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The originality of this thesis has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

ISBN 978-951-29-7513-6 (PRINT)
ISBN 978-951-29-7514-3 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama Oy – Turku, Finland 2018

To Sakke

ABSTRACT

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Home Blood Pressure Variability − Assessment and Clinical Significance
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Annales Universitatis Turkuensis
Painosalama Oy – Turku, Finland 2018

Blood pressure (BP) variability is an independent risk factor for cardiovascular adverse events over and beyond the BP level. The clinical significance of BP variability has been extensively studied in the past few decades. Inconsistency between measurement methods has complicated the exploitation of BP variability in clinical practice. This thesis aims at defining optimal methods for assessing self-measured home BP variability.

The data for this thesis was gathered from three studies. Study sample I consisted of 527 individuals recruited from the general population or newly-diagnosed hypertensives. The participants had BP measured in the clinic, at home as well as undergoing 24-hour ambulatory BP monitoring. Study sample II consisted of 2103 participants of the Finn-Home study, a population sample in which BP measurements were made in the clinic and at home. Study sample III consisted of 6238 individuals who participated in the Finn-Home, Ohasama, Tsurugaya, and Didima population studies and were included in the IDHOCO (International Database for HOme blood pressure in relation to Cardiovascular Outcome).

In study sample I, we observed that estimates of BP variability measured with office, home, and ambulatory monitoring correlated only weakly with each other. In study sample II, we observed that home blood pressure was slightly higher on Mondays than during the weekend. We also demonstrated that the risk of cardiovascular outcomes related to systolic/diastolic home BP variability could be reliably assessed using 3/7 measurement days. In study sample III, we defined outcome-driven thresholds for increased home BP variability.

The results of this thesis can assist clinicians and guidelines on how best to identify those patients with increased BP variability who have an increased cardiovascular risk. It should, however, be kept in mind that the incremental prognostic value of BP variability over traditional cardiovascular risk factors, including BP itself, is modest.

Keywords: blood pressure variability, home blood pressure, cardiovascular risk, epidemiology

TIIVISTELMÄ

Eeva Juhanoja
Kotona itse mitatun verenpaineen vaihtelu – Arviointi ja kliininen merkitys
Turun yliopisto, Lääketieteellinen tiedekunta, Sisätautioppi, Turun kliininen tohtoriohjelma
Annales Universitatis Turkuensis
Painosalama Oy – Turku, Finland 2018

Lisääntynyt verenpaineen vaihtelu on itsenäinen sydän- ja verisuonitautitapahtumien riskitekijä. Verenpaineen vaihtelun kliinistä merkitystä on tutkittu runsaasti parina viime vuosikymmenenä. Ilmiön mittaamista käytännössä hankaloittaa se, että eri tutkimuksissa on käytetty erilaisia mittaustapoja, jolloin verenpaineen vaihtelun systemaattinen tarkastelu on hankalaa. Tämän väitöskirjatutkimuksen tarkoituksena on selvittää, miten verenpaineen vaihtelua tulisi mitata.

Väitöskirjan osatöissä käytettiin kolmea eri aineistoa. Yksi niistä oli 527 henkilön otos, jossa puolet tutkittavista oli valittu satunnaisotannalla väestörekisteristä ja puolella oli tuore verenpainetautidiagnoosi. Henkilöille tehtiin verenpaineen mittaukset vastaanotolla, kotona ja pitkäaikaisrekisteröinnillä. Toinen tutkimusväestö koostui 2103 henkilöstä, jotka osallistuivat Terveys 2000-tutkimuksen syventävään Finn-Home -osaan. Kolmannen tutkimuspopulaation muodostivat 6238 kansainvälisen IDHOCO (International Database for HOme blood pressure in relation to Cardiovascular Outcome) -tietokannan henkilöä.

Ensimmäisessä tutkimusotoksessamme totesimme, että vastaanotolla mitattu, kotimittauksiin perustuva ja pitkäaikaisrekisteröinnin perusteella laskettu verenpaineen vaihtelu korreloivat heikosti toistensa kanssa. Toisessa otoksessa havaitsimme kotona mitatun verenpaineen olevan maanantaisin hieman korkeampi kuin muina viikonpäivinä. Osoitimme myös, että kun kotona mitatun systolisen/diastolisen verenpaineen vaihtelua tutkitaan myöhemmän sydän- ja verisuonitapahtumien sairastuvuuden valossa, 3/7 päivän mittausjakso on riittävä. Kolmannessa otoksessa määritimme viitearvot kotiverenpaineen vaihtelulle.

Väitöstutkimuksen löydökset voisivat auttaa lääkäreitä tunnistamaan ne potilaat, joilla verenpaineen vaihtelu on lisääntynyttä ja joilla on siten korostunut riski sairastua valtimotautiin. Tulee kuitenkin muistaa, että tähänastisissa tutkimuksissa verenpaineen vaihtelun tuoma lisäarvo sairausriskin arviointiin on melko pieni.

Avainsanat: verenpaineen vaihtelu, kotona mitattu verenpaine, sydän- ja verisuonitautiriski, epidemiologia

TABLE OF CONTENTS

ABBREVIATIONS

ABP	Ambulatory blood pressure
ARV	Average real variability
BMI	Body mass index
BP	Blood pressure
BPV	Blood pressure variability
CI	Confidence interval
CV	Coefficient of variation
ECG	Electrocardiography
ESC	European Society of Cardiology
ESH	European Society of Hypertension
HBP	Home blood pressure
HR	Hazard ratio
ICD	International Classification of Diseases, Injuries, and Causes of Death
JNC	Joint National Committee
JSH	Japanese Society of Hypertension
MMD	Maximum−minimum difference
OBP	Office blood pressure
SD	Standard deviation
VIM	Variability independent of the mean

LIST OF ORIGINAL PUBLICATIONS

I **Juhanoja EP, Niiranen TJ, Johansson JK, Puukka PJ, Jula AM.** Agreement between ambulatory, home, and office blood pressure variability. J Hypertens. 2016 Jan;34(1):61−7.

II **Juhanoja EP, Puukka PJ, Johansson JK, Niiranen TJ, Jula AM.** The impact of the day of the week on home blood pressure: the Finn-Home study. Blood Press Monit. 2016 Apr;21(2):63−8.

III **Juhanoja EP, Johansson JK, Puukka PJ, Jula AM, Niiranen TJ.** Optimal Schedule for Assessing Home BP Variability: The Finn-Home Study. Am J Hypertens. 2018 May7;31(6):715-725.

