limited number of patients have also been conflicting. Several studies have examined whether sympathetic overactivity exists in ICH, but the results have been variable, with sympathetic activity suggested as being increased [92, 93] or normal [94].

Several authors have concluded that in individuals with ICH the cardiovascular risk is nearly identical to those who have normal BP [81, 82, 87, 95-97]. However some [98, 99], although not all studies [83, 100, 101], have reported this condition to be associated with a prevalence of organ damage and metabolic abnormalities greater than that of normotensive subjects, which suggest that it may not be a clinically innocent phenomenon. It has also been suggested that patients with ICH initially have a low short-term incidence of stroke, but later on develop an increased risk for stroke as compared with patients with sustained hypertension [102]. The clinical significance of ICH has therefore been somewhat unclear. However, recent larger population studies have elucidated the prognosis of ICH to some extent, as they have demonstrated that the cardiovascular risk of individuals with ICH appears to be intermediate between that of subjects in whom normal BP and hypertension are found both in and out of office [51, 103].

Although much attention has been focused on ICH, there is still debate in the scientific community as to whether it truly is a distinct clinical entity, especially when dealing with large epidemiological data and not with a single patient who is visibly anxious over BP measurements. For example, the reproducibility of ICH is not good as 42–61% of the patients initially classified as having ICH with ambulatory measurement can no longer be classified as such from repeated monitoring [99, 104]. The major determinant of ICH also appears to be mildly elevated hypertension [83, 86]. Therefore ICH could be due to selection bias resulting from subjects having a BP level close to the diagnostic thresholds, as proposed by some [99, 105]. The fact that the cardiovascular risk and BP level of individuals with ICH appears to be intermediate between normotensives and sustained hypertensives, and that a large portion of subjects with ICH show a spontaneous progression towards true hypertension also support this assumption [51, 103, 106].

2.3.3 Masked hypertension

Approximately 20 years after the discovery of the white coat effect, attention was drawn to a fourth group of patients in addition to those with sustained normotension, sustained hypertension and ICH. This group of patients has a normal clinic BP but an elevated ambulatory or home BP [107]. This phenomenon, which has also been previously observed in Finnish patients, was dubbed "masked hypertension", and it quickly gained widespread use [107-109]. The prevalence of masked hypertension appears to approximately same as for ICH in the general population [103]. Masked hypertension should be diagnosed whenever home BP or 24-hour mean/daytime ambulatory BP is ≥ 135/85 mmHg, while clinic BP is within normal range (< 140/90 mmHg). Home-measured BP also appears to be an appropriate method for assessing masked hypertension, as similar proportions of subjects with masked hypertension are detected by ambulatory and home BP monitoring, although slight disagreement exists between the two methods [110].

Masked hypertension, determined with ambulatory BP measurement, has been associated with end-organ damage, such as increased left ventricular mass, carotid intima-media thickness (IMT), pulse wave velocity (PWV) and urinary albumin level [108, 111-113]. The risk for cardiovascular events also is higher for patients with masked hypertension than for subjects with normal clinic and ambulatory BP, but lower than for those with sustained hypertension [51, 81, 87, 103].

The concept of masked hypertension, like ICH, has several weaknesses. Again, as for ICH, the major determinant for masked hypertension appears to be a BP level close to the diagnostic thresholds [51, 114], and two studies that have examined the persistence of masked hypertension with repeated ambulatory measurement found reproducibility rates of only 38% and 72%, respectively [104, 115]. In 4 repeated home measurements performed on hypertensive patients, 50% had masked hypertension during the entire study, while only 2% consistently had masked hypertension on each visit [116]. It is therefore quite likely that patients with masked hypertension are mildly hypertensive patients with normal BP variation around the mean. Some authors have even compared the concept of masked hypertension to "statistical gymnastics" as a patient who has BP of 138/88 mmHg at home and in the clinic would have masked hypertension. [117]. Furthermore, the clinical significance of masked hypertension remains quite unclear as "unmasking" these masked patients would necessitate performing ambulatory or home BP monitoring on subjects who appear to have normal BP.

2.4 Home blood pressure measurement and the management of hypertension

A recent meta-analysis of 18 randomised controlled trials by Cappuccio et al. showed that in the general healthcare system, hypertensive subjects using home BP measurement had 4.2/2.4 mmHg (2.2/1.9 mmHg after publication bias was allowed for) lower BP values and were more likely to achieve their target BP value than subjects without home measurement [118]. The reasons for this finding are still somewhat unclear. Part of this may be explained by the fact that home BP measurement is the most acceptable method for patients, when compared to ambulatory monitoring, measurement by a doctor or a nurse, or self-measurement in a room provided by the hospital [119]. Self-measurement is also free from observer bias and digit preference and enables patients to be more actively involved in their treatment, thereby improving adherence to treatment [120, 121].

Home measurement might also be cost-effective when compared with clinic BP measurement. A study of 430 patients randomized to either usual care or home monitoring in a closed model health maintenance organization found that the costs of care were 29% lower in the self-monitoring group, and BP was equally well controlled in both groups at the end of one year [122]. A mathematical model based on the Japanese Ohasama study also proposed that the introduction of home BP measurement for the diagnosis and treatment of hypertension would effectively reduce costs [123].

So far, only two randomized, controlled trials have compared the use of home and clinic BP measurement for the adjustment of antihypertensive treatment. Both studies concluded that self-measurement leads to lower costs, less medication use than clinic BP measurement, and slightly poorer BP control, although with no differences in end-organ damage [124, 125]. From these results, one may be inclined to conclude that it is better to base antihypertensive treatment on clinic BP instead of on home BP measurement. However, both of these studies used the same target BP for clinic and home BP groups, although clinic BP is nearly always higher than home BP and 5 mmHg lower BP targets should be used for home measurement according to current guidelines [30, 59]. This limitation, also acknowledged by Verberk et al. in their article, in these studies unsurprisingly leads to more intensive drug therapy and greater BP decreases in the clinic BP group and somewhat nullifies the results of these studies [125].

2.5 Association with end-organ damage and prognostic significance

Already in 1977, it was reported that the changes in electrocardiographic evidence of left ventricular hypertrophy (ECG-LVH) were related to the degree of BP control and correlated better with home BP than with clinic BP [126]. After this a few small studies with selected hypertensive patients have concluded that clinic BP shows very poor or no correlation at all with hypertension-induced end-organ damage whereas home BP correlates significantly with echocardiographic left ventricular mass, PWV, and albumin excretion rate [127-130]. No association was found between home BP and PWV or carotid IMT in two of these studies so the results are still slightly mixed, although the small selected study cohorts and ongoing antihypertensive treatment work as confounding factors [128, 129]. On the other hand, one study with 239 treated hypertensive patients also concluded that very meticulously controlled clinic BP measured by a nurse could be as reliable as home BP in predicting end-organ damage [131]. In any case, data on the association between end-organ damage and home BP from population-based studies remain very scarce as only two studies, one examining carotid IMT and the other echocardiographic left ventricular mass, have concluded that home BP could predict end-organ damage better than clinic BP [78, 112].

Until recently, no prognostic data have been available for home BP as a risk factor of cardiovascular morbidity and mortality. The results from two large population studies have recently been published, the community-based Ohasama and Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) studies [52, 53, 60]. Results from the Ohasama study show that home BP has a stronger predictive power for strokes than clinic BP, and both studies have concluded that home BP is more closely associated with future cardiovascular mortality than clinic BP, even when only a few home measurements are used [52, 53, 60]. Elevated home BP also predicted cardiovascular events better than elevated clinic BP in a study with 4939 elderly treated hypertensives. [87]. One smaller population study with only 662 subjects and an 8-year follow-up did not find any prognostic superiority of home BP compared to clinic BP [132]. Morning home BP and evening home BP seem to provide equally useful information for stroke risk [133].

2.6 Limitations of home blood pressure measurement

Home BP measurement also has its disadvantages. The accuracy of some home monitors is inadequate, especially with wrist and finger monitors [29, 30]. Reporting bias is possible as patients tend to under-report measurements if the patient reports

the BP readings him/herself [134]. BP measurements can easily be performed incorrectly. One study concluded that most patients with home monitors had never been informed by anyone of proper BP measurement techniques and that only about half of them knew how to place the cuff correctly, which led to poor measurement accuracy [135]. However, these shortcomings can often be avoided by following the current recommendations for home BP measurement [14, 42]. The clinical use of home measurement should require the use of validated and calibrated home monitors and good patient training. Some guidelines also recommend using a home monitor with a printed or electronic report of the measurements, although this does not completely eliminate the possibility of reporting bias [42].

Home BP monitors use the oscillometric technique, which may yield results that differ substantially from BP readings taken with a sphygmomanometer. This is particularly true in elderly subjects and diabetics [136, 137]. BP measuring devices also vary greatly in their ability to measure BP accurately in patients with arrhythmias, indicating that that devices should be validated independently in patients with arrhythmias [138]. Home BP also cannot be measured at night, which is possible with ambulatory BP measurement, although home BP devices with the capacity to perform measurements at predetermined times are coming to the market [139]. Some patient selection for home BP measurement may also be necessary because of its complexity as it still requires some instruction before the patients understand the procedure correctly. Furthermore, home BP measurement may induce anxiety in some patients, who might take an obsessional interest in BP.

2.7 Indications for home blood pressure measurement

Although home BP is starting to be used in almost every aspect of BP measurement from screening to follow-up, there are still some areas where it is particularly useful. Home BP measurement eliminates the white-coat effect and allows the detection of ICH. Home BP may also be used in virtually any patient in whom there is a suspicion that the clinic readings may be unrepresentative of the patients true BP. Home BP measurement should also be considered as a first option for a patient with resistant hypertension, further reducing the need for ambulatory monitoring, which cannot be performed in primary care and which is inconvenient for the patient. Home BP measurement can also be used for improving adherence to treatment in patients with poor compliance [120, 121]. In clinical drug trials, the duration of action of an antihypertensive drug can be assessed by measuring BP a number of times each day over several weeks [58].

2.8 Summary

It can be concluded that home BP measurement offers clear advantages not only over conventional clinic BP measurement, but also over ambulatory monitoring (Table 2). Home BP measurement allows the identification of ICH patients with readings under standardized conditions, little measurement variability and good reproducibility [63]. Home monitoring is a method preferred by patients that can lead to better BP control by increasing awareness of hypertension and compliance with drug treatment [119-121]. Preliminary data, although mostly from small, selected hypertensive populations, show that home BP correlates better than clinic BP with target-organ damage [78, 112, 126-130]. Early data of the prognostic superiority of home BP, when compared with clinic BP, also exist [52, 53, 60]. There are, however, some shortcomings to home BP measurement, which can mostly be avoided with good patient training and by using only validated and calibrated home monitors. The worst birth pains of home BP measurement are over, but several aspects require further elucidation.

Table 2. ***Features of different methods of blood pressure measurement.***

Feature	Clinic BP	Ambulatory BP	Home BP
Outcome prediction [52, 53, 60]	Poor	Good	Good
Evaluation of treatment	Yes	Limited	Yes
Preferred by patients [119]	No	No	Yes
Improves adherence [120, 121]	No	No	Yes
Diurnal rhythm assessment [139]	No	Yes	Yes/No
Cost	Moderate	Costly	Inexpensive
Measurement bias [134]	Yes	No	Yes/No
Measurement frequency	Low	High	Moderate
Reproducibility [63]	Poor	Good	Good
White-coat effect	Yes	No	No
Estimation of paroxysmal hypertension	No	Yes	No

BP, blood pressure.

So far only two studies with major limitations have compared antihypertensive treatment based on home measurement instead of clinic measurement [124, 125]. However, no studies have directly compared ambulatory BP monitoring, considered by many as the gold standard of BP measurement, and home BP measurement in the management of hypertensive patients.

Nearly all studies that have examined the different aspects of home BP measurement (i.e. agreement in diagnosis, prevalence and determinants of ICH, association with end-organ damage) have been performed with small cohorts of selected hypertensive patients in specialized hypertension clinics or academic settings. Until now, no nationwide studies assessing these issues have been published. Only two larger population-based studies exist, the PAMELA study with approximately 2000 participants, and the Ohasama study with approximately 1800 participants [52, 60]. However, both are based on only one single community, the PAMELA study in the city of Monza, Italy and the Ohasama study in the rural town of Ohasama, Japan. The characteristics and lifestyle of the Japanese Ohasama population differ from European or North American populations. The results of the Ohasama study can not therefore be generalized to Caucasian populations. Furthermore, only two home measurements were performed by the participants of the PAMELA population and both the Ohasama and the PAMELA studies have published limited data on the association between home BP and end-organ damage [78, 112]. In addition, very little attention has been focused on the possible psychological determinants of ICH, although ICH is partly considered to be a consequence of a psychological anxiety reaction associated with the presence of a doctor or a nurse.

3 AIMS OF THE STUDY

This thesis was set out to provide physicians with evidence that home BP measurement can be used effectively in clinical practice, and that it is superior to conventional clinic measurement. The specific goals are:

1. To compare agreement between clinic and self-measured home BP measurement in a representative sample of the Finnish adult population (I).
2. To study the prevalence and determinants of ICH in this population (II).
3. To assess in this population whether home-measured BP is more strongly associated with end-organ damage than is clinic BP (III-V).
4. To examine the independent roles of clinic BP, home BP and other risk factors in end-organ damage (III-V).
5. To propose a schedule for home BP measurement based on our findings (I, III-V)
6. To compare home and ambulatory BP in the adjustment of antihypertensive treatment in hypertensive patients (VI).

4 MATERIALS AND METHODS

4.1 Studies I-V

4.1.1 Study populations

The study sample for the Finnish home BP monitoring study (Finn-HOME study) was drawn from the participants of a multidisciplinary epidemiological survey, the Health 2000 study, which was carried out in Finland from the fall of 2000 to the spring of 2001. Stratification and sampling were conducted as follows: the strata were the five university hospital districts, each serving approximately one million inhabitants and differing in several features related to geography, economic structure, health services and the socio-demographic characteristics of the population. First, the 15 largest cities were included with the probability of one. Next, within each of the five districts, all 65 other areas were sampled applying the PPS-method (probability proportional to population size). Finally, from each of these 80 areas, a random sample of individuals was drawn from the national population register. A total of 8028 persons aged 30 years or older were sampled from these clusters. Full details of the sampling procedure and non-responsives have been published elsewhere [140].