IV **Juhanoja EP, Niiranen TJ, Johansson JK, Puukka PJ, Thijs L, Asayama K, Langén VL, Hozawa A, Aparicio LS, Ohkubo T, Tsuji I, Imai Y, Stergiou GS, Jula AM, Staessen JA.** Outcome-Driven Thresholds for Increased Home Blood Pressure Variability. Hypertension. 2017 Apr;69(4):599-607.

1 INTRODUCTION

Blood pressure variability (BPV) is considered to be an independent cardiovascular disease risk factor that has prognostic significance over and beyond the blood pressure (BP) level. Several studies on long-term (1), mid-term (2), and short-term (3) variability of BP have observed a positive correlation between BP variability and adverse cardiovascular disease events. In these studies, analyses were adjusted by BP level. In contrast, some other studies have found no significant associations between BPV and outcomes (4,5), suggesting that only the BP level has to be taken into account in cardiovascular risk stratification.

The inconsistent results of the significance of BPV in determining cardiovascular risk may be partially due to differences in BP measurement techniques, protocols (for example number of readings, duration of monitoring) and the mathematical indexes used for quantifying BPV across different studies. Long- and short-term BPV may therefore have different backgrounds and may also carry different prognostic significances.

Home BP measurement is an effective method for the assessment of BPV. It is also generally well accepted by patients. It enables obtaining a large number of BP values during several days and is free from the white-coat effect that is present when BP is measured in the clinical setting. However, the optimal number of measurement days for a reliable estimation of home BPV is unclear, as well as the potential impact of the day of the week on the BP measurements. In addition, the thresholds for normal versus elevated home BPV are unknown. These thresholds would enable the diagnosis and thus potentially treatment of BPV. Furthermore, a more standardized protocol for measuring home BPV could also enable a wider use of BPV in clinical risk assessment, as recommended by international hypertension guidelines (6,7).

2 REVIEW OF LITERATURE

This review of the literature focuses on studies performed in adult humans (at least 18-year-old). In addition, an inclusion criterion for articles was access to full text in English. BPV during temporary states, such as in pregnancy, will not be covered in this review of literature.

2.1 Blood pressure variation as a physiological phenomenon

BP is characterized by degree of variability by time. Variability can be observed over readings by minute to minute, hours, days, months or seasons. BP is regulated by various different humoral and neural factors (8). BP effectively adapts to the needs of the body to maintain homeostasis. The principal mechanisms of BP regulation are changes in heart rate, cardiac output, and vascular resistance, modified via the sympathetic and parasympathetic nervous systems. When rapid responses of BP are needed, for example when an individual stands up, baroreceptors that can react to vascular stretching are essential. There are two types of baroreceptors located in different parts of the cardiovascular system: high-pressure baroreceptors in the carotid artery sinus and aortic arch, and low-pressure baroreceptors in the cardiopulmonary region. They transmit the afferent neural signals to the vasomotor center in the brainstem. The vasomotor center then transmits efferent neural impulses via the sympathetic and parasympathetic nerves to the heart and blood vessels. (8) When an individual stands up from a supine position, BP in the upper parts of the body decreases. In response to that change in the vessel wall stretching, the baroreceptors react, leading to an activation of the vasomotor center. This, in turn, leads to accelerated heart rate, contraction of the blood vessels and increased cardiac output, resulting in increased BP. These reactions are transmitted by adrenaline and noradrenaline, two catecholamine hormones secreted by adrenal glands due to a sympathetic nerve impulse. When the individual lies down, an opposite reaction occurs. (8) With advancing age, the baroreflex function becomes impaired, which alters the physiological BP regulation and may increase inadequate BP variations (9). BPV during 24 hours, measured at 15-minute intervals, is believed to reflect baroreflex sensitivity, independently of the BP level (10).

The renin-angiotensin-aldosterone system, coordinated mainly by the kidneys, is also a crucial humoral regulatory pathway of BP regulation over a longer time scale. When BP increases, the renal excretion of sodium and water also increases in order to return the BP to its normal levels. In contrast, in response to decreasing BP, the kidneys are able to decrease the amount of sodium and water excretion.

The BP increase is achieved by a secretion of renin hormone from the juxtaglomerular cells of the kidney, where it is stored. Renin is the enzyme causing the formation of angiotensin I from angiotensinogen, and angiotensin converting enzyme converts angiotensin I to angiotensin II. After the production of angiotensin II, the constriction of the arterioles and the secretion of aldosterone and vasopressin occurs, which increases the amount of water and sodium reabsorbed by the kidneys. (8) The organs that are most involved in the regulation of BP are depicted in Figure 1.

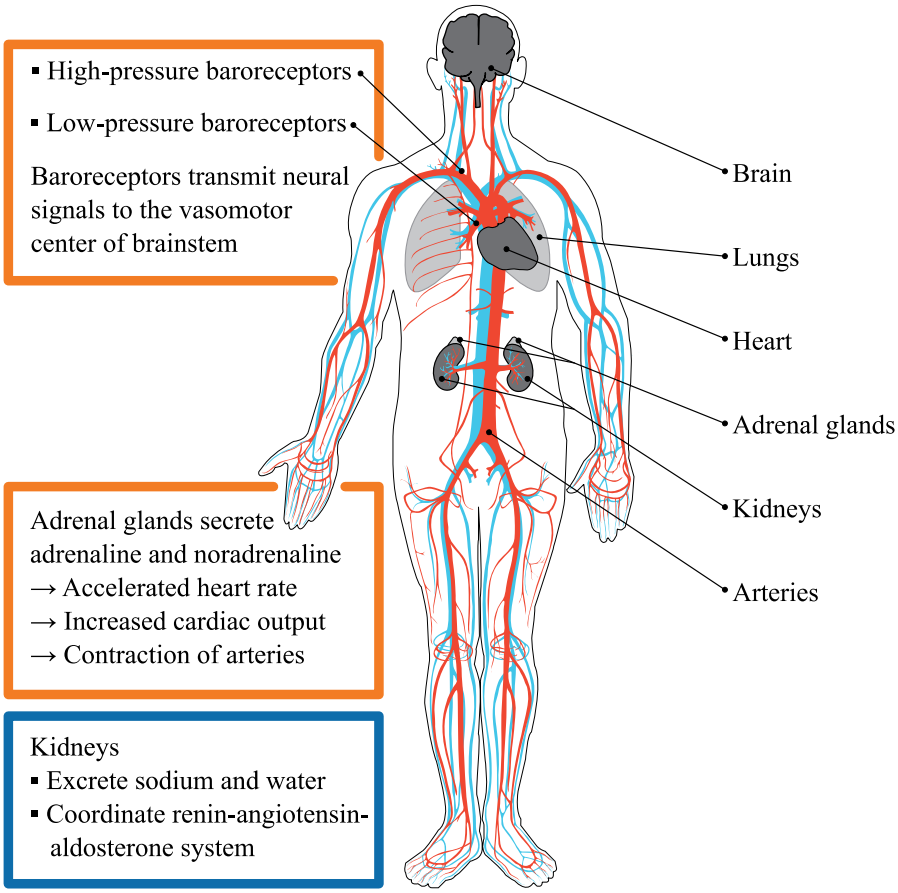

Figure 1. Regulation of BP. Rapid regulatory mechanisms are shown in orange and slow in blue.

2.2 Assessment of blood pressure variability

Measurement of BPV is a complex entity. Several methodological discrepancies have been found across different studies of BPV. In their review and meta-analysis,

published in 2015, Taylor et al. observed that as many as 36 different measures had been utilized in the 24 ambulatory BPV measurement studies assessed (11). The number of measurements and the duration of measurement periods differed between studies. In addition, for day- and night-time periods, 13 definitions were used. SD was used more frequently than CV as the variability index. The researchers concluded that greater standardization of methods would be required to enhance the reliability of the studies.

2.2.1 Measurement methods: office, home, ambulatory and beat-to-beat monitoring

Office BPV

Office BPV variability occurs over a long timeframe. It may reflect people's adherence to antihypertensive medication (12) and blood pressure related life-style factors (13,14), errors in BP measurements (15), and seasonal variations (16). Office BP fluctuates to a significant extent even after several visits, and one study from the 1980s suggested that office BP should be measured on as many as six visits to the clinic in order to reliably determine the individual's true BP level (17). Thereafter, visit-to-visit BPV has been shown to be a reproducible phenomenon (1,18) and not some "background noise" that impairs the accurate assessment of BP level.

Standardized methodology for measuring office visit-to-visit BPV is, however, lacking. For example the number of visits utilized to calculate visit-to-visit variability, the number of measurements obtained during a visit, and time interval between consecutive visits have varied between studies (19). The number of clinic visits and BP measurements used in quantifying BPV correlated positively with the magnitude of BPV (20).

In addition, the white-coat effect, the rise in BP due to the presence of a health care professional, is often present when assessing a person's office BP. Thus, office BP measurements may provide especially among prehypertensive and hypertensive subjects higher BP values than those obtained in the individual's home environment.

Home BPV

Home BPV represents mid-term, day-to-day, BPV. Home measurement of BPV has certain advantages over conventional office measurements. It provides higher number of readings over a longer period of time and is free from the white-coat effect, reflecting more reliably the person's actual BP level. Additionally, HBP

monitors are nowadays readily available and HBP measurement is widely accepted by people. Home BPV measurement, as well as office measurement, has its challenges. If one wishes to assess home BPV, then it is important to adopt a systematic approach, including the number of measurements needed, the thresholds for a normal variability, and the indexes to be used, etc. This has proved difficult, because the methods used in different studies are inconsistent.

Ambulatory BPV

Ambulatory blood pressure (ABP) monitoring provides information about an individual's daytime, night-time and 24-hour BPV that cannot be obtained from either OBP or HBP measurements. The circadian variations due to activity and asleep-awake BP differences can be best observed by the ambulatory method (12). In ambulatory monitoring, BP is measured intermittently, usually at 15 minute intervals during the daytime and at 20-30 minute intervals during the nighttime (21-23). Ambulatory BPV has, however, poor reproducibility (24). The circadian BPV showed a lower reproducibility than the 24-hour BP level, which may be a natural consequence of the fluctuating levels of daily activity and differences in sleep quality between nights (24).

Beat-to-beat BPV

Finally, continuous BP monitoring is especially informative and elucidates the beat-to-beat, i.e. the very short-term BP variability. Spectral analysis, a method used to recognize frequency components in a time-domain signal, has been proposed as a suitable approach to obtain a thorough image of rapid cardiovascular regulatory mechanisms. Autonomic influences are involved in the regulation of fast fluctuations of BP, especially at frequencies between 0.2 and 0.4 Hz and around 0.1 Hz (25,26). However, invasive monitoring also has its obstacles; for instance, it is not easily available in a real-life setting.

The different timeframes and diagnostic methods for BPV are depicted in Figure 2.

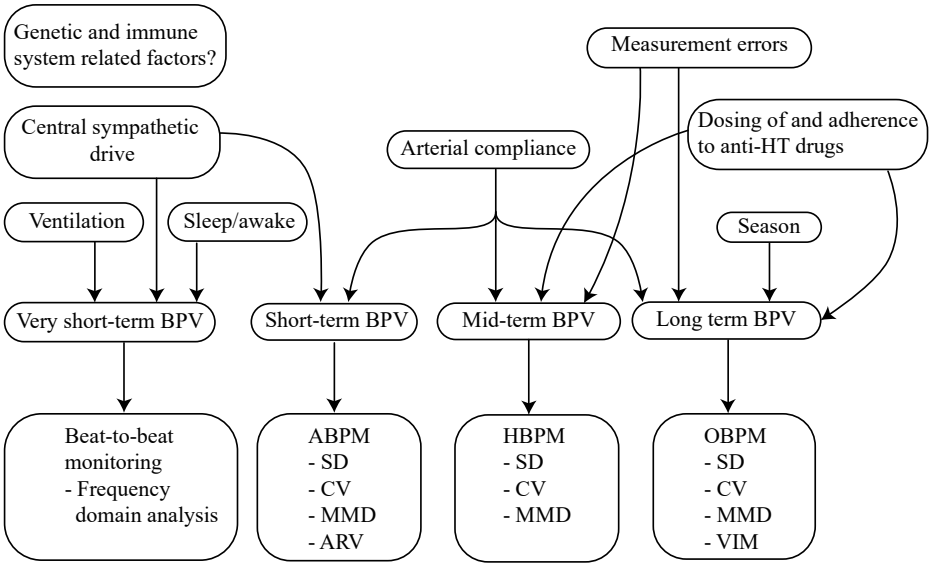

Figure 2. Different timeframes and measurement methods for blood pressure variability.