Of the subjects aged 45–74 years (n = 4 388), 84% (n = 3 672) agreed to participate in the interview and attended the health examination (Figure 2). Out of these subjects, 2 120 participated in the home BP measurement sub-study (Finn-HOME study) for persons aged 45–74 years. Home measurement of BP was not performed on all subjects willing to participate due to the limited number of home monitors (approximately 1 000). Thus, study subjects willing to participate the home BP measurement sub-study were practically randomly selected on the basis of monitor availability. These 2 120 subjects formed the basic study cohort for studies I-V.

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 signed informed consent.

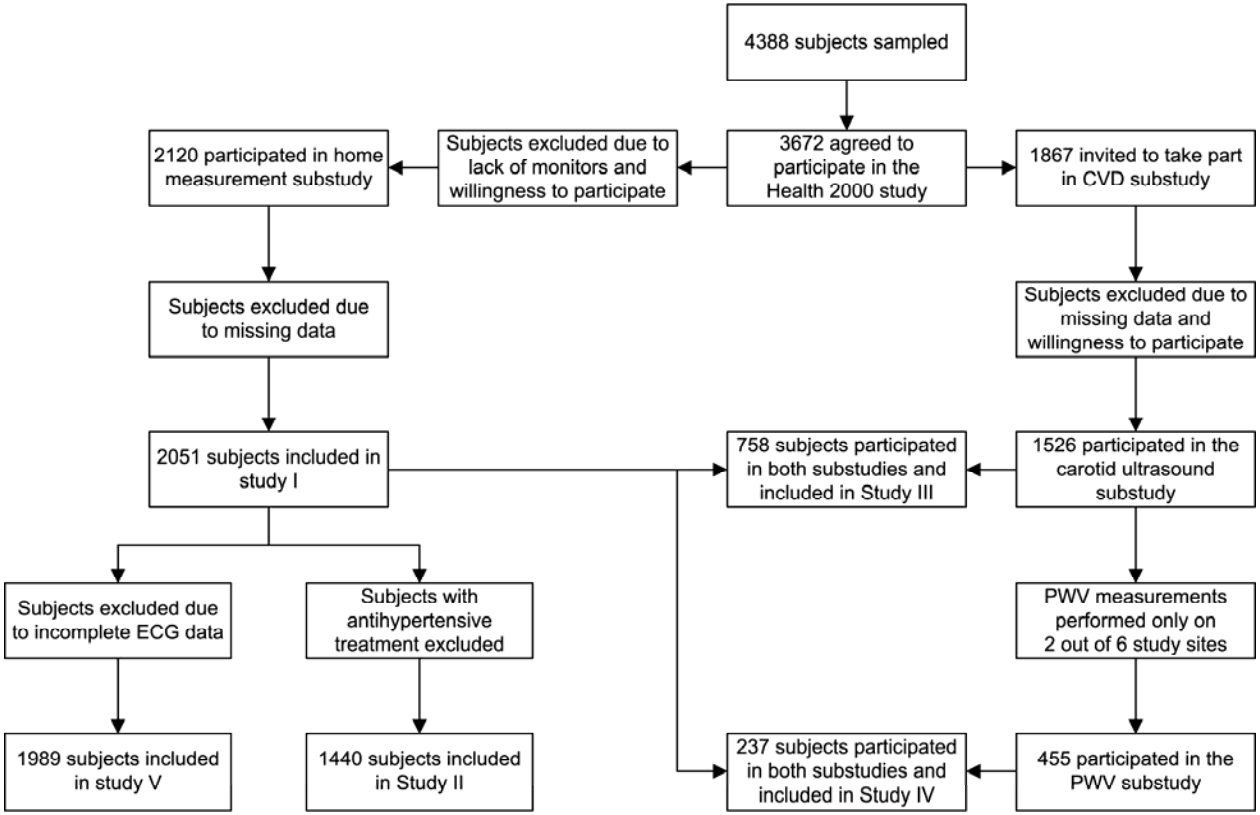

Figure 2. ***A flow chart illustrating the evolution of study samples in studies I-V. CVD, cardiovascular disease; PWV, pulse wave velocity.***

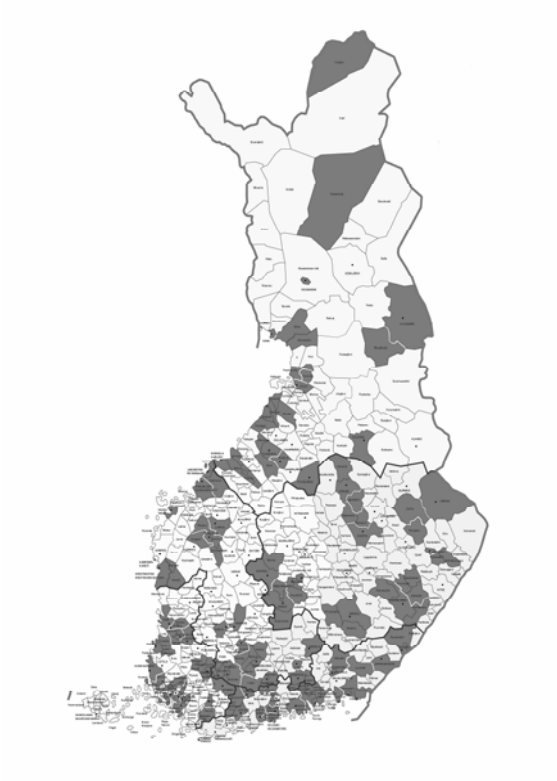

Figure 3. ***Map of Finland. Study locations of the Health 2000 survey marked in grey.***

Study I

Subjects of the Finn-HOME cohort who had missing laboratory or health examination data (n = 17) or had not performed ≥ 14 valid home measurements of BP (n = 56) were excluded from the study. After removing subjects with one or more exclusion factors, the study population consisted of 2 051 subjects of 45–74 years of age (Figure 2).

Subjects included in the study population differed slightly from the same-aged subjects of the Health 2000 study, who were not included in the home-measurement substudy, by having a lower BMI, a lower clinic systolic BP and by smoking less (Study I, Table 1).

Study II

Subjects of the Finn-HOME cohort who were using antihypertensive medication (n = 481) were excluded from the study to avoid the confounding effect of a decrease in BP, and the possible reclassification of patients. Subjects who had missing laboratory or health examination data (n = 53), had not performed ≥ 14 valid home measurements of BP (n = 69) or had failed to return or complete the self-report psychometric questionnaires (n = 224) were also excluded from the study. After removing subjects with one or more exclusion factors, the final study population consisted of 1 440 subjects, 45–74 years of age (Figure 2).

The study population differed slightly from the respective non-participants of the home measurement substudy by being younger and smoking less, and by having a lower BMI, a lower clinic systolic BP, and a higher education level (Study II, Table 1).

Study III

1 867 45–74 year-old subjects who participated in the Health 2000 survey were invited to participate in a cardiovascular disease substudy, which included measurement of carotid IMT. 1 526 (82%) agreed to participate. In the present study, analyses were restricted to those 45–74 year-old subjects of the Health 2000 survey who had participated in both the home BP monitoring and carotid ultrasound substudies (n = 801). Subjects who had not completed the health examination or the interview properly (n = 1), had missing carotid ultrasound data (n = 21), had not performed ≥ 14 valid home measurements of BP (n = 19), or had incomplete laboratory values (n = 2) were excluded from the study. After removing subjects with one or more exclusion factors, the study population consisted of 758 subjects of 45–74 years of age (Figure 2).

Subjects included in the study population differed very slightly from the same aged subjects of the Health 2000 Study, who did not participate in the home measurement and carotid IMT substudies by having a lower BMI, a lower clinic systolic BP, a lower serum triglyceride level and a higher serum high density lipoprotein (HDL) level (Study III, Table 1).

Study IV

Subjects of the Finn-HOME cohort who had not performed ≥ 14 valid home measurements of BP (n = 56), had missing clinic BP values (n = 16), electrocardiograph (ECG) measurements (n = 34), or intraventricular conduction abnormalities (n = 47) were excluded from the study. After removing subjects with one or more exclusion factors, the final study population consisted of 1 989 subjects of 45–74 years of age (Figure 2).

Characteristicts of the study population were very similar to the Finnish 45–74-year-old general population (Study I, Table 1).

S t u d y V

Out of the total of 1 526 participants of the Health 2000 survey's cardiovascular disease substudy, 455 subjects aged 45–74 were examined at the Turku and Tampere university hospital districts, where the measurement of PWV was also performed on all subjects. In study VI, analyses were restricted to those 45–74 year-old subjects of the Health 2000 survey who had participated in both the home BP monitoring and PWV substudies (n = 243). Subjects who had not performed ≥ 14 valid home measurements of BP (n = 3), or had incomplete laboratory values (n = 3) were excluded from the study. After removing subjects with one or more exclusion factors, the study population consisted of 237 subjects of 45–74 years of age (Figure 2).

Subjects included in the study population differed slightly from the same aged subjects of the Health 2000, who did not participate in the home BP measurement and PWV substudies by having a lower waist-to hip ratio, a lower pulse pressure, a higher serum HDL-cholesterol level, and by having proportionally more men (Study V, Table 1).

4.1.2 Flow of the studies

At an initial health interview at the subject's home, basic background and socio-demographic characteristics, information about health, illnesses and use of medication was gathered by centrally trained interviewers. A self-report questionnaire for the Beck Depression Inventory [141] and General Health Questionnaire [142], given to the study subjects to fill in and bring along to the physical examination. If a home monitor was available, the subjects were invited to participate in the home measurement sub-study. 2 120 subjects 45–74 years of age who were willing to participate received home BP monitors for measuring BP at home during the week following the health interview.

A physical examination was performed on each subject 1–6 weeks after the health interview at a local health center by centrally trained doctors and nurses. Each subject's height, weight, body circumference and clinic BP were measured. Fasting blood samples for serum glucose and lipids were taken. A 12-lead ECG was also recorded. After the physical examination, the subjects received a self-report questionnaires for the Whiteley Index [143] and Toronto Alexithymia Scale [144, 145] to be filled in at home and mailed to the National Public Health Institute.

The cardiovascular disease substudy with IMT and PWV measurement was performed after the Health 2000 survey from December 2001 through August 2002. Full details of the methodology of the project have been published elsewhere [140].

4.1.3 Blood pressure measurement

Clinic BP was measured by a nurse with a conventional, calibrated, mercury sphygmomanometer from the sitting individual's right arm after a ten-minute rest. The last five minutes of rest were spent in the measuring room with the cuff around the right upper arm. BP was measured using a pressure cuff of appropriate size and methods that were in accordance to current guidelines [146]. Systolic BP and diastolic BP were defined according to Korotkoff sounds I and V. Means of two measurements performed at a two-minute interval were used to determine clinic BP.

Home BP was self-measured with a validated, semi-automatic oscillometric device (Omron model HEM-722C, Omron Corp., Kyoto, Japan) according to the current guidelines [42, 147]. Subjects received written instructions and individual guidance on how to measure BP correctly. Preparations for self-measurement of BP were the same as for clinic BP. Seated BP was measured twice, approximately at a two-minute interval every morning between 6 AM and 9 AM and every evening between 6 PM and 9 PM on seven consecutive days. Home BP was determined as the mean of 14 duplicate measurements (28 measurements). The mean number of home BP measurements performed varied between 27.0 ± 2.8 and 27.1 ± 2.6 in the different studies.

4.1.4 Laboratory analyses

Venous blood samples were drawn from the antecubital vein after an overnight fast. HDL-cholesterol, low density lipoprotein (LDL)-cholesterol, total cholesterol, triglyceride, and glucose concentrations were determined enzymatically (Roche Diagnostics, Mannheim, Germany, for HDL- and LDL-cholesterol; Olympus System Reagent, Hamburg, Germany, for total cholesterol, triglyceride, and glucose) with a clinical chemistry analyzer (Olympus, AU400, Hamburg, Germany).

4.1.5 Psychometric tests (II)

Depressive symptoms and other psychopathological items were evaluated using several self-report questionnaires, which included: the seven-item Whiteley index rated on a five-point Likert scale (Whiteley-7, range 7–35) [143], which measures worrying and convictions about illness and somatoform disorders; a minimally

modified version of the 21-item Beck Depression Inventory (BDI, range 0–63) [141], used for assessing the existence and severity of symptoms of depression; the 12-item General Health Questionnaire (GHQ-12, range 0–12) [142], used to detect the presence of non-psychotic psychiatric morbidity, especially depression and anxiety; and the 20-item Toronto Alexithymia Scale (TAS-20, range 20–100) for measuring alexithymia [144, 145]. A higher score in all previous psychometric tests indicates a greater risk of psychological disease. When no more than one item was missing from the BDI (n = 70), Whiteley-7 (n = 51), GHQ-12 (n = 28) or TAS-20 (n = 66), missing or incomplete data were imputed with the average score of the completed items and rounded to the nearest whole number.

4.1.6 Carotid intima-media measurement (III)

High-resolution B-mode carotid ultrasound examination of the right carotid artery was performed according to a standardized protocol using a 7.5 MHz linear array transducer. The examinations were performed by centrally trained and certified sonographers at five study locations. IMT measurements were performed off-line with the use of automated imaging processing software. One reader was responsible for reading all ultrasound images.

The distal 1 cm of the common carotid artery using the beginning of the carotid artery bulb (the site where the two parallel walls of the common carotid artery diverge) as an anatomical landmark was examined first. The transducer was positioned to visualize both the far wall and near wall lumen-intima and media-adventitia interfaces at a single (lateral) angle. A cine loop was recorded for 4–5 seconds and stored on super-VHS tape. Then the sonographer focused on the carotid artery bulb whose distal boundary was the flow divider and proximal boundary the site where the two parallel walls of the common carotid artery diverge. The transducer was positioned to visualize the far wall. A cine loop was recorded for 4–5 seconds of three interrogation angles (lateral, anterior, and posterior) and stored on a super VHS tape.

The computer program PROSOUND (Prosound, California, USA) was used for the first 500 ultrasound examinations and its Windows version PROWIN 23.1 for the remaining 1 000 examinations to track the far wall lumen-intima and media-adventitia echoes to determine IMT over the distal 1 cm segment of the common carotid artery and the carotid bulb [148, 149]. The IMT was measured from three digitized end-diastole images of the common carotid artery (lateral angle) and the carotid bulb (three interrogation angles). Three summary measures were calculated: 1) the mean of the three average IMT measurements of the common carotid artery, 2) the mean of the three average IMT measurements of the carotid bulb, and 3) the

mean of these two means (mean IMT). The mean IMT was used for all analyses in this study.

The ultrasound examinations measured using the PROSOUND software were randomly distributed across the five study centers and glucose tolerance categories. To assess comparability of IMT measurements done by the two versions of the software, 363 randomly selected images of 60 study subjects measured by the PROSOUND software were measured again by the same reader using the PROWIN 23.1 software. The mean difference of the IMT measured using the two versions of the software was 0.025±0.237 mm and the intra-class correlation of the two measurements was moderate ($r = 0.780$, $p < 0.001$) and coefficient of variation was 17.4%. The intra-reader reproducibility of the IMT measurements using the PROWIN 23.1 software was also assessed. The reader measured the IMT twice from 571 randomly selected images of 95 study subjects several weeks apart. The mean difference of the two measurements was 0.001±0.123 mm and the intra-class correlation was high ($r = 0.934$ ($p < 0.001$) and coefficient of variation was 9.2%.

4.1.7 Pulse wave velocity measurement (IV)

PWV measurements have been usually carried out with Doppler ultrasound or mechanoelectrical pulse transducers. PWV can also be measured by whole-body impedance cardiography, which produces a useful and reliable tool for evaluating arterial stiffness. In this study, the whole-body impedance cardiography measurements were carried out by a commercially available circulation monitor device CircMon B202 (JR Medical Ltd, Tallinn, Estonia). The CircMon software estimates the point of the whole-body impedance cardiogram that coincides with pulse transmission in the aortic arch. The distal impedance plethysmogram was recorded from a popliteal artery at the level of the knee joint. When the pulse pressure wave enters the aortic arch and the diameter of the aorta changes, the whole-body impedance decreases, and this can be measured by the voltage-sensing electrodes on the distal parts of the extremities. The CircMon software measures the time difference between the onset of the decrease in impedance in the whole-body impedance signal and, later, the popliteal artery signal. By means of this time difference and the estimated distance between the electrodes, the software calculates the PWV value. The impedance cardiography method has been described in detail previously [150]. Previous results have shown that PWV values calculated using the whole-body impedance cardiogram have an excellent correlation with the Doppler method ($r = 0.91$, $p < 0.0001$), but systematically slightly overestimate those made by the Doppler method. The reproducibility values of the PWV measurement are

similar for whole-body impedance cardiography and Doppler ultrasound (2.17 and 2.42 m/s, respectively) [151].

4.1.8 Electrocardiography (V)

Standard resting 12-lead ECGs were digitally recorded with a Marquette MAC 5000 device and stored as digital data on a Marquette MUSE CV 5B system (Marquette Hellige, Milwaukee, WI, USA). All ECGs were overread, and the computerized diagnoses and measurements corrected if needed, by a single physician experienced with electrocardiography before being stored into the database. QRS duration was measured to the nearest 4 ms and the QRS amplitudes to the nearest 0.5 mm. ECG-LVH was assessed with three commonly used ECG criteria: 1) the Sokolow-Lyon voltage (S_{V1} + $R_{V5/6}$) [152], 2) the Cornell voltage (R_{aVL} + S_{V3}, plus 6 mm for women) [153, 154], and 3) the Cornell product (Cornell voltage x QRS duration) [155] as indicators of ECG-LVH. Threshold values of 35 mm, 26 mm and 2440 mm x ms were used to identify LVH using the Sokolow-Lyon, Cornell voltage and Cornell product criteria, respectively.

4.1.9 Definitions

Clinic hypertension was defined as a clinic BP ≥ 140/90 mmHg. Home hypertension was defined as a clinic BP ≥ 135/85 mmHg [42]. Subjects were identified as exhibiting ICH if their clinic BP was ≥ 140/90 mmHg and home BP was < 135/90 mmHg [29]. Diabetes mellitus was defined as a fasting serum glucose level of 7.0 mmol/l or greater or a history of the use of oral hypoglycemic agents or insulin injections. Antihypertensive therapy was defined as a current use of antihypertensive medication. Smoking was defined as a daily use of tobacco products.

4.1.10 Statistical analyses

Database management and statistical analysis were performed with the statistical software SAS, version 9.1 (SAS Institute, Cary, NC, USA). Data are reported as mean ± standard deviation. P-value < 0.05 was considered significant in studies III-VI and a p-value < 0.01 in study II.

S t u d y I

Continuous variables were compared using the Student's t-test for dual comparison and the Tukey correction for multiple comparisons. Categorical variables were evaluated with the chi-square test (baseline characteristics), kappa coefficient

(agreement in diagnosing hypertension) or the McNemar's test (achievement of BP thresholds). The mean and standard deviation of the difference between the home and clinic BP measurement were not constant, and adjusted difference against mean scatter-plots, as recommended by Bland-Altman, were used to assess the agreement between the two methods [23, 24].

Study II

Population weighting was used to correct the prevalence of ICH of the sample to correspond to that of the general Finnish population. One-way ANOVA and post-hoc comparisons (Tukey test) were used to compare the clinically normotensive group, the group ICH and the group with sustained hypertension. Multivariate logistic regression with backward selection was used to identify the clinical, demographic and psychological determinants that were independently associated with ICH. The independent variables included in the model were those considered epidemiologically relevant, (i.e. gender, BMI, age, smoking status and level of education) as well as those that reached statistical significance in univariate analysis (i.e. clinic systolic and diastolic BP and heart rate, BDI score and TAS-20 score). Only significant variables ($p < 0.05$) were retained in the model.

Studies III-V

The difference between home BP and clinic BP was compared by the paired t-test. Means of continuous variables were compared using a two-sample t-test. Pearson's correlation was used to describe the association between continuous variables. Multivariate linear regression with all the variables from the univariate analysis included as independent variables was used to identify the determinants that were independently associated with increased carotid IMT or PWV. Testing equality of two correlations was carried out in a LISREL model (LISREL, version 8.54, SSI Inc., Chicago, IL, USA) by using the chi-square difference test for correlation matrices with and without the equality constraint [156].

4.2 Study VI

4.2.1 Study population

The study cohort consisted of previously treated or untreated patients 40–80 years of age, with an off-treatment daytime ambulatory diastolic BP between 86 and 110 mmHg. Subjects were excluded if they had one or more of the following findings: secondary hypertension, childbearing potential, a stroke or myocardial infarction within 12 months prior to randomization, decompensated congestive heart failure,

other serious concomitant diseases which might affect survival, other indication than hypertension for drugs used in the trial, hypersensitivity to drugs used in the trial, heart rate < 50/min, insulin-treated diabetes mellitus, hepatic or renal insufficiency, atrial fibrillation or BMI > 35 kg/m^2.

110 patients met the inclusion criteria and underwent randomization, 56 in the home BP group and 54 in the ambulatory BP group (Figure 4). In the home BP group 52 patients (92.9%) completed the study successfully, as did 46 patients (85.2%) in the ambulatory BP group. The baseline characteristics of the patients in the ambulatory BP group and home BP group were similar (I, Table 1). Most patients had taken antihypertensive medication. No serious adverse events were reported during the study.

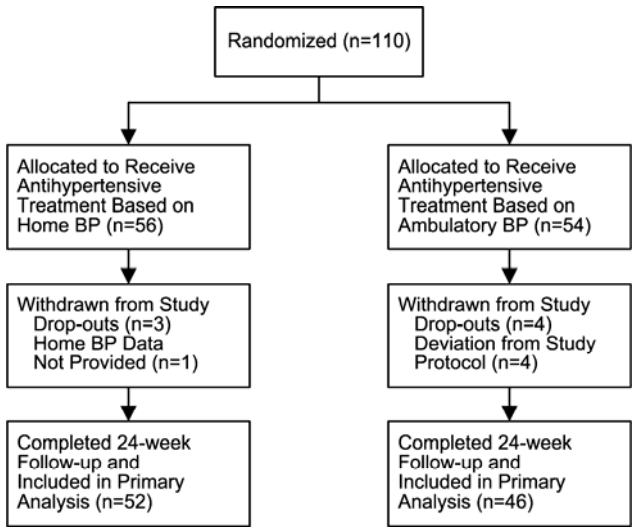

Figure 4. ***Flow of study participants. BP, blood pressure.***

4.2.2 Flow of the study

The study was a blinded, randomized, controlled clinical trial which took place between April 1999 and November 2003 in the outpatient clinic of Turku University Hospital. The protocol for the study was approved by the Ethics Committee of the University of Turku, Finland. The study was conducted according to the Declaration of Helsinki and written informed consent was obtained from all patients.

At an initial pre-entry screening, a medical history for all patients was obtained and a standard physical examination was performed. Any previous antihypertensive medication was discontinued and the patients underwent a four-week placebo washout period. During the last week of the pre-entry period the patients measured their BP daily using a home monitor to obtain a baseline BP estimate. At the end of the four-week wash-out period a 24-hour ambulatory BP measurement was performed on all patients.

Patients who met the inclusion criteria and who had no identifiable cause for exclusion were included in the study and were randomly allocated by random number generator to be treated either according to their home or ambulatory BP.

After randomization, follow-up visits were scheduled at 6, 12, 18 and 24 weeks. All patients measured their home BP during the week preceding the follow-up visit. Ambulatory BP monitoring was also performed on all patients one day before the follow-up visit. The treating physician was blinded to randomization and received only the BP values for the method of measurement to which the patient was randomized, but was not told which method was used to obtain the BP values. All patients were treated by a single physician. The target pressure in the study for both the home- and ambulatory-based BP measurement groups was a diastolic BP $\leq$ 80 mmHg. To achieve this goal, a standardized stepped-care antihypertensive drug regimen was implemented. After randomization, all patients began therapy with candesartan, 8 mg/d (step 1). At later visits, if the mean diastolic pressure guiding treatment was above the target pressure (> 80 mmHg), the treatment was intensified stepwise to candesartan 16 mg/d (step 2), candesartan 16 mg/d + hydroclorothiazide 12.5 mg/d (step 3) and candesartan 16 mg/d + hydroclorothiazide 12.5 mg/d + felodipine 5 mg/d (step 4). Previous treatment was continued if BP was below target pressure, or was reduced if the patient had symptoms of hypotension.

4.2.3 Blood pressure measurement

Before the pre-entry screening period, all patients received individual guidance on how to measure BP correctly. Home BP was measured according to the current guidelines using a semi-automatic, oscillometric, validated Omron M4, model HEM-722C (Omron Corp., Kyoto, Japan) home monitor [42, 147]. After 5 minutes of rest in the sitting position, patients performed two consecutive self-measurements of BP twice daily, in the morning between 6 and 10 AM at trough and in the evening between 6 and 10 PM. The BP values and the time of day were self-recorded. The self-measured BP was the average of all 28 readings collected during seven consecutive days preceding each follow-up visit.

The 24-hour ambulatory BP monitoring was performed at 0, 6, 12, 18 and 24 weeks on all patients using a validated oscillometric SpaceLabs Medical 90207 (Spacelabs Inc., Redmond, WA, USA) ambulatory BP monitor [157]. Measurements were performed at 15–minute intervals during the day (6 AM to 11 PM) and at 30–minute intervals at night (11 PM to 6 AM). All patients received verbal and written instructions about the operation and care of the BP monitor. All recipients completed a sleep and activity diary during the ambulatory BP monitoring and night times were defined as full hours of self-reported actual patient sleep times.

In addition, clinic BP measurement was performed at 0, 6, 12, 18 and 24 weeks on all patients. The values from these measurements were not used in guiding antihypertensive treatment and were not disclosed to the doctor. Systolic and diastolic clinic BP (Korotkoff sounds, phase V) was the mean of three consecutive BP measurements taken at two-minute intervals after the patients had been seated for five minutes by a nurse using a calibrated conventional sphygmomanometer.

4.2.4 Statistical analyses

With a type I error of 5% (“false positive”) and a type II error of 20% (“false negative”), approximately 44 patients per treatment group were needed to detect differences of 3 mmHg for systolic and diastolic BP, assuming a standard deviation of 5 mmHg for both. The number of patients withdrawing from the study was estimated at 10%, and therefore approximately 50 patients were enrolled per treatment group.

Database analysis and management were performed with SAS statistical software, version 8.2 (SAS Institute Inc., Cary, NC, USA). The between-group differences in continuous measurements were calculated by subtracting the mean changes from baseline in the home BP group from those of the ambulatory BP group. The variables were tested for normality. The between-group comparisons for baseline characteristics and BP changes were performed with the two-sample Student’s t-test or the Mann-Whitney U-test for continuous variables, or the Chi-square test in case of categorical variables. The within-group comparisons for BPs were made with the paired Student’s t-test. A repeated-measures analysis of variance (ANOVA) was used to evaluate the between-group changes in BP during the study. P-values < 0.05 were considered significant.

5 RESULTS

5.1 Agreement between clinic and home blood pressure measurement in the Finnish population (I)

Mean clinic BP was 137.4 ± 20.2/83.7 ± 10.7 mmHg. Mean home BP was 129.7 ± 18.8/80.3 ± 9.4 mmHg. Mean home BP of the initial monitoring day (132.9 ± 20.8/81.7 ± 10.4 mmHg) gave the highest and most variable (highest SD) values. The greatest decrease in home BP occurred between the first and second monitoring day. The mean difference was 2.4/1.0 mmHg (95% confidence limit 2.0–2.8, $p < 0.001$ for systolic BP and 95% confidence limit 0.8–1.2, $p < 0.001$ for diastolic BP). Thereafter mean home BP remained fairly steady with a small gradual decline (Table 3). Among untreated subjects, the systolic and diastolic home BP were significantly higher in the evening than in the morning (morning: 124.9 ± 18.9/78.9 ± 9.6 mmHg, evening: 129.0 ± 18.5/79.3 ± 9.3 mmHg, $p < 0.001$ for both systolic and diastolic BP), but among subjects treated for hypertension this difference was non-existent for systolic BP and reversed for diastolic BP (morning: 139.2 ± 18.3/85.1 ± 9.6 mmHg, evening: 139.7 ± 17.6/83.7 ± 9.1 mmHg, $p = 0.35$ for systolic and $p < 0.001$ for diastolic BP difference). The mean difference between the first and second measurement of each measurement occasion was 3.0/1.2 mmHg ($p < 0.001$ for systolic and diastolic BP).