Correlations between different blood pressure variabilities

Some studies have compared the correlation between BP variabilities measured by different methods in an attempt to resolve whether BPV in different measurements and different timeframes reflects the same physiological or pathological phenomena. In the analysis of the Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA) and The United Kingdom Transient Ischaemic Attack (UK-TIA) cohorts (1), the researchers found that the difference in daytime systolic BP levels between consecutive ambulatory monitoring periods correlated with visit-to-visit office BPV measured during the same time period. The correlation coefficients (r) for residual SDs were as follows: r=0.34 when ambulatory monitoring was performed ≥ 4 times, r=0.43 when ambulatory monitoring was performed ≥ 5 times. This finding indicates that possibly the BPV obtained from several ambulatory monitoring periods have a stronger association with visit-to-visit BPV.

Imai et al. have compared the variabilities of HBP and ABP in a Japanese, unselected population (27). SD and CV were used as variability indexes. The relationships between systolic and diastolic morning HBP and ABP were weak (r=0.21−0.31/0.07−0.14) in their untreated participants.

Johansson et al. compared beat-to-beat, ambulatory hour-to-hour and home day-to-day BP variabilities with each other and with target organ damage (28). In that

study, home blood pressure/pulse pressure variability parameters and low frequency power of beat-to-beat blood pressure/pulse pressure variability were associated with left ventricular mass index in models adjusted for age, sex, and blood pressure/pulse pressure level. The authors detected that reading-to-reading blood pressure/pulse pressure variability parameters and their corresponding beat-to-beat variability parameters are partially connected, possibly due to common regulatory mechanisms.

In addition to the ability to identify clinically relevant BP values, when measuring BPV, it is also important to take into account patients' adherence to different measurement methods. For example, the ABP monitoring, performed through the night as well as during the day, may be disturbing to the individual. Nasothimiou et al. (29) and Lindroos et al. (30) have shown that patients tend to accept and prefer HBP measurement rather than ABP monitoring. On the other hand, home BP measurement also has its challenges: it is dependent of the patient's reliability when reporting the reading and the ability to follow the instructions.

2.2.2 Indexes for blood pressure variability

BPV is dependent upon BP mean levels. This strong correlation between the BP level and its variability should always be taken into account when analyzing the prognostic value of BP variability. Thus, analyses regarding BPV need to be adjusted for the mean BP level and also other potential confounding factors. Some variability indexes that are independent of BP level can be used when evaluating the collinearity in the analyses.

In the assessment of BPV, several different mathematical indexes can be utilized. Standard deviation (SD) is the simplest statistical index for measurement of variation but is highly influenced by the individual's BP level. SD can be modified into weighted SD when 24-hour BP is examined. Thus, the nighttime BP fall can be taken into account. The weighted SD is, however, dependent on the average BP as well as the unweighted SD. SD is utilized in long-term, mid-term, and short-term BPV.

$$SD = \sqrt{\frac{\sum(xi - \bar{x})^2}{n - 1}}$$

Coefficient of variation (CV) is formed by dividing the SD by the mean. Consequently, CV is less dependent on the BP level and is therefore considered an appropriate index in variability studies (31). However, CV also has some drawbacks as

different SDs and mean BP values may provide similar CVs of BP, but these similar CVs achieved by different values may well have different clinical significances. CV is used in analyzing long-term, mid-term, and short-term BP variations.

$$CV = \frac{SD}{x} \times 100$$

Maximum−minimum difference (MMD) is the difference between the highest and the lowest BP reading in mmHg (32-34). It can be used when assessing long- or short-term BPV.

$$MMD = BP_{max} - BP_{min}$$

Average real variability (ARV), on the other hand, takes into account the order of measurements. It is calculated from the mean absolute difference between successive BP readings (3,35). The equation to define the ARV is shown below. In the equation, N denotes the number of valid BP measurements in the data corresponding to a given subject, and k ranges from 1 to n−1. ARV has been used especially in analyses of short-term BPV.

$$ARV = \frac{1}{N-1} \sum_{k=1}^{N-1} |BP_{k+1} - BP_k|$$

Variability independent of the mean (VIM), in turn, is a modification of SD that is not correlated with mean BP (1,36). VIM is calculated as the SD divided by the mean to the power x and multiplied by the population mean to the power x. The power x is obtained by fitting a curve through a plot of SD against mean using the model $SD=a \times mean^x$, where x is derived from nonlinear regression analysis. VIM is utilized especially in analyzing long-term BPV.

$$VIM = \frac{SD}{x^c} \times k$$

where c is the power at which the mean BP is raised to and derives from curve fitting and k is a constant, computed as described by Rothwell et al (1).

2.2.3 Home blood pressure variability: morning, evening, and daily blood pressure variability

Home BPV has been examined by focusing on different details: morning day-to-day variability, day-to-day variability calculated from average BPs obtained in the

morning and in the evening, evening day-to-day variability, morning-evening difference, and the difference between the first and second measurement during one measurement occasion.

Morning day-to-day BPV has been shown to predict future cardiovascular events, whereas the results regarding evening BPV have been inconsistent (2). The significance of home BPV measured by different ways may also be due to different morning versus evening BP patterns across different ethnicities. In several Japanese studies, home BP measured in the morning has been higher than that measured in the evening (37-40). According to the researchers of those studies, that kind of BP profile is probably due to alcohol drinking and bathing in the evening. In contrast, in European studies, opposite observations have been made, as morning BPs seem to be generally lower than those taken in the evening (41-44).

2.3 Determinants of increased blood pressure variability

2.3.1 Determinants of increased long-term (office) blood pressure variability

Table 1 shows some of the most important determinants of increased long-term BPV.

Table 1. Determinants of increased long-term BPV.

Determinant	Effect on OBPV	Reference
High BP level	increases	(20,45,46)
Number of readings	increases	(20)
Female gender	increases	(1,45)
Advanced age	increases	(1,45)
Antihypertensive medication		
Poor adherence	increases	(47)
Sleep-related factors		
Sleep loss	increases	(48)
Long sleep duration	increases	(48)
Obstructive sleep apnea	increases	(49)
History of cardiovascular disease	increases	(1,45)
Season		
Winter	increases	(50-52)
Summer	decreases	(50-52)

Diseases		
Rheumatoid arthritis	increases	(53)
Immunological factors		
Interleukin-6	increases	(54)
High-sensitivity C-reactive protein	increases	(54)
Genetic factors	increases/decreases	(55-57)

OBPV, office blood pressure variability. The most important determinants of increased long-term BPV are high BP level, female gender and advanced age.