Clinic systolic BP and diastolic BP were significantly ($p < 0.05$) and markedly higher than home BP in all age groups and in the study population as a whole (Figures 5 and 6). The differences against mean scatter-plots are summarized by the mean difference between groups, and the positive Pearson's correlations (systolic BP: $r = 0.10$, $p < 0.001$; diastolic BP: $r = 0.16$, $p < 0.001$, Figure 5). The home–clinic BP difference and the 95% limits of agreement increased with higher levels of BP. Using the currently recommended cut-off points (140/90 mmHg for clinic BP and 135/85 mmHg for home BP [42]), the agreement between the methods was moderate (overall agreement 75.2%, [kappa] coefficient 0.50, 95% confidence limit 0.47–0.54). Clinic BP values had a sensitivity of 78.3% and a specificity of 73.0% in predicting high home BP (Table 4).

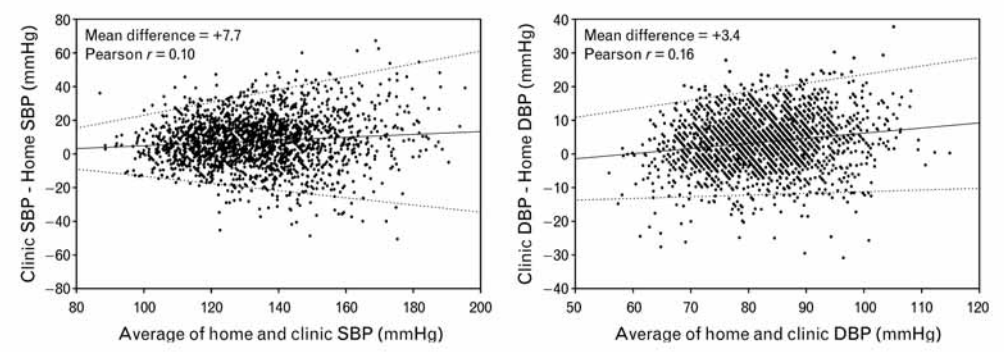

Figure 5. ***Scatter-plots of difference between systolic/diastolic clinic and home blood pressure (BP) against mean systolic/diastolic blood pressure. Dashed lines indicate 95% limit of agreement between methods; continuous line indicates mean difference. DBP, diastolic blood pressure; SBP, systolic blood pressure.***

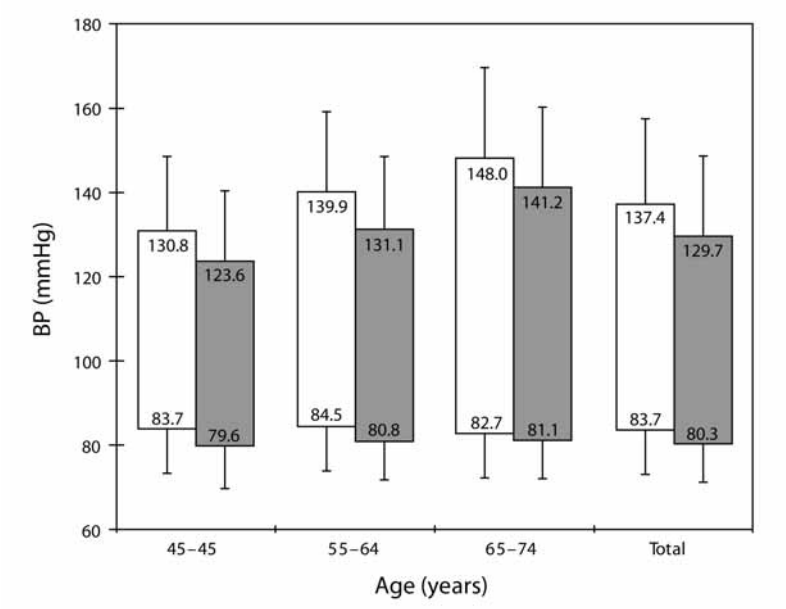

Figure 6. ***Mean systolic and diastolic blood pressures for different age groups and whole population. Error bars indicate standard deviation and values indicate mean systolic or diastolic blood pressure (BP). White color indicates clinic blood pressure and gray color indicates home blood pressure.***

Table 3. ***Mean blood pressures of the study subjects during seven consecutive days of home measurement.***

	Day of measurement						
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
All Subjects (n = 2051)							
Systolic	132.9 ± 20.8[234567]	130.5 ± 20.2[17]	129.6 ± 19.8[1]	129.1 ± 19.7[1]	128.9 ± 19.5[1]	128.5 ± 19.3[1]	128.4 ± 19.2[12]
Diastolic	81.7 ± 10.4[34567]	80.7 ± 10.2	80.4 ± 10.0[1]	80.0 ± 10.1[1]	79.8 ± 10.0[1]	79.8 ± 9.9[1]	79.7 ± 10.0[1]
Treated (n = 464)							
Systolic	143.1 ± 19.4[567]	140.4 ± 19.1	139.4 ± 18.5	138.9 ± 18.9	138.6 ± 18.2[1]	137.7 ± 18.5[1]	137.5 ± 18.0[1]
Diastolic	85.9 ± 9.9	84.6 ± 9.8	84.6 ± 9.8	84.1 ± 10.0	84.0 ± 9.8	83.9 ± 9.8	83.8 ± 10.1
Not Treated (n = 1587)							
Systolic	130.0 ± 20.2[234567]	127.7 ± 19.7[1]	126.7 ± 19.3[1]	126.3 ± 19.0[1]	126.0 ± 19.0[1]	125.8 ± 18.7[1]	125.7 ± 18.7[1]
Diastolic	80.5 ± 10.2[34567]	79.6 ± 10.0	79.1 ± 9.7[1]	78.9 ± 9.9[1]	78.6 ± 9.7[1]	78.6 ± 9.6[1]	78.5 ± 9.7[1]

Values reported as mean ± SD. Superscript numbers indicate a significant difference (ANOVA, $p < 0.01$) as compared with the mean BP of the day indicated by the number.

Table 4. ***Agreement between methods, and the sensitivity, specificity, and likelihood ratios for a positive and negative test of clinic blood pressure in predicting high home blood pressure.***

Measurement	Agreement (%)	Sensitivity (%)	Specificity (%)	Likelihood ratio (positive)	Likelihood ratio (negative)	Kappa coefficient (95% Cl)
Systolic	75.3	74.0	76.1	3.1	0.3	0.49 (0.45–0.52)
Diastolic	78.6	61.0	85.7	4.3	0.5	0.47 (0.43–0.51)
Both	75.2	78.3	73.0	2.9	0.3	0.50 (0.47–0.54)

The positive likelihood ratio indicates how much the odds of home hypertension increase when a patient is clinic hypertensive. The negative likelihood ratio indicates how much the odds of the home hypertension decrease when a patient is clinic normotensive. 95% Cl, 95% confidence limit.

To assess home BP status in the Finnish population, home BP values in subjects determined normotensive by clinic BP (clinic BP < 140/90 mmHg, n = 918), untreated hypertensive subjects (no self-reported use of antihypertensive medication and clinic BP ≥ 140/90 mmHg, n = 669) and treated hypertensive subjects (self-reported use of antihypertensive medication, n = 464) were analyzed. The mean clinic and home BP and control rates are shown in Table 5.

Normotensive subjects had significantly lower clinic and home BP values than untreated and treated hypertensive individuals. Untreated hypertensive individuals had higher clinic BP values than treated hypertensive individuals, but home BP values were similar for both groups. Among all subjects, clinic BP measurements (clinic BP ≥ 140/90 mmHg) slightly overestimated the prevalence of high BP as compared with home measurements (home BP ≥ 135/85 mmHg), 48.8% versus 42.5%, p < 0.001. Control of hypertension assessed with home BP was non-significantly higher among the treated hypertensive individuals than with clinic BP, 32.8% versus 28.7%, p = 0.11. The control of hypertension tended to be higher with home BP than with clinic BP in women (37.6% versus 31.4%, p = 0.07), but not in men (26.6% versus 25.1%, p = 0.71).

Table 5. ***Mean blood pressure values for clinic normotensive, treated hypertensive and untreated hypertensive subjects.***

Characteristic	All Subjects	Normotensive	Treated HT	Untreated HT	p
n	2051	918	464	669	
Male, n	952 (46.4%)	395 (43.0%)	203 (43.8%)	354 (52.9%)	
Age, years	56.4 ± 8.5	53.7 ± 7.6	60.1 ± 8.1	57.4 ± 8.8	< 0.01
Clinic Systolic BP, mmHg	137.4 ± 20.2	122.0 ± 10.7	146.7 ± 18.9 *	152.2 ± 15.5 *†	< 0.01
Clinic Diastolic BP, mmHg	83.7 ± 10.7	77.3 ± 7.3	86.5 ± 10.7 *	90.6 ± 9.3 *†	< 0.01
Home Systolic BP, mmHg	129.7 ± 18.8	117.7 ± 13.4	139.4 ± 17.3 *	139.5 ± 16.5 *	< 0.01
Home Diastolic BP, mmHg	80.3 ± 9.4	74.9 ± 7.2	84.4 ± 8.9 *	84.8 ± 8.5 *	< 0.01
Clinic BP < 140/90 mmHg, n	1050 (51.2%)	918 (100%)	133 (28.7%)	0 (0%)	
Home BP < 135/85 mmHg, n	1180 (57.5%)	788 (85.8%)	152 (32.8%)	240 (35.9%)	

Values reported as mean ± SD. † indicates p < 0.05 versus treated HT, * indicates p < 0.05 versus normotensive.
BP, Blood Pressure; HT, hypertensive; p, p-value for analysis of covariance between the 3 groups.

5.2 Prevalence and determinants of isolated clinic hypertension in the Finnish population (II)

The prevalence of ICH in the study population was 15.4%. After population weighting, the prevalence of ICH in the Finnish population of 45–74 year olds was 15.6%, insignificantly higher in men than in women (17.0% versus 14.3%, $p = 0.18$). Among untreated clinic hypertensive individuals, the weighted prevalence of ICH was 37.5%. The comparisons between the normotensive group, the ICH group and the sustained hypertensive group for the demographic, psychological and clinical characteristics are reported in Table 6.

The age and sex distribution and educational level of subjects with ICH was between those of the sustained hypertensive and normotensive individuals (Table 6). There were non-significantly fewer smokers among the subjects with ICH than among the normotensive ($p = 0.07$) or sustained hypertensive individuals ($p = 0.25$).

Clinic and home BP levels of the subjects with ICH were between those of the sustained hypertensive and normotensive individuals (Table 6). However, the systolic and diastolic white-coat effect (clinic minus home BP) was significantly higher ($p < 0.001$) in the ICH group than in the two other groups. The reduction in BP between the first and second clinic BP measurements was similar for all groups. Sustained hypertensive individuals had higher clinic and home heart rates than subjects with ICH and normotensive individuals. The ICH group had higher clinic ($p = 0.02$) but similar home heart rates compared with normotensive individuals ($p = 0.99$).

There was no significant difference in the BMI between the subjects with ICH and normotensive individuals ($p = 0.43$), but the sustained hypertensive individuals were more obese than subjects in the other groups ($p < 0.001$). There were no significant differences between the subjects with ICH and sustained hypertensive individuals in diabetes prevalence, serum glucose or serum lipid levels. The ICH group had higher levels of serum glucose ($p = 0.009$), total cholesterol ($p = 0.002$) and triglycerides ($p = 0.006$) than the normotensive group. The difference in glucose levels became non-significant after adjusting for age and sex.

In the psychometric tests, there were no between-group differences in the GHQ-12 and Whiteley-7 scores. Sustained hypertensive individuals had significantly higher scores in the BDI and TAS-20 than the two other groups. After adjusting for age and sex, the difference in the TAS-20 score between the sustained hypertensive and normotensive individuals became non-significant.

Table 6. ***Characteristics of subjects grouped by hypertension status.***

Characteristic	1. ST (n=371)	2. ICH (n=222)	3. NT (n=847)	Overall (p)	1 vs. 2 (p)	1 vs. 3 (p)	2 vs. 3 (p)
Age, y	57.9 ± 8.6	55.8 ± 8.3	53.5 ± 7.6	< 0.001	0.006	< 0.001	< 0.001
Men, %	54.5	51.4	42.5	< 0.001	0.74	< 0.001	0.0048
Smokers, %	20.8	15.3	22.1	0.09	0.25	0.86	0.07
Upper level education, %	19.4	21.6	30.8	< 0.001	0.82	< 0.001	0.02*
Medium level education, %	28.6	32.4	32.6	0.36	0.59	0.35	0.99
Lower level education, %	52.0	46.0	36.6	< 0.001	0.31	< 0.001	0.03*
BMI, kg/m^2	28.8 ± 4.1	26.4 ± 4.0	26.0 ± 3.8	< 0.001	< 0.001	< 0.001	0.43
Waist-to-hip ratio	0.94 ± 0.08	0.91 ± 0.09	0.90 ± 0.08	< 0.001	< 0.001	< 0.001	0.02*
Diabetes, %	6.5	4.5	2.5	0.003	0.45	0.002*	0.34
Serum glucose, mmol/l	5.6 ± 1.0	5.6 ± 1.1	5.4 ± 0.7	< 0.001	0.53	< 0.001	0.009*
Serum total cholesterol, mmol/l	6.4 ± 1.2	6.3 ± 1.2	6.0 ± 1.0	< 0.001	0.30	< 0.001	0.002
Serum HDL-cholesterol, mmol/l	1.3 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	< 0.001	0.08	< 0.001	0.66
Serum LDL-cholesterol, mmol/l	4.2 ± 1.3	4.1 ± 1.2	3.9 ± 1.1	< 0.001	0.44	< 0.001	0.17
Serum triglycerides, mmol/l	1.7 ± 1.1	1.6 ± 1.1	1.4 ± 0.8	< 0.001	0.49	< 0.001	0.006
Clinic systolic BP, mmHg	155.2 ± 16.3	146.0 ± 10.2	121.9 ± 10.6	< 0.001	< 0.001	< 0.001	< 0.001

Clinic diastolic BP, mmHg	92.3 ± 9.6	88.0 ± 7.6	77.4 ± 7.2	< 0.001	< 0.001	< 0.001	< 0.001
Clinic heart rate, per min	69.8 ± 11.3	67.8 ± 10.5	65.7 ± 9.6	< 0.001	0.06**	< 0.001	0.02
1st-2nd systolic BP difference, mmHg	1.3 ± 5.9	2.0 ± 6.0	1.7 ± 4.9	0.20	0.21	0.33	0.75
1st-2nd diastolic BP difference, mmHg	1.1 ± 4.0	1.2 ± 3.4	0.8 ± 4.1	0.19	0.99	0.30	0.34
Home systolic BP, mmHg	147.5 ± 13.3	124.0 ± 7.3	117.3 ± 13.1	< 0.001	< 0.001	< 0.001	< 0.001
Home diastolic BP, mmHg	88.8 ± 7.1	77.8 ± 4.8	74.7 ± 7.1	< 0.001	< 0.001	< 0.001	< 0.001
Home heart rate, per min	70.3 ± 9.0	67.9 ± 9.2	67.9 ± 8.5	< 0.001	0.004	< 0.001	0.99
Systolic white coat effect, mmHg	7.7 ± 15.1	22.1 ± 10.6	4.6 ± 11.8	< 0.001	< 0.001	< 0.001	< 0.001
Diastolic white coat effect, mmHg	3.5 ± 8.0	10.3 ± 6.5	2.7 ± 7.2	< 0.001	< 0.001	0.19	< 0.001
BDI, points	7.6 ± 7.0	6.1 ± 5.6	6.7 ± 6.5	0.02	0.02	0.08	0.41
GHQ-12, points	1.8 ± 2.9	1.4 ± 2.5	1.8 ± 2.9	0.11	0.13	0.94	0.14
Whiteley-7, points	13.6 ± 4.1	13.6 ± 3.6	13.6 ± 3.9	0.99	0.99	0.99	0.99
TAS-20, points	48.2 ± 10.9	45.2 ± 10.8	45.1 ± 10.8	< 0.001	0.004	< 0.001*	0.99

Values expressed as mean ± SD. * indicates nonsignificance ($p > 0.05$) and ** significance ($p < 0.05$) after adjusting for age and gender. ST, sustained Hypertensives; ICH, isolated clinic hypertension; NT, normotensives; p, p-value; BMI, body mass index; BP, blood pressure; BDI, Beck Depression Inventory; GHQ-12, 12-item General Health Questionnaire; Whiteley-7, 7-item Whiteley Index; TAS-20, 20-Item Toronto Alexithymia Scale; 1st-2nd BP difference, difference between 1st and 2nd clinic blood pressure measurements.

Two multivariate logistic regression models were performed to identify independent determinants of ICH. The whole study population was analyzed in the first regression model. Normotensive individuals were excluded from the second regression model to further examine the factors that would help identify the subjects with ICH from the sustained hypertensive individuals.

In the first regression model with ICH set as the dependent variable, higher clinic systolic and diastolic BP, lower BMI and a non-smoking status were associated with ICH after controlling with sex, age, clinic heart rate, educational level and scores from the BDI and TAS-20 (Table 7).

Table 7. ***Multivariate-adjusted odds ratios of selected clinical variables for isolated clinic hypertension, whole study population included in analysis.***

Variable	β	Odds Ratio	95% Cl	p
BMI, kg/m^2	-0.09	0.91	0.87–0.95	< 0.01
Smoking (yes = 0, no = 1)	0.21	1.51	1.00–2.27	0.048
Office systolic BP, mmHg	0.03	1.03	1.02–1.04	< 0.01
Office diastolic BP, mmHg	0.03	1.04	1.02–1.05	< 0.01

R-square = 0.22, p < 0.001. BMI, body mass index; BP, blood pressure; TAS-20, 20-item Toronto Alexithymia Scale; 95% Cl, 95% confidence limit; p, p-value.

In the second regression model, including only sustained hypertensive individuals and subjects with ICH, lower clinic systolic and diastolic BP, lower BMI, lower score in the TAS-20 and a non-smoking status were associated with ICH after controlling for sex, age, clinic heart rate, educational level and score from the BDI (Table 8). In this population, the prevalence of ICH was inversely proportional to the severity of clinic BP values (Figure 7).

In the first regression model, including the whole study population, higher clinic BP was a predictor of ICH, and in the second regression model, including only clinic hypertensive individuals, lower clinic BP was a predictor of ICH. Therefore, ICH seems to be associated with mildly elevated clinic BP.

Table 8. ***Multivariate-adjusted odds ratios of selected clinical variables for isolated clinic hypertension, only clinic hypertensives included in analysis.***

Variable	β	Odds Ratio	95 % Cl	p
BMI, kg/m^2	-0.15	0.86	0.82–0.91	< 0.01
Smoking (yes = 0, no = 1)	0.33	1.92	1.17–3.16	0.01
Office systolic BP, mmHg	-0.05	0.95	0.93–0.96	< 0.01
Office diastolic BP, mmHg	-0.04	0.96	0.94–0.98	< 0.01
TAS-20, points	-0.03	0.98	0.96–0.99	0.005

R-square = 0.09, p < 0.001. BMI, body mass index; BP, blood pressure; TAS-20, 20-item Toronto Alexithymia Scale; 95% Cl, 95% confidence limit; p, p-value.

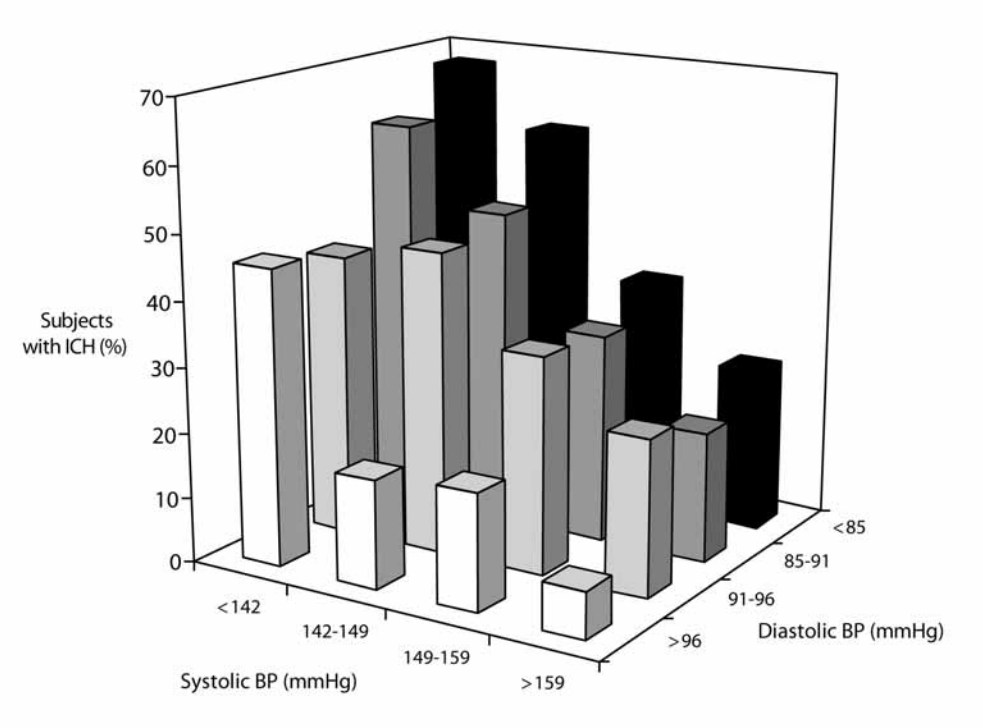

Figure 7. ***Frequency of isolated clinic hypertension (ICH) among clinic hypertensive individuals by quartiles of systolic and diastolic clinic blood pressure (BP).***

5.3 Home blood pressure and end-organ damage (III-V)

5.3.1 Carotid atherosclerosis (III)

The associations between carotid IMT and various BP parameters are presented in Table 9 and Figure 8. All BP parameters correlated significantly with carotid IMT ($p < 0.001$ for all), except for clinic diastolic BP, which did not reach statistical significance ($p = 0.07$). Systolic BP and pulse pressure had a stronger correlation with IMT than did diastolic BP for both clinic and home measurements. The Pearson correlation coefficients for carotid IMT and home/clinic BP differed significantly in favour of the home measurement of BP ($p < 0.001$ for systolic BP, diastolic BP and pulse pressure).

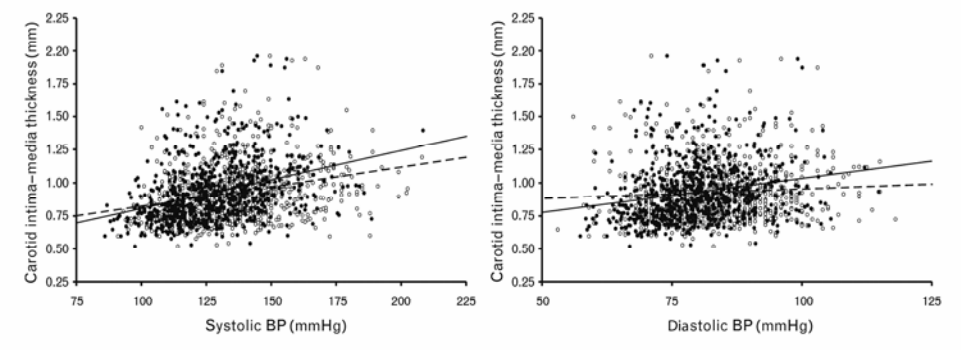

Figure 8. ***Scatter plots of systolic and diastolic blood pressure (BP) versus carotid intima-media thickness. White dots represent clinic blood pressure, and black dots home blood pressure. Regression lines represent the relationship between clinic (dashed lines) or home (solid lines) blood pressure and carotid intima-media thickness.***

Table 9. ***Association between carotid intima–media thickness or pulse wave velocity and selected clinical variables.***

	Intima-media thickness (n = 758)			Pulse wave velocity (n = 237)		
Continuous variable	r	p-value	Difference	r	p-value	Difference
Home SBP	0.35	< 0.001	< 0.001	0.65	< 0.001	< 0.001
Clinic SBP	0.25	< 0.001		0.50	< 0.001	
Home DBP	0.20	< 0.001	< 0.001	0.51	< 0.001	< 0.001
Clinic DBP	0.07	0.07		0.37	< 0.001	
Home PP	0.37	< 0.001	< 0.001	0.62	< 0.001	< 0.001
Clinic PP	0.28	< 0.001		0.40	< 0.001	
Age	0.50	< 0.001		0.51	< 0.001	
Triglycerides	0.20	< 0.001		0.26	< 0.001	
HDL-cholesterol	-0.20	< 0.001		-0.23	0.001	
LDL-cholesterol	0.13	< 0.001		0.07	0.27	
Total cholesterol	0.10	< 0.001		0.08	0.24	
Glucose	0.12	0.001		0.44	< 0.001	
WH ratio	0.21	< 0.001		0.34	< 0.001	
Body mass index	0.14	< 0.001		0.28	< 0.001	

Categorical variable	Mean IMT, mm	p-value	Mean PWV, m/s	p-value
Smoking				
Present	0.94 ± 0.26	0.68	12.7 ± 2.9	0.70
Absent	0.93 ± 0.23		12.9 ± 3.1	
Gender				
Male	0.97 ± 0.26	< 0.001	13.9 ± 2.9	< 0.001
Female	0.90 ± 0.20		12.2 ± 2.9	
Diabetes				
Present	1.08 ± 0.38	0.007	17.2 ± 2.9	< 0.001
Absent	0.92 ± 0.22		12.6 ± 2.6	

IMT reported as mean ± SD. Difference, p-value for difference in correlations; IMT, intima-media thickness; r, Pearson's correlation coefficient; PP, pulse pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure, WH, waist-to-hip, PWV, pulse wave velocity.

In a univariate analysis, age, triglycerides, serum glucose, waist-to-hip ratio, BMI, LDL-cholesterol, and total cholesterol showed a significant positive correlation with carotid IMT, whereas HDL-cholesterol was negatively associated with carotid IMT (Table 9). In addition, men and individuals with diabetes had a significantly thicker carotid IMT than women and individuals without diabetes. A linear regression was performed to identify the determinants that are independently associated with carotid IMT (Table 10). With IMT set as the dependent variable, age, home systolic BP,

triglycerides, male sex, smoking, diabetes, and LDL-cholesterol were independently associated with increased IMT. These determinants explained 32% of the variance in carotid IMT ($p < 0.001$). Clinic systolic BP, HDL-cholesterol, and BMI were not independently associated with IMT, and did not increase the coefficient of determination.

Table 10. ***Multivariate linear regression for carotid intima-media thickness (n = 758).***

Variable	β	SE	p-value
Intercept	-0.045	-	-
Age, years	0.013	0.45	< 0.001
Home systolic BP, mmHg	0.002	0.15	0.002
Triglycerides, mmol/L	0.019	0.10	0.006
Gender (male = 0, female = 1)	-0.041	-0.09	0.009
Smoking (no = 0, yes = 1)	0.045	0.07	0.017
Diabetes (no = 0, yes = 1)	0.067	0.07	0.035
LDL-cholesterol, mmol/l	0.014	0.06	0.041
Clinic systolic BP, mmHg	0.000	-0.04	0.412
HDL-cholesterol, mmol/l	-0.017	-0.03	0.456
Body mass index, kg/m^2	0.000	0.01	0.882

R-square = 0.32, $p < 0.001$. IMT, intima-media thickness; SE, standardized estimate; BP, blood pressure.

To investigate further how the number of home BP measurements affects the association between home BP and carotid IMT, the relationship between IMT and BP averaged over a cumulative number of days of home BP measurement was evaluated (Table 11). The correlation coefficients between systolic or diastolic BP and carotid IMT did not increase with the number of measurements. The associations between home BP and carotid IMT were, however, stronger compared with clinic BP, even with a low number of home measurements. When individual days of measurement and their correlation with carotid IMT were examined, there was no difference in the strength of the association provided by different home BP monitoring days. The r value of the first day was arithmetically the highest (Table 11).