Visit-to-visit BPV is probably influenced by inconsistent BP control among patients treated with antihypertensive medications (58). Low patient adherence to antihypertensive medication is common among hypertensive individuals and it has been suggested to be one reason contributing to the high visit-to-visit BPV (59-61). However, there was found to be a low correlation between drug adherence and SD of systolic BP in a study of 1391 hypertensive individuals (47). These data suggest that low adherence to antihypertensive drugs can influence visit-to-visit BPV but is probably not its main determinant (62,63). Additionally, in one study, BPV was rather similar among those with high and those with low drug adherence (47). In many studies assessing drug adherence, however, drug adherence data is based on patient self-reporting, which may limit its objectivity.

Especially in the elderly, both sleep loss and long sleep duration seem to display associations with exaggerated visit-to-visit BPV (48) . Older age (1,45), female gender (1,45), a history of stroke (1) or myocardial infarction (45), and a high mean systolic BP or pulse pressure level (45,46), have also been recognized as determinants of a pronounced office BPV. On the other hand, an observation of a U-shaped curve association between systolic BP level and visit-to-visit BPV has also been reported in a large study that showed baseline systolic BP 120-140 mmHg to be associated with the lowest SD and CV of BP (64). Additionally, seasonal changes have been observed in OBP; higher values are measured during the winter and lower values during the summer (50-52).

Some diseases have been shown to be associated with higher visit-to-visit BPV. For example, in 442 rheumatoid arthritis patients, visit-to-visit variability of systolic BP was higher than in their 424 control patients without rheumatoid arthritis (53).

In addition, obstructive sleep apnea has been shown to affect not only the day-night short-term BPV where its influence may be more obvious, but also long-term visit-to-visit BPV. Shiina et al. studied the association between obstructive sleep apnea and visit-to-visit BPV in 56 individuals with obstructive sleep apnea and 26 without this disorder (49). Those with sleep apnea had a higher SD and CV of

systolic BP. In addition, plasma levels of noradrenaline and the apnea-hypopnea index correlated independently with BPV indexes. In that study, a good adherence to continuous positive airway pressure therapy reduced BPV.

The immune system seems to also have some influence on long-term BPV. In the data of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), with 3794 participants, associations between markers of inflammation (interleukin-6 and high sensitivity C-reactive protein), endothelial function (tissue plasminogen activator antigen and Von Willebrand factor antigen), renal function (eGFR), and glucose metabolism (fasting glucose and fasting insulin levels), separately and combined, and visit-to-visit BPV were examined (54). After multivariable-adjusted models, only interleukin-6 remained significantly associated with greater systolic and diastolic BPV. When interleukin-6 was excluded from the model, high sensitivity C-reactive protein was also a determinant of greater BPV, which is a biologically meaningful finding, because interleukin-6 stimulates the production of C-reactive protein. However, no causal link could be detected between the immunological changes and increased BPV.

The difference in long-term BPV between men and women may result from differences in BP regulation. A review article by Joyner et al. revealed several gender-related differences in BP homeostasis, such as the balance of vasodilating and vasoconstricting adrenergic receptor activities (65).

In addition to environmental and lifestyle factors, genetic factors are probably related to long-term BPV. In a UK study with twins, data from 1454 monozygotic and 1435 dizygotic twin pairs were analyzed (55). Long-term BPV was calculated from at least two visits' BP values assessed as the CV and ARV. The authors estimated the heritability of BP changes by using structural equation modelling to decompose the phenotypic variance into different latent sources of variation: additive genetic variance, shared/common environmental variance, and unique environmental variance. The results showed that in a younger group, aged below 51.3 years, the contribution of additive genetic variance to systolic BPV was 0.25–0.50 and to diastolic it was in the range 0.08–0.23. In contrast, among the older participants, the vast majority, more than 80 % of systolic/diastolic BPV, was attributable to random environmental effects. This finding suggests that the components of BPV and their proportions in its prediction differ according to an individual's age.

In a Japanese study, the hypothesis was that renin-angiotensin system –related gene polymorphisms, which affect the individual's BP level, would exert an influence also on BPV (56). The authors of this study analyzed data from 427 patients with essential hypertension whose BP was measured on at least six clinic visits. BPV was assessed as visit-to-visit variability and SD and CV were used as varia-

bility indexes. Conventional genotyping methods were used to screen for insertion/deletion polymorphisms in BP and renin-angiotensin system genes. The authors observed that only angiotensin converting enzyme insertion/deletion polymorphisms were significantly associated with diastolic BPV whereas there were no genetic polymorphisms that correlated with systolic BPV.

In an Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) substudy, the researchers reported some evidence that genetic variants at the Neuroligin-1 (NLGN1) locus have associations with long-term BPV (57). However, this locus and ischemic stroke and BPV did not display any associations in their genome wide association studies.

2.3.2 Determinants of increased mid-term (home) blood pressure variability

Table 2 shows some of the most important determinants of mid-term BPV.

Table 2. Determinants of increased mid-term BPV.

Determinant	Effect on HBPV	Reference
High BP level	increases	(66-70)
Number of readings	increases	(20)
Advanced age	increases	(37,66-70)
Female gender	increases	(66-70,73-75)
Low BMI	increases	(66,68)
Excessive alcohol consumption	increases	(69,70,76)
Smoking	increases	(75,76)
History of cardiovascular disease	increases	(66,69,74)
Sedentary lifestyle	increases	(70)
Sleep-related factors		
Obstructive sleep apnea	increases	(77)
Sleep loss	increases	(77)
Depression	increases	(78)
Relaxing	decreases	(82)

HBPV, home blood pressure variability. The most important determinants of increased mid-term BPV are high BP level and advanced age.

Increased home BPV has been associated with many physiological and behavioral factors and some diseases. Advanced age has been shown to correlate with increased home BPV (4,37,66-69). In females, home BPV has also been higher than in males in several studies conducted in different populations (4,66,67,69-72).

Individuals with a lower body mass index (BMI) seem to be more likely to have increased home BPV than those with high BMI (4,69). On the other hand, one study detected no association between either subcutaneous adipose tissue or liver fat and BP levels or BPV, suggesting that the interaction between body mass, fat distribution, and BPV may be more complex (73). In addition, increased home BPV has been shown to be associated with low heart rate (67-69,71), but on the other hand, with higher heart rate variability (67,69,71). Some studies have observed greater home BPV in the evening than in the morning (37,71).