Table 11. ***Correlation between carotid intima–media thickness or pulse wave velocity and blood pressure.***

BP Parameter	First 2	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Cumulative - IMT								
Systolic BP	-	-	0.353	0.350	0.348	0.343	0.347	0.348
Diastolic BP	-	-	0.215	0.211	0.206	0.201	0.201	0.204
Individual - IMT								
Systolic BP	0.342	0.346	0.343	0.323	0.324	0.306	0.343	0.332
Diastolic BP	0.227	0.214	0.203	0.191	0.173	0.169	0.182	0.200
Cumulative - PWV								
Systolic BP	-	-	0.643	0.656	0.651	0.653	0.657	0.653
Diastolic BP	-	-	0.504	0.507	0.494	0.504	0.514	0.511
Individual - PWV								
Systolic BP	0.589	0.622	0.633	0.644	0.572	0.611	0.643	0.600
Diastolic BP	0.471	0.493	0.488	0.461	0.406	0.502	0.528	0.481

Correlations are reported as Pearson's correlations. $p < 0.001$ for all correlations. BP, blood pressure; IMT, intima-media thickness; PWV pulse wave velocity; First 2, mean of the first two morning measurements. Cumulative, relationship between IMT/PWV and BP averaged over cumulative number of days of home BP measurements; Individual, the relationship between IMT/PWV and BP on individual days of measurement.

5.3.2 Arterial stiffness (IV)

The associations between PWV and various BP parameters are reported in Table 9 and Figure 9. All BP parameters correlated significantly with PWV ($p < 0.001$ for all). Systolic BP and pulse pressure had a stronger correlation with PWV than did diastolic BP for both clinic and home measurements. The Pearson correlation coefficients for PWV and home/clinic BP differed significantly in favor of home measurement of BP ($p < 0.001$ for systolic BP, diastolic BP and pulse pressure).

In a univariate analysis, age, triglycerides, BMI, waist-to-hip ratio, and serum fasting glucose showed a significant positive correlation with PWV, while HDL-cholesterol was negatively associated with PWV (Table 9). In addition, men and diabetics had a significantly greater PWV than women and non-diabetics. A linear regression was performed to identify the determinants that are independently associated with PWV (Table 12). With PWV set as the dependent variable, age, home systolic BP, and diabetes were independently associated with increased PWV. These determinants explained 60% of the variance in PWV ($p < 0.001$). Clinic systolic BP, triglycerides, LDL-cholesterol, smoking, HDL-cholesterol, gender, waist-to-hip ratio and BMI were not independently associated with PWV, and did not increase the coefficient of determination.

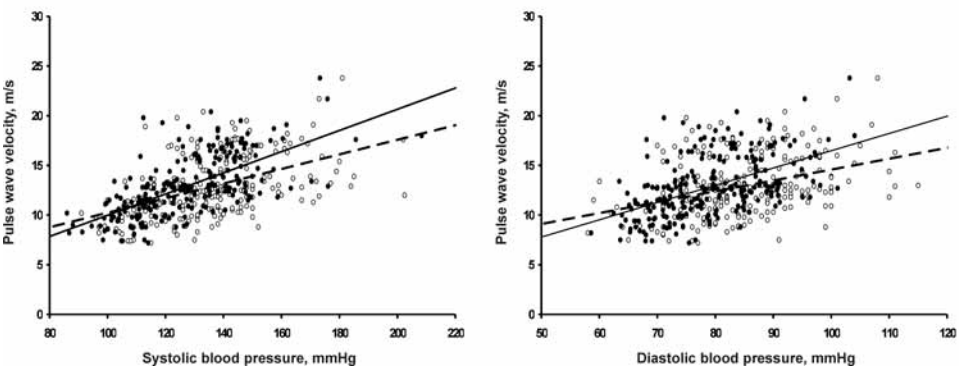

Figure 9. ***Scatter plots of systolic and diastolic blood pressure (BP) versus pulse wave velocity. White dots represent clinic blood pressure, and black dots home blood pressure. Regression lines represent the relationship between clinic (dashed lines) or home (solid lines) blood pressure and pulse wave velocity.***

Table 12. ***Multivariate linear regression for pulse wave velocity (n = 237).***

Variable	β	SE	p-value
Intercept	-6.29	-	-
Home systolic BP, mmHg	0.07	0.44	< 0.001
Age, years	0.15	0.37	< 0.001
Diabetes (no = 0, yes = 1)	2.42	0.19	< 0.001
LDL-cholesterol, mmol/l	-0.17	-0.06	0.21
WH ratio	2.77	0.08	0.32
Triglycerides, mmol/L	0.13	0.04	0.41
Gender (male = 0, female = 1)	-0.33	-0.05	0.42
Smoking (no = 0, yes = 1)	0.29	0.03	0.43
Body mass index, kg/m^2	-0.02	-0.03	0.55
Clinic systolic BP, mmHg	0.00	0.03	0.72
HDL-cholesterol, mmol/l	-0.04	0.00	0.93

R-square = 0.60, $p < 0.001$. PWV, pulse wave velocity; SE, standardized estimate; BP, blood pressure.

To investigate further how the number of home BP measurements affects the association between home BP and PWV, the relationship between PWV and BP averaged over a cumulative number of days of home BP measurement was evaluated (Table 11). The correlation coefficients increased only slightly with the number of measurements, especially for diastolic BP. No significant increase occurred after the third day. Exclusion of measurements performed during the first day of measurement from the mean home BP did not result in a higher correlation

coefficient for home BP. The associations between home BP and PWV were stronger as compared with clinic BP, even with a low number of home measurements. When individual days of measurements and their correlation with PWV were examined, there was no significant difference in the strength of the association provided by different home BP monitoring days (Table 11).

5.3.3 Left ventricular hypertrophy (V)

The correlation coefficients for home or clinic BP and ECG-LVH are presented in Table 13. Both home and clinic BP were significantly associated with ECG-LVH ($p < 0.001$ for all correlations). Home BP, however, correlated significantly better with ECG-LVH than did clinic BP, except for the association between systolic BP and the Sokolow–Lyon voltage (Table 13). Even the mean of the initial two home BP measurements correlated equally well (systolic BP), or better (diastolic BP) with ECG-LVH than did clinic BP (Table 13). The Cornell voltage and Cornell product were more closely associated with BP than the Sokolow–Lyon voltage, especially for home BP.

Table 13. ***Correlation coefficients for home or clinic blood pressure and ECG parameters.***

		Systolic BP			Diastolic BP		
ECG Parameter		Clinic	Home wk	Home 2	Clinic	Home wk	Home 2
Sokolow-Lyon	Pearson's r	0.22	0.23	0.21	0.12	0.17	0.16
	p-value	-	0.60	0.17	-	0.009	0.05
Cornell Voltage	Pearson's r	0.25	0.30	0.28	0.12	0.21	0.20
	p-value	-	0.004	0.14	-	< 0.001	< 0.001
Cornell Product	Pearson's r	0.24	0.30	0.27	0.14	0.22	0.21
	p-value	-	0.001	0.10	-	< 0.001	< 0.001

All correlations were statistically significant ($p < 0.001$). BP, blood pressure; p-value, p-value for the difference between clinic and home correlation; home wk, mean of all home BP measurements included in the analysis; home 2, mean of the 2 initial home measurements included in the analysis.

The risk ratios of ECG-LVH were calculated to assess whether home hypertension (home BP ≥ 135/85 mm Hg) poses a higher risk than clinic hypertension (clinic BP ≥ 140/90 mm Hg) [42]. Subjects on antihypertensive medication (n = 450) were excluded from this analysis to avoid any confounding effects. An equal share of home and clinic hypertensives met the criteria for ECG-LVH as reported in Table 14. No difference was seen in the prevalence of ECG-LVH between clinic and home

hypertensives. The prevalence and risk of ECG-LVH were slightly, but not significantly higher in subjects who had elevated home and clinic BP.

To investigate further how the number of home BP measurements affects the association between home BP and ECG-LVH, the relationship between the number of days of home BP measurement and the correlation between home BP and ECG-LVH was evaluated (Figure 10). The correlation coefficients increased only slightly with the number of measurements, especially for diastolic BP. Exclusion of measurements performed during the first day of measurement from mean home BP did not result in a higher correlation coefficients, and the best possible correlation between systolic and diastolic BP and ECG-LVH was achieved by using the mean of all measurements as home BP.

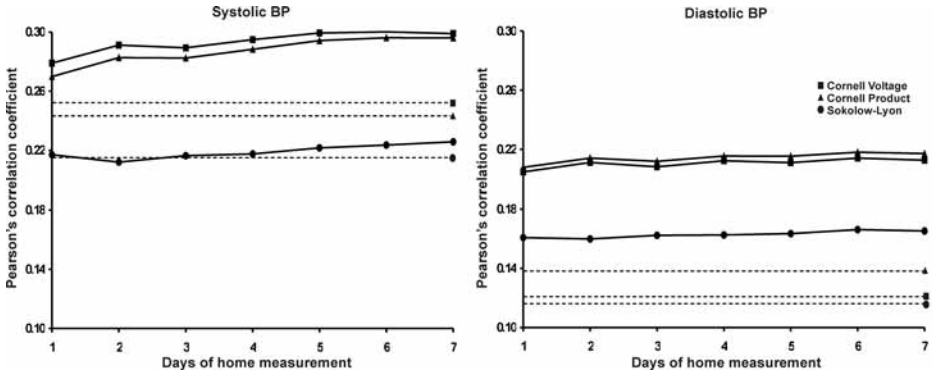

Figure 10. ***The relationship between the number of days of home blood pressure (BP) measurement and the correlation between home blood pressure and ECG-LVH. Dashed lines indicate correlation between clinic blood pressure and ECG-LVH.***

Table 14. ***Proportion of unmedicated subjects (n = 1539) with ECG diagnosis.***

	Home BP (%)		Clinic BP (%)		Home and clinic BP (%)		Risk Ratios (95% Cl)		
ECG criteria	NT (n=1005)	HT (n=534)	NT (n=895)	HT (n=644)	NT (n=1127)	HT (n=412)	Home HT	Clinic HT	Home and clinic HT
Cornell Product ≥ 2440 mm*ms	6.4	14.6	5.7	14.1	6.7	16.0	2.3 (1.7–3.1)	2.5 (1.8–3.4)	2.6 (1.9–3.7)
Cornell Voltage ≥ 26 mm	5.2	15.0	4.9	13.7	5.8	16.3	2.9 (2.1–4.0)	2.8 (2.0–3.9)	3.2 (2.2–4.6)
Sokolow-Lyon ≥ 35 mm	6.9	16.7	7.2	14.6	7.7	17.2	2.4 (1.8–3.3)	2.0 (1.5–2.8)	2.5 (1.8–3.5)

Values reported as % of subjects with ECG diagnosis of left ventricular hypertrophy. Home hypertension was defined as a home blood pressure ≥ 135/85 mmHg, and clinic hypertension as a clinic blood pressure ≥ 140/90 mmHg. Risk ratios are reported as clinic or home hypertensives' risk for electrocardiographic evidence of left ventricular hypertrophy. BP, blood pressure; NT, normotensives; HT, hypertensives; H, home; C, clinic.

5.4 Home versus ambulatory monitoring in the adjustment of antihypertensive therapy (VI)

Home, ambulatory, and clinic BP decreased significantly ($p < 0.001$), both in the home and ambulatory BP groups during the 24-week follow-up. No significant differences between the two groups were seen in home, daytime ambulatory, or clinic BP curves (Figure 11). There were no significant between-group differences in BP changes at the end of the study (Table 15).

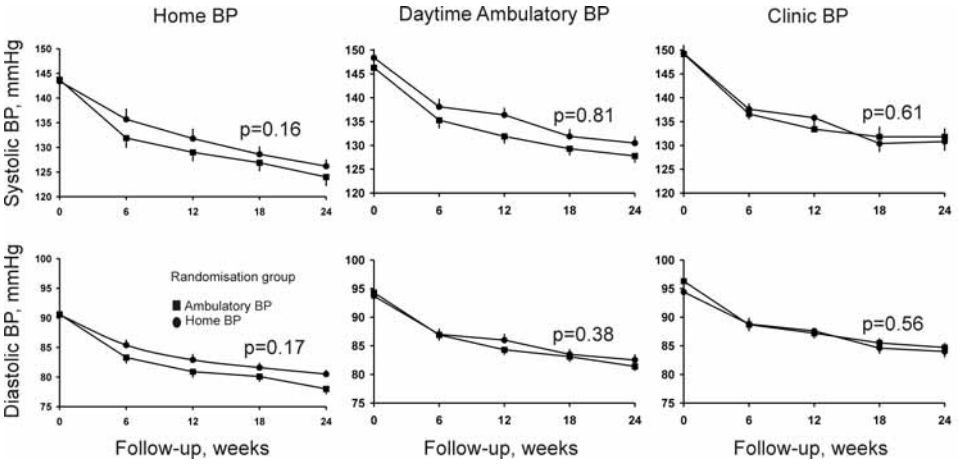

Figure 11. ***Mean home, daytime ambulatory, and clinic blood pressures (BP) during the study. Error bars indicate SEs. P-values refer to comparison of curves by ANOVA for repeated measures.***

The pre-specified BP guiding treatment (diastolic home BP or ambulatory daytime BP) was 0.9 mm Hg lower in the home BP group at the end of the study (Figure 12). The achieved corresponding BP values were 80.5 ± 5.4 mm Hg in the home BP group and 81.4 ± 5.2 mm Hg in the ambulatory BP group.

Table 15. ***Blood pressures for the two treatment groups at randomization and after a 24-week follow-up.***

BP	HBP Group (n = 52)	ABP Group (n = 46)	Difference, (95% Cl)	p-value
Home				
Systolic				
At Randomization	143.4 ± 15.1	143.7 ± 14.6	-0.3 (-6.3–5.6)	0.91
Change	-17.1 ± 1.7	-19.7 ± 1.7	2.6 (-2.3–7.4)	0.29
Diastolic				
At Randomization	90.5 ± 6.7	90.6 ± 6.3	-0.1 (-2.8–2.5)	0.91
Change	-10.0 ± 0.8	-12.6 ± 1.1	2.6 (-0.1–5.2)	0.06
Ambulatory: 24-h				
Systolic				
At Randomization	144.9 ± 12.0	143.2 ± 11.0	1.7 (-2.9–6.4)	0.46
Change	-17.3 ± 1.2	-17.9 ± 1.3	0.6 (-3.0–4.3)	0.72
Diastolic				
At Randomization	90.7 ± 7.1	91.7 ± 5.9	-1.0 (-3.6–1.7)	0.46
Change	-10.8 ± 0.9	-12.3 ± 0.8	1.5 (-1.0–3.9)	0.23
Ambulatory: Day				
Systolic				
At Randomization	148.4 ± 12.8	146.3 ± 11.0	2.1 (-2.7–6.9)	0.39
Change	-17.9 ± 1.3	-18.6 ± 1.4	0.6 (-3.2–4.4)	0.75
Diastolic				
At Randomization	93.7 ± 7.6	94.3 ± 6.0	-0.7 (-3.4–2.1)	0.63
Change	-11.2 ± 1.0	-12.9 ± 0.8	1.7 (-0.9–4.4)	0.20
Ambulatory: Night				
Systolic				
At Randomization	128.4 ± 13.1	127.5 ± 12.0	0.9 (-4.1–6.0)	0.72
Change	-14.8 ± 1.3	-15.8 ± 1.5	1.0 (-2.9–4.9)	0.62
Diastolic				
At Randomization	76.6 ± 7.9	78.8 ± 7.5	-2.2 (-5.3–0.9)	0.16
Change	-9.8 ± 1.0	-11.2 ± 1.0	1.4 (-1.4–4.2)	0.34
Clinic				
Systolic				
At Randomization	149.3 ± 17.5	149.2 ± 16.0	0.1 (-6.6–6.9)	0.97
Change	-18.5 ± 1.8	-17.5 ± 1.6	1.1 (-3.7–5.9)	0.66
Diastolic				
At Randomization	94.4 ± 9.6	96.3 ± 8.1	-2.0 (-5.6–1.6)	0.28
Change	-10.3 ± 1.3	-11.7 ± 1.2	1.3 (-5.0–2.3)	0.46

Values at randomization are expressed as mean ± SD. Change refers to the mean changes (SE) from randomization to the end of the follow-up period. All within group differences were significant ($p < 0.001$).
BP, blood pressure; HBP, home blood pressure; ABM, ambulatory blood pressure; Cl., confidence limit.

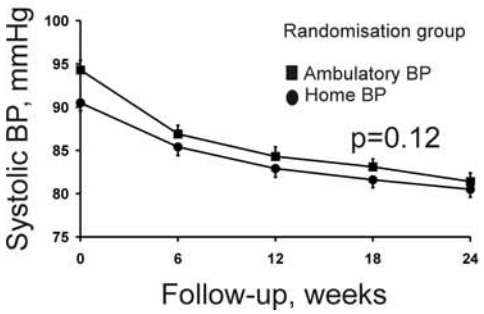

Figure 12. ***Mean blood pressures (BP) guiding treatment during the study. Error bars indicate SEs. P-value refers to comparison of curves by ANOVA for repeated measures.***

By week 24, diastolic home BP was ≤ 80 mm Hg for 30 of 52 patients (57.7%) in the home BP group and for 28 of 46 patients (60.9%) in the ambulatory BP group. Diastolic daytime ambulatory BP was ≤ 80 mm Hg for 20 of 52 patients (38.5%) in the home BP group and for 20 of 46 patients (43.5%) in the ambulatory BP group. Thus, the pre-specified target BP in the home BP group (diastolic home BP ≤ 80 mm Hg) was reached in 57.7% of the patients and in the ambulatory BP group (diastolic daytime ambulatory BP ≤ 80 mm Hg) in 43.5% of the patients. This 14.2% difference between groups did not reach statistical significance (95% confidence limit -5.4% to 33.8%, p = 0.16).

A similar share of patients had progressed to combination drug therapy in both treatment groups by the end of the study (65.4% versus 67.4%, p = 0.83). Non-significantly more patients were receiving drug therapy step 4 in the ambulatory BP group (19.2% versus 32.6%, p = 0.13) (Table 16).

Table 16. ***Treatment status of the patients at the end of the study.***

Treatment step	HBP group (n = 52)	ABP group (n = 46)	p-value
Step 1 (CS 8 mg)	17.3	15.2	0.78
Step 2 (CS 16 mg)	17.3	17.4	0.99
Step 3 (CS 16 mg + HCTZ 12,5 mg)	46.2	34.8	0.25
Step 4 (CS 16 mg + HCTZ 12,5 mg + FD 5 mg)	19.2	32.6	0.13

Values expressed as percentage. CS, candesartan; HCTZ, hydrochlorothiazide; FD, felodipine; HBP, home blood Pressure; ABP, ambulatory blood pressure.

6 DISCUSSION

6.1 Diagnosing hypertension with home blood pressure measurement (I)

Values obtained with clinic BP measurements in a nation-wide population are significantly higher than those obtained with home measurements, and their agreement in diagnosing hypertension is moderate at best. Clinic BP slightly overestimates the prevalence of hypertension when compared to home BP (49% versus 43%), but no significant difference was observed in the share of treated hypertensives with good BP control (33% versus 29%).

Mean clinic BP was 7.7/3.4 mmHg higher than mean home BP in this population, well in line with results from multinational meta-analyses [61, 62]. The mean difference and the 95% limits of agreement increased with BP. The relationship between clinic-home difference and higher BP has been shown in a recent meta-analysis by Verberk but, in contrast to the present study, only for systolic BP among untreated hypertensive subjects [61]. However, the results of the meta-analysis are undermined by the fact that there were marked differences in the study cohorts and in the methods used for measuring clinic and home BP. According to the findings of the present study, the difference between home and clinic BP appears to be greater among hypertensive subjects, for whom precise BP measurement can more effectively prevent unnecessary treatment and costs.

The worldwide prevalence of hypertension was 26% in the year 2000 using the recommended threshold of 140/90 mmHg [1]. In developed countries the control of hypertension is relatively poor as only 30–50% of treated hypertensives reach the target BP [158]. However, the population studies which these meta-analyses are based on have used conventional clinic BP measurements. Since home BP has a better prognostic accuracy than clinic BP the assessment of prevalence and control of hypertension at a population level would also be more accurate when based on home BP [87, 159]. The majority of studies assessing the agreement between home and clinic BP measurement have been performed on selected hypertensive populations or have used the same thresholds for elevated home and clinic BP [69, 70]. Only two Japanese population-based studies (one community-based study and one nationwide study with only treated hypertensives) have assessed the control of BP with home and clinic measurements according to the current guidelines [88, 160]. In the present study the prevalence of hypertension among the Finnish 45–74 year-old population was slightly higher when defined with clinic instead of home

measurements. In Japan, the proportion of hypertensives assessed with home BP was similar to that assessed by clinic BP [88]. No significant differences in control rates were observed in Japan or in Finland when assessed by clinic or home BP [160]. The currently recommended 5 mmHg lower BP thresholds for home BP measurement therefore seem to work quite well [30, 42]. The control of hypertension assessed by home measurement appears to be better in Japan (45.3%) than in Finland (32.8%) [160]. These levels of control are far from excellent and indicate that poor BP control is not only a reflection of the white-coat effect, but also reveal a true lack of sufficient BP control and adherence to treatment.

In this study, clinic BP was significantly higher in untreated hypertensives than in treated hypertensives, despite a similar home BP. This is in line with the findings of earlier studies showing that antihypertensive medication reduces, but does not eliminate the white-coat effect [88, 161, 162]. Some antihypertensive drugs have been reported to reduce the cardiovascular stress responses that clinic BP measurement incites [163]. A part of the reduction in the white-coat effect could also result from the treated subjects measuring their morning home BP before taking their medication at the trough while clinic BP, on the other hand, was measured during the day when the effect of the medication is at its peak. Thus, home BP values would be closer to the clinic BP values due to minimum and maximum effects of the treatment. Furthermore, treated hypertensives could be more accustomed to medical settings and exhibit a smaller alerting reaction in BP during clinic BP measurements.

6.2 Diagnosing isolated clinic hypertension with home blood pressure measurements (II)

This was the first study examining the prevalence and determinants of ICH on a nationwide level. The prevalence of ICH in the untreated Finnish adult population was 15.6%, and 37.5% among untreated subjects with elevated clinic BP. ICH was associated with mildly elevated systolic and diastolic BP, lower BMI, and non-smoking status, but not with any psychosocial disorders. The metabolic cardiovascular risk factors of subjects with ICH were between those of the hypertensives and normotensives.

Most of the previous studies have assessed the prevalence and determinants of ICH in selected groups of hypertensive subjects using ambulatory BP monitoring [74, 82-86, 164]. Because of a selection bias, the prevalence of ICH at the population level cannot be estimated from data collected in those studies. The prevalence of ICH in the general untreated Finnish population was less than reported in most previous studies including only hypertensive subjects [74, 82, 83, 85, 164], but very close to

that of 12% reported in the untreated subjects of the Italian PAMELA study [78]. The findings of this study support 12–15% to be very close to the true prevalence of ICH in a western adult population not treated for hypertension. In addition, the prevalence of ICH was 37.5% among untreated hypertensives. Thus, one patient in every third with newly diagnosed hypertension could be overdiagnosed as hypertensive in a screening situation. In Japan, the prevalence of ICH appears to be even higher, as 60% of the untreated hypertensive subjects had normal home BP values [88].

ICH was independently associated with mildly elevated systolic and diastolic BP, lower BMI, and non-smoking status. The probability of ICH increases with mildly elevated BP levels [83, 84, 86], because smaller differences between clinic and home BP are needed to meet the criteria for ICH. Therefore special attention should be focused on patients with mild to moderate hypertension before commencing antihypertensive medication. The association of ICH with a non-smoking status seen in this study has also been demonstrated in studies by Verdecchia [86] and Dolan [84]. A population-based study on elderly men by Björklund et al. has reported that a lower BMI characterized subjects with future development of ICH as compared to those with future sustained hypertension [80]. Also, in a study with 292 borderline hypertensives, subjects with ICH were more likely to weigh less [74]. Other studies, although with selected hypertensive study populations, have found no association between BMI and ICH [165, 166]. The BP-raising effects of smoking [167, 168] and BMI [74, 83, 84, 86] are well known, but the role of nonsmoking status as a marker of increased prevalence of ICH requires additional study. In any case, the findings of this study state that subjects with ICH tend to lead a slightly healthier way of life than sustained hypertensives by smoking less and having a lower BMI, which might also contribute to their lower BP levels.

Many previous studies [74, 83, 84, 86] have demonstrated a higher prevalence of ICH in women, but no such difference was found in the present study. Again, these studies were performed on selected hypertensive individuals. In the PAMELA study (49% women), there were not significantly more women in the subjects with systolic (37% women) or diastolic (52% women) ICH [74, 82]. The present study and the PAMELA study both suggest that female gender is not associated with ICH in the general untreated population. Age has also been proposed as a determinant of ICH. However, the results from previously published studies with selected patients are very conflicting as ICH has been associated with younger age in two studies [84], with older age in one study [83, 86], and no association has been found in two studies [89-91, 169]. In the present study, no independent connection was observed between age and ICH, although the study population included only subjects aged 45–74 years.

Our data do not support the notion that a specific personality structure may predispose some individuals to ICH. Previous studies have also concluded that subjects with ICH did not show abnormal hostility, anxiety, or depression, when compared to subjects with sustained hypertension [89-91, 169]. The study by Muneta et al. suggested that subjects with ICH tend to suppress their own emotions and become over-adaptive to their surroundings [89]. Crippa et al. suggested that ICH might be associated with healthcare-related fears and emotional instability [169]. However, the sample sizes of all these previous studies have been rather small (70-218 patients) and have only included patients with previously diagnosed hypertension. Although ICH does not seem to be associated with any psychological characteristic, subjects with ICH might still have a behavioral trait of over-reactivity to stress.

The demographic, clinic and metabolic characteristics of subjects with ICH were mostly between those of the hypertensive and normotensive subjects. Subjects with ICH had a lower BP, a lower BMI and were younger than sustained hypertensives. Otherwise, their risk profile was similar to the subjects with sustained hypertension in terms of gender distribution, diabetes prevalence, serum fasting glucose, and serum lipid profile. Normotensives differed from sustained hypertensives more noticeably in all of these previously listed risk factors. Normotensive subjects were also younger, and had a lower BP, serum total cholesterol and triglyceride level than subjects with ICH. The data from this study suggest that subjects with ICH do not differentiate from sustained hypertensives where metabolic cardiovascular risk factors are concerned but they lead healthier lives than the sustained hypertensives do. The evidence that subjects with ICH are at a higher risk for future permanent hypertension [170, 171] and cardiovascular events [112, 127-129] is in line with these findings. Therefore, it is important to assess their BP, risk factor status and lifestyle periodically.

6.3 Association between home blood pressure and end-organ damage (III-V)

Our results extend previous evidence suggesting that home BP has a more important role in predicting target organ damage than does clinic BP [172-175]. In this study with a representative sample of a nationwide adult population aged 45–74 years it was shown that home BP has a stronger association with carotid IMT, ECG-LVH, and PWV than clinic BP, even for a very low number of home measurements. The association between home BP and ECG-LVH or PWV becomes slightly stronger with an increasing number of home measurements, but not for carotid IMT. Carotid IMT is independently associated with age, home BP, serum triglycerides, male

gender, smoking, diabetes, and LDL-cholesterol. PWV is independently associated with home BP, age, and diabetes, with home BP being the most important factor affecting arterial stiffness.

Carotid IMT is an important predictor for cardiovascular morbidity and mortality, and the rate of carotid IMT thickening can be attenuated with antihypertensive medication [176, 177]. Carotid IMT is therefore an important factor in assessing cardiovascular risk in a hypertensive patient. Consequently, the treating physician should use a BP measurement method that provides a good image of the patient's true BP level, and also has a strong correlation with carotid IMT. Home BP fulfills these requirements, as demonstrated by this study. The factors associated with IMT presented in this study are well in line with findings of other studies. Previous population studies, such as the Atherosclerosis Risk in Communities (ARIC) study, have established an association between carotid IMT and cardiovascular risk factors such as age, smoking, LDL-cholesterol, diabetes, triglycerides and BP [178, 179]. Many studies, including ours, have suggested that BP is one of the most important factors affecting carotid IMT [180]. Considering that most of the previous population studies assessing risk factors for carotid atherosclerosis have used conventional clinic BP measurement as a method for measuring BP, the significance of BP in the pathogenesis of atherosclerosis might be even more important than previously assumed.