In a total of 1114 type 2 diabetic patients, female sex, duration of diabetes mellitus, heart rate, smoking, white coat hypertension and the use of calcium channel blockers were independent determinants of morning systolic BPV. In the same study, age, duration of diabetes mellitus, heart rate, and smoking were determinants of morning diastolic BPV. In that study, BP measurements during winter were avoided because seasonal fluctuations in temperature may cause increased BPV.

With respect to evening BPV, the determinants were substantially the same, although administration of a renin-angiotensin system inhibitor and habitual alcohol drinking were also found to exhibit an association of increased evening BPV. (74)

BPV is dependent on the BP level, and individuals with higher BP values have also greater BPV (4,66-69). Home BPV is higher among those who are diagnosed with sustained hypertension or masked hypertension (normal BP in the clinic measurements but elevated home BP), than among those with normotension or white-coat hypertension (elevated BP in the clinic measurements but normal in home measurements) (75). In some studies, home BPV has been interpreted to be mainly caused by antihypertensive treatment status (37,70). A short duration of antihypertensive drug treatment (69) and a greater number of antihypertensive drugs (71) seem to be determinants of increased home BPV. In particular, the use of beta-blockers has been associated with increased home BPV in observational studies with a general population sample or type 2 diabetes patients (4,68). The effect of an antihypertensive drug on BPV is also likely to be dependent of the long-acting or short-acting type of the drug.

In addition to hypertension status and BP level, some cardiovascular diseases are associated with increased BPV. One study has shown that peripheral arterial disease is related to increased home BPV (4), while another reported an association between different cardiovascular diseases and increased home BPV (66). Individuals with diabetes (66) and diabetic nephropathy (71), tend to have higher home BPV. Increased arterial stiffness is also a determinant of high home BPV, and increased BP may reflect a reduced arterial elasticity (34,68,76).

Moreover, several lifestyle factors seem to correlate with increased home BPV. Smoking may influence especially the variability between two consecutive measurements on one occasion (72), and excessive alcohol consumption has also been associated with higher BPV (66,67). One study also found a link between a sedentary lifestyle and increased BPV (67). In addition, duration of sleep and self-reported insomnia have been recognized as determinants of home BPV (77). In that study, morning-evening, day-by-day, and first-second home BPV were consistently associated with insomnia.

The possible association between BPV and self-reported quality of life has also been examined. In a Korean study with 56 mildly hypertensive participants, the effect of a cognitive behavior therapy-based, so-called ‘forest therapy’, was examined by randomizing half of the participants to receive the therapy (78). Home BP was measured once every morning and once every evening during 8 weeks and BPV was assessed as day-today variability. Quality of life, assessed with a multidimensional score, was inversely correlated to home BPV indexes. A higher quality of life was associated with lower day-to-day BPV on a follow-up visit. The

authors claimed that the forest therapy intervention might have improved the BPV, because BPV was less extensive in the intervention group, although the control group also showed some increase in their quality of life during the follow-up.

A 328-person study, primarily conducted to examine the effects of depression and sleep problems with masked, white-coat, and sustained hypertension, also studied their associations with home BPV (79). The researchers found that increased values of both morning and night-time home BPV were significantly more prevalent in depressive than in non-depressive patients. They postulated that depressive disorders may be determinants of increased BPV.

2.3.3 Determinants of increased circadian (ambulatory) blood pressure variability

Table 3 shows some of the most important determinants of increased ambulatory BPV.

Table 3. Determinants of increased ambulatory BPV.

Determinant	Effect on ABPV	Reference
High BP level	increases	(87)
Advanced age	increases	(86,87)
Arterial stiffening	increases	(69,83-86)
Blood concentrations of cardiovascular risk markers		
High serum homocysteine level	increases	(93)
High uric acid level	increases	(95)
High sensitivity C-reactive protein level	increases	(96)
Immune system related factors		
HIV infection	increases	(109)
Genetic factors	increases/decreases	(113,114)
Kidney diseases	increases	(112)

ABPV, ambulatory blood pressure variability. The most important determinants of increased ambulatory BPV are high BP level, advanced age and arterial stiffening.

Ambulatory BPV, while capturing short-term BP changes, is subject to many modulating factors. Physiological mechanisms, such as sympathetic nervous activity and its fluctuations in response to arterial and cardio-pulmonary reflexes, regulate BP throughout the 24-hour period (26,84-86).

As well as for office and home BPV, advanced age is also a determinant of increased ambulatory BPV (87,88), even if the BP remains normal (88). Additionally, excessive salt consumption seems to be associated with increased ambulatory BPV (14).

Several humoral mechanisms, for instance the vasodilating agents, bradykinin and nitric oxide, and the vasoconstrictors, endothelin-1 and angiotensin II, as well as catecholamines which act as vasoconstrictors in systemic arteries, are also involved in diurnal BP regulation. Additionally, the elastic properties of the arteries have a role in the regulation of BP; stiffening of the arteries seems to be associated with ambulatory BPV (68,80-83). A study with 152 adults aged 20−49 years who were free from diabetes and cardiac, cerebrovascular, and renal diseases, found that SD, weighted SD, and ARV of 24-hour BP were significantly correlated with aortic stiffness (89). In particular, measures that quantified the distensibility of the aorta, showed stronger links between arterial stiffness and BPV. In individuals with reduced aortic compliance, BP is likely to vary due to changes in cardiac output and contractility. The finding of a significant link between arterial stiffness and increased short-term BPV in the young may suggest that measurement of BPV is important in early adulthood because if the possible surrogate markers of increased cardiovascular disease risk could be identified sufficiently early, then the development of the disease could be prevented.

In a Chinese study, increased serum homocysteine levels were correlated with increased 24-hour ambulatory BPV in hypertensive patients (90). This may reinforce the hypothesis for BPV being a cardiovascular risk marker or a surrogate risk marker for other pathological processes leading to adverse cardiovascular consequences. Another study has interpreted short-term BPV as a mediator of the link between adverse effects of BP and arterial stiffness (91).

Several biomarkers, such as serum uric acid, have been shown to correlate with 24-hour BPV in newly diagnosed hypertensives (92). Previously, the uric acid concentration has been associated with the development of hypertension, probably due to its pro-oxidant effects, endothelial dysfunction, and proinflammatory effects on smooth muscle. The clinical significance of the recent finding of the association between uric acid and BPV is unclear but it may reflect the vascular changes extending beyond increased BPV. In addition, positive associations have been found between markers of inflammation, such as C-reactive protein and tumor necrosis factor -alpha, and increased 24-hour BPV, suggesting that inflammation might be one of the factors contributing to variations of BP (93). In a study with 190 patients, performed by Tatasciore et al., it was shown that two inflammatory markers, high

sensitivity C-reactive protein and soluble E-selectin, which is an endothelium-specific molecule, were associated with awake systolic 24-hour BPV in newly diagnosed hypertensives after adjustments (94).

ABP monitoring can make it possible to observe different daytime-nighttime BP profiles. In healthy individuals, the normal nighttime dipping is associated with a significant reduction in the sympathetic nervous system drive during sleep (95). In the morning, during the awakening period, a marked sympathetic activation and a sudden BP surge occur (96). If an increased sympathetic drive is present, the normal day-night BP difference may be diminished (97). In some circumstances, BP does not fall or it even increases during the nighttime. These non-dipping or even reverse-dipping BP patterns have been observed not only to be due to increased sympathetic activity (97) but also to be linked with a reduced renal sodium excretion (98), an increased leptin resistance in the obese (99), endothelial dysfunction (100), or the use of glucocorticoids (101) or cyclosporine (102). One study was performed in 86 hypertensive individuals to examine if obstructive sleep apnea diagnosed by polysomnography influenced ambulatory BPV. It was reported that obstructive sleep apnea increased night-time systolic BPV and also 24-hour diastolic BPV (103). On the other hand, data collected from 4 randomized controlled trials and published recently, have shown that withdrawal from continuous positive airway pressure (CPAP) therapy had only a marginal effect on the patients' BPV (104). However, BPV was assessed as office BP and home BP measurements instead of 24-hour monitoring in that study.

The dipping pattern of ambulatory BPV is also a variable phenomenon. Individuals can be categorized into 4 groups according to their daytime vs. nighttime BP profile: 1) the normal dipping pattern (i.e. those who, compared with average daytime BP values, display a reduction in average nighttime systolic and diastolic BP >10% and <20%), 2) extreme dippers whose nighttime BP is reduced by >20%, 3) non-dippers whose BP reduces <10%, and 4) those with no reduction at all or an increase in BP during nighttime (97). In a study with 115 untreated individuals, ABP monitoring was performed three times, at approximately one-week intervals (105). The researchers found that although 24-hour BP was fairly stable over repeated monitoring periods, there was extensive variability in BP dipping. The differences in dipping between the monitoring days were attributed to differences in sleep quality. It seems that performing more than one ABP monitoring would provide a more thorough image of an individual's 24-hour BP profile, but in a real-life setting, repeated monitoring may not be feasible. It is possible that the immune system also participates in the regulation and variation of ambulatory BP. For example, HIV-infected patients, naïve for anti-retroviral HIV treatment, were shown to have an attenuated day-to-night BP decline in a comparative study conducted with 152 HIV-patients and 156 HIV-negative controls (106). The researchers suggested

that HIV infection would be an independent factor for a poor daily BP profile, though the evidence was preliminary, and additional research on the topic would be needed.

The determinants of day-night BP difference were also studied in a family study with 1564 European participants (107). The participants consisted of nuclear families. In that study, 24-hour, daytime and night-time systolic and diastolic BP values showed remarkable heritability (18−43 %), whereas the day-night systolic BP difference showed a lower heritability, and the heritability of day-night diastolic BP difference was nonsignificant. The results of that study suggested that several lifestyle factors, such as age, plasma lipids, and smoking, were determinants of diurnal BP variations, while genetics probably had a small role in the variability of day-night BP.

The associations of short-term BPV and hypertension status were studied in a Spanish population-based study with elderly participants (≥60 years) (108). It was found that 24-hour, daytime or nighttime systolic BPV was significantly higher in individuals with white-coat hypertension in comparison with those with normotension, and were similar to those with sustained hypertension. In untreated individuals, 24-hour, but not daytime or nighttime BPV separately, was higher among white-coat hypertensives than in normotensives. In addition, a blunted nocturnal BP decline was observed more frequently in those with masked hypertension. These results reveal correlations between short-term BPV and hypertension status.

The association between increased 24-hour BPV and simultaneous chronic kidney disease was studied in 1022 Jackson Heart Study participants (109). The study was a community-based observational study identifying cardiovascular disease risk factors in African Americans. The authors found that 24-hour BPV was higher in the individuals with chronic kidney disease. This association, however, became non-significant after adjusting for BP mean levels.

The role of genetics in short-term BPV has also been examined. For example, Xu et al. investigated the relative contributions of genetic and environmental factors in twin populations (110). They analyzed a total of 1133 young persons, which included 495 twin pairs and 143 singletons, the study population consisting of blacks and whites. BPV was measured with 24-hour ambulatory monitoring and calculated as SD weighted by the durations of daytime and night-time. The role of genetics was assessed with structural equation modeling, which is based on a comparison of the variance-covariance matrices in dizygotic and monozygotic twins making it possible to separate genetic and environmental components. They found that genetic influences explained approximately 25 % of the variance in systolic/diastolic BPV. Their analyses were adjusted for 24-hour BP average values,

which suggests that the heritability of BPV seemed to be independent of the BP level.

Moreover, the relevance of single nucleotide polymorphisms in the gene coding for endothelial nitric oxide synthase on short-term BPV has been studied in a sample of 152 young adults (111). The hypothesis was that because nitric oxide plays a role in BPV control, polymorphisms in genes that contribute to nitric oxide production could affect BPV. The study was performed in young individuals who were healthy and free from atherosclerosis which may mask the genetic differences in BPV. It was observed that with respect to the T-786C single nucleotide polymorphisms, the carriers of the less frequent alleles (CC homozygotes and TC heterozygotes) showed significantly higher systolic BPV compared to TT homozygotes. In contrast, no significant differences were found between carriers of different genotypes of the other examined polymorphism, the G894T.

2.4 Prognostic significance of increased blood pressure variability

2.4.1 Blood pressure variability and target organ damage

Long-term blood pressure variability

Many studies have examined the association between long-term visit-to-visit BPV and different forms of subclinical target organ damage, such as vascular remodeling. Some studies have revealed a relationship between increased visit-to-visit BPV and increased carotid intima-media thickness and stiffness (34,112,113). A study with healthy individuals found evidence for an association between decreased brachial endothelial function and elevated visit-to-visit BPV (114). Furthermore, the progression of coronary artery calcification has been shown to have an association with a pronounced visit-to-visit BPV (115). An association has also been observed between visit-to-visit variability in BP and left ventricular diastolic dysfunction in treated hypertensive patients (33). In addition, a cross-sectional study in treated hypertensives showed an association between visit-to-visit variability and arterial stiffness and myocardial perfusion changes (116).

The effects of long-term BPV on kidney function have also been examined in many studies. A large proportion of these studies have been performed on diabetic individuals. Systolic visit-to-visit BPV correlated with the development (76) and progression (117,118) of diabetic nephropathy in type 2 and type 1 diabetic patients (119) and renal dysfunction in hospitalized patients (120). A study with non-dia-

betic chronic kidney disease patients has found visit-to-visit BPV to be an independent determinant of deteriorating kidney function also in non-diabetics (121). In addition, a 15-year retrospective cohort study of 825 hypertensive patients, 43 % of whom were diabetic at baseline, revealed a correlation between long-term visit-to-visit systolic BPV and renal deterioration (122). Moreover, in a retrospective primary care study in 19 175 individuals, a small increase in visit-to-visit BPV was related to a worsening renal function (123). An analysis from the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) trial showed in a population of patients with at least one cardiovascular disease risk factor, that higher visit-to-visit BPV predicted renal outcomes, development of end-stage renal disease or a 50 % decline in eGFR, during a period of 3.5 years (124). The effect of increased visit-to-visit BPV on outcomes has also been examined in patients with primary proteinuric glomerulopathies (125). These authors examined 296 adults with a glomerulopathy and observed that increased long-term BPV was associated with poorer outcome, evaluated as a progression to end-stage renal disease, after a 2-year follow-up. In a large meta-analysis, based on data of more than 16 000 patients, chronic kidney failure was associated with increased BPV (126).

Increased visit-to-visit BPV correlates also with a future incidence of cerebrovascular disease (127), late-life brain white matter lesions and ventricular atrophy (128). Among patients with a history of ischemic stroke, increased systolic BPV between visits has been recognized as an independent risk factor for deep and infratentorial cerebral microbleed progression (129). In elderly persons with a high cardiovascular risk, exaggerated visit-to-visit BPV also seemed to be a determinant of cognitive impairment (130). In addition, in a study on the elderly subjects in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) substudy, 4745 participants were analyzed for visit-to-visit BPV and a functional decline (131). Greater systolic BPV between clinic visits was associated with a steeper decline in functional status, assessed as activities of daily living and instrumental activities of daily living. In addition to studies performed among the elderly, increased long-term visit-to-visit BPV has also been demonstrated to predict a worse function in psychomotor speed and verbal memory tests in midlife (132). In a study based on the data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, BP data were collected during 25 years and the tests for cognitive function were conducted after the follow-up, when the mean age of the participants was 50.4 years.

A prospective 200-individual study assessed the association between visit-to-visit BPV and growth of intracranial aneurysms (133). They found that increased BPV was significantly and independently associated with un-ruptured intracranial aneurysm growth.

In diabetic patients, increased systolic visit-to-visit BPV was associated with future lower extremity amputations (134).

The prognostic value of increased visit-to-visit BPV has also been studied in a large Lifestyle Interventions and Independence for Elders (LIFE) substudy which included 8505 hypertensive patients that were randomized to receive either losartan vs. atenolol-based treatment (135). In that study, increased visit-to-visit BPV was not associated with the incidence of left ventricular hypertrophy or urine albumin/creatinine ratio, which may be due to the relatively short follow-up of 24 months.

Mid-term blood pressure variability

In addition to visit-to-visit BPV, also variability of home-measured BP has been found to be a predictor of development of subclinical target organ damage. For example, a Japanese study examined untreated hypertensive individuals and revealed that maximum systolic home BP was associated with both left ventricular mass index and carotid intima-media thickness independently of BP level and other confounding factors (136). Increased arterial stiffness, measured as pulse wave velocity, was shown to be more common among persons who have greater morning systolic home BPV in patients with type 2 diabetes (68).

Several studies have also found associations between increased home BPV and the incidence or progression of kidney-related adverse target organ changes. Urinary albumin excretion is more common in hypertensive individuals that have greater day-by-day home BPV (136,137). Another study with type 2 diabetic individuals revealed that those subjects with higher systolic and diastolic morning and higher systolic evening home BPV are more likely to present with macroalbuminuria (urinary albumin excretion ≥300 mg/g creatinine) (138). Additionally, in a study with type 2 diabetic patients who had a diagnosis of microalbuminuria, a higher systolic home BPV was associated with the lowest estimated GFR (glomerular filtration rate) (139), whereas another study among patients with chronic kidney disease from different causes found no association between increased day-by-day home BPV (140).

In addition to left ventricular mass, arterial stiffness, and renal insufficiency, also cognitive decline (141) and the development of dementia have been shown to be more likely in individuals with a higher day-to-day BPV. In the Japanese Hisayama study, 1674 community-dwelling elderly self-measured their HBP in the morning for 3−28 days (142). The participants were followed-up for a mean of 5.3 years, and their cognitive function was examined by the Mini Mental State Examination and other questionnaires as well as with a clinical examination. The re-

searchers found that both vascular dementia and Alzheimer disease were more frequently diagnosed in participants with higher home BPV. When BPV was assessed in quartiles, the increased risk for vascular dementia was observed in those individuals with increased BP level and increased BPV but not in those with normal BP level and increased BPV. In contrast, the risk of Alzheimer's disease was pronounced in those subjects with increased BPV, regardless of hypertension status.

Short-term blood pressure variability

Short-term and very short-term BPV also have prognostic significance over BP level(28). Increased BPV, measured with ambulatory 24-hour registration, correlates with left ventricular hypertrophy (143-147) and increased carotid intima-media thickness (145,148,149). Short-term BPV, obesity, and left ventricular mechanical function also seem to undergo interactions with each other. The study of Tadic et al. has shown that BPV and left ventricular deformation are significantly influenced by obesity in untreated hypertensives (150).

A South-African study compared the prognostic value of 24-hour BPV in relation to left ventricular hypertrophy (151). In 409 African and Caucasian individuals, they observed weak correlations between increased BPV and left ventricular mass measured with electrocardiograms (ECG). In normotensive Africans, an independent association was observed between 24-hour systolic BP and left ventricular mass when the BP level was also included in the model. The authors suggested