Arterial PWV has been identified as a marker of elastic artery stiffening, and also a strong independent predictor of cardiovascular mortality [181]. Arterial stiffness and hypertension appear to interact in a bidirectional manner. On the one hand, untreated hypertension accelerates the rate of large artery stiffness and thus perpetuates a vicious cycle of accelerated hypertension and further increases in large artery stiffness, and on the other hand, arterial stiffness has been identified as a predictor of future hypertension in normotensive individuals [182]. The factors associated with PWV presented in this study are in accord with the findings of other studies. Progression of arterial stiffness is more pronounced in older subjects, and age has been generally considered to be the most important factor affecting PWV. However, BP elevation promotes accelerated vascular aging [183]. In this study, home BP was actually a slightly more important determinant for increased PWV than age. Considering that most of the previous studies assessing risk factors for arterial stiffness have used conventional clinic BP measurement as a method for measuring BP, the role of BP in the pathogenesis of arterial stiffness and vascular aging might be even more important than previously thought. As in this study, diabetes and insulin resistance have been previously associated with increased arterial stiffness.[184] Cholesterol levels, however, seem to play a smaller part in the pathogenesis of arterial stiffness [185].

Left ventricular hypertrophy (LVH) is an independent risk factor for increased cardiovascular mortality [186]. LVH is linearly related to the level of BP, and can eventually lead to congestive heart failure, of which approximately half is caused by hypertension [127, 187]. Some studies have already reported that home BP is more strongly associated with the degree of LVH as determined by echocardiography [14, 59]. However, echocardiography is not widely available and despite a poor sensitivity, ECG is often the only method available for assessing LVH in the hypertensive patient, especially in typical primary care settings. Home BP measured during one week had a stronger association with ECG-LVH than did clinic BP in this study. Home and clinic hypertensives had an equally high risk for ECG-LVH. The currently recommended 5 mmHg lower BP thresholds for home BP measurement therefore seem to be appropriate, at least in terms of ECG-LVH prevalence and risk [60]. The prevalence and risk of ECG-LVH were slightly, but not significantly higher in subjects who had elevated home and clinic BP. This finding is in line with the results of the PAMELA study, as the overall ability to predict death was increased by the combination of clinic and home values [69, 188].

The association between home BP and hypertensive end-organ damage increased slightly with an increasing number of measurements in the present study. However, home BP was more closely associated with end-organ damage than was clinic BP even when only the first two measurements were used. More importantly, home BP also seems to be a stronger predictor of cardiovascular risk than clinic BP as the two initial home BP measurements were more closely associated with cardiovascular risk than the two initial clinic BP measurements in the Ohasama study [53]. In addition, in the PAMELA study only two home readings were obtained, and these were stronger predictors of cardiovascular risk than were six clinic measurements [51]. The benefits of home BP measurement are thus not based solely on the statistical advantages associated with the availability of repeated measurements, but also on the information obtained outside of the clinical setting. This conclusion is also supported by the cross-sectional findings of the present study.

6.4 Proposed schedule for home blood pressure measurement (I, III–V)

The current ESH guidelines recommend measuring home BP twice every morning and evening for one week and discarding the first day of measurement, while the North American guidelines advise taking three readings on one occasion every morning and evening, but do not mention for how many days [30, 42]. The conflicting guidelines demonstrate that agreement over the optimal schedule for home BP measurement has not yet been reached. A schedule for home BP

measurement is now proposed based on findings from the present and previous studies.

In this study, home BP decreased noticeably between the first and second days of measurement and stabilized from the third day onwards. The association between end-organ damage and home BP increased slightly with the number of home measurements, but most of this increase occurred during the first three days of measurement. It is therefore proposed that home BP measurement should be performed for a minimum of three days.

It has been previously demonstrated in the Ohasama study that the predictive value for stroke risk associated with home BP increases progressively within the range of 1–14 measurements performed during one week without any clear threshold [55]. The findings of the present study comparing the association between ECG-LVH or PWV and home BP in the Finn-HOME population are in accord with the findings of the Ohasama study as the correlation increased slightly but steadily over a one-week period. However, home BP was measured twice on each occasion and 28 measurements were obtained. No significant increase in the correlation between end-organ damage and home BP occurred after the sixth day of measurement. Seven days of measurement, as recommended by the ESH guidelines, therefore appear to be sufficient.

Mean home BP of the initial monitoring day produced the highest and most variable values. This phenomenon has been shown in some [49, 131] but not all [53] studies on selected hypertensive populations, and it appears to be present also in the population as a whole [42, 53]. The plateau level that is reached with an increasing number of home BP measurements, as the patient becomes acquainted with home measurement, could therefore best represent the subjects' "true" BP level. The ESH guidelines recommend discarding home BP values obtained on the first day of measurement because of their instability [42]. However, results from the Ohasama study suggest that discarding the first day of measurements could not necessarily be applicable from the view point of prognostic significance [53]. In addition, the first days of measurement did not show a weaker correlation with end-organ damage than did the other days in the present study. Further prognostic research is therefore warranted to clarify whether BP values obtained on the first day of home measurement should be discarded before this policy can be recommended.

In accordance with previously published studies, small differences in evening and morning home BP existed in the Finnish population [55, 56]. Evening BP was slightly higher in subjects who were not on antihypertensive medication, but this difference was non-existent for systolic BP and reversed for diastolic BP among treated hypertensives. Most antihypertensive medications are administered once a

day, usually in the morning. Home BP was measured in the morning at trough when the effect of the medication is at its lowest, which explains the observed difference between treated and untreated subjects. Because of the diurnal variation in BP, home measurements in the morning and in the evening are recommended to obtain a thorough image of the average BP and to evaluate the round-the-clock efficacy of antihypertensive medication and the differences between various antihypertensive drugs [59].

Almost all guidelines recommend two or three consecutive measurements on each occasion [30, 42]. This recommendation is based on the evidence that regression to the mean during consecutive measurements on each occasion is frequently observed even after long term monitoring [49]. In accordance with the findings from previous studies, the second measurement produced on average 3/1 mmHg lower BP values than the first measurement in the present study. The Japanese Society of Hypertension guidelines for self-monitoring of BP at home recommend at least one measurement on each occasion without denying that multiple measurements might be of value, but this recommendation is based mostly on speculation that it would be more convenient and result in better compliance [189]. Unfortunately, no prognostic data on this matter is yet available since the two largest epidemiological studies have been performed with only one measurement on each occasion [51, 53]. Until such data become available, home BP should be measured twice on each occasion because of the regression to the mean effect.

In conclusion, based on the results from this and previous studies, measurement of BP twice in the morning and in the evening preferably for a period of seven days, or for at least three days, is recommended for obtaining a thorough image of a patient's true BP level. More prognostic data are still needed before discarding the measurements performed on the first day can be recommended.

6.5 Home blood pressure measurement in the adjustment of antihypertensive therapy (VI)

Antihypertensive treatment based on either home BP measurement or ambulatory BP monitoring while using the same target pressure (diastolic BP $\leq$ 80 mmHg) led to equally good BP control with both methods in patients with mild to moderate hypertension. Drug therapy was tended to be more intensive in the ambulatory BP group and slightly more patients reached the target pressure in the home BP group, but these differences were non-significant. No studies have been published earlier that have directly compared antihypertensive treatment based on home BP with ambulatory BP.

The small difference in BP changes between home and ambulatory BP groups at the end of the study were slightly in favor of the ambulatory BP monitoring group, and these differences might have become statistically significant if a larger number of patients had been included. The clinical significance of these differences (range 0.6–2.6 mmHg) would nevertheless be relatively small because a 1 mmHg lower systolic BP would involve, for example, an approximately 5.6% lower risk for stroke in younger adults, dropping to a 1.8% lower risk in adults aged 75 years and over [190]. The small between-group difference in BP changes at the end of the follow-up period is most likely explained by the difference in the BP guiding treatment at randomization. Diastolic ambulatory daytime BP was 3.8 mmHg higher in the ambulatory BP group than the diastolic home BP in the home BP group at randomization, which probably resulted in slightly more intensive treatment and a greater reduction in BP. Although BP decreased more in the ambulatory group, a larger share of the patients reached the target BP in the home BP group because the difference between target BP and BP guiding treatment was smaller at randomization.

The marked difference in clinic and home BP values at baseline while using the same target pressure was the main limitation in previous studies that have compared antihypertensive treatment based on home or clinic BP [124, 125]. For example, in the 2004 THOP study the diastolic BP guiding treatment was 9.5 mmHg higher at randomization for the clinic BP group than for the home BP group using the same target BP [124]. This unsurprisingly led to more intensive drug therapy and greater BP decrease in the office BP group. In the present study, when comparing home and ambulatory BP, the problem of a difference in BP values still exists, but to a much lesser extent. More importantly, current guidelines recommend the same treatment threshold for home and daytime ambulatory BP [30, 42]. A target pressure which is 5 mmHg higher should be used for clinic BP than for home BP. This was not taken into account in the THOP and HOMERUS trials and partially nullifies their results [30, 42, 124, 125].

Home monitoring has many of the benefits of ambulatory BP monitoring, and is even better in some aspects (Table 2). Low compliance to treatment is one of the most important causes for poor control of hypertension. Home measurement of BP allows the patient be more actively involved in their treatment, thereby improving adherence to treatment [120, 121]. Ambulatory monitoring causes discomfort and disturbance of sleep and is greatly disliked by patients, unlike home BP monitoring which is the most acceptable method for patients, when compared to ambulatory monitoring, measurement by a doctor or a nurse, or self-measurement in a room provided by the hospital [119]. Home measurement of BP is also relatively inexpensive and feasible when compared to ambulatory monitoring and can be easily performed in the basic

healthcare system. A meta-analysis of 18 randomized controlled trials by Cappuccio et al. reported that using home BP measurement rather than office BP measurements in the healthcare system resulted in better BP control (4.2/2.4 mmHg, and 2.2/1.9 mmHg, when allowing for publication bias) and greater achievement of BP targets (10% greater proportion on target) [118]. A recent study in a Finnish primary care setting also confirmed these findings [191]. Home BP should therefore be considered as an attractive option for measuring BP and even as the method of choice when guiding antihypertensive treatment in the primary care setting.

6.6 Study limitations

6.6.1 Studies I–V

First, clinic BP, although very meticulously assessed, was measured in a screening situation on one day only and duplicate home BP readings were performed twice daily for seven days. Therefore, the possibility that clinic BP values over multiple days could have resulted in values closer to home BP cannot be excluded. However, in real life, home BP measurement always produces a larger number of BP readings than clinic measurement. Furthermore, as demonstrated by the Ohasama study and this study, the benefits of home BP measurement are not based solely on the statistical advantages associated with the availability of repeated measurements, but also on obtaining information outside of the clinical setting with even a few home BP measurements [53, 54]. Second, clinic BP was measured with a mercury sphygmomanometer and home BP with an automated oscillometric device. On the other hand, clinic BP is still widely measured with a mercury sphygmomanometer in Finland, so this also reflects reality. In addition, all large epidemiological studies, on which the prognostic evidence of clinic BP is based, have used conventional mercury sphygmomanometers. Third, participants in the Finn-HOME substudy had a 2.3 mmHg lower systolic BP than the non-participants, which might have resulted in a small underestimation in the prevalence of hypertension. Fourth, because of the cross-sectional nature of this study, no cause-effect relationships can be drawn from the findings, and more outcome studies are needed.

6.6.2 Study VI

First, this study of 110 patients spanned a follow-up period of 24 weeks and the findings may require further validation in larger, long-term prospective studies. Second, if the study would have included a clinic measurement group, there would have been a possibility to compare all three methods of BP measurement in the management of hypertension.

7 CONCLUSIONS

Home BP is 8/3 mmHg lower than clinic BP in a representative Finnish adult population. This significant difference between home and clinic BP becomes even larger at higher levels of BP. The agreement between home and clinic BP in diagnosing hypertension according to the current guidelines is moderate at best. Clinic BP slightly overestimates the prevalence of hypertension when compared to home BP.

Home BP decreases noticeably between the first and second days of measurement and stabilizes from the third day onwards. Morning and evening variation in home BP exists and should be taken into consideration when measuring home BP or assessing the round-the-clock efficacy of antihypertensive treatment.

The prevalence of ICH, or "white-coat hypertension", in this population not treated for hypertension was 16%. Among untreated hypertensives, the prevalence of ICH was 38%. Thus, hypertension could be overdiagnosed in every third patient in a screening situation. This relatively high prevalence of ICH emphasizes the importance of identifying these subjects.

The demographic, clinical and metabolic characteristics of subjects with ICH were mostly between those of the hypertensive and normotensive subjects. Physicians should suspect ICH when a hypertensive patient has mildly elevated systolic or diastolic BP, low BMI, and does not smoke. Physicians should disassociate the diagnosis of ICH from specific psychological symptoms, but should remember that subjects with ICH are at an increased risk for the development of cardiovascular disease and require periodic follow-ups.

Home BP is one of the most important determinants of cardiovascular end-organ damage and is more strongly associated with end-organ damage than is clinic BP, even with a low number of home measurements.

Measurement of BP twice in the morning and evening preferably for a period of seven days, or for at least three days, is recommended for obtaining a thorough image of a patient's true BP level.

The present findings suggest that adjustment of antihypertensive treatment based on home BP measurement is effective as it led to equally good BP control as did ambulatory BP monitoring, which has been considered by many as the gold standard.

Additional large-scale prognostic population studies are still needed to provide further evidence of home BP's prognostic superiority over clinic BP and to determine a definitive schedule for home BP measurement and the exact diagnostic and treatment thresholds for home-measured BP. This information should become available from the follow-up phase of the Finn-HOME study. Furthermore, larger follow-up studies using currently recommended treatment thresholds are needed to provide further confirmation of the benefits of home BP measurement in guiding antihypertensive treatment as compared with other methods.

On the basis of the results from this study and data from previous studies, it can be concluded that home BP measurement offers specific advantages over conventional clinic measurement. Home monitoring of BP is a convenient, accurate, and widely available option and may become the method of choice for diagnosing and treating hypertension. A paradigm shift is needed in BP measurement as evidence-based medicine suggests that clinic BP measurement should mainly be restricted for screening purposes.

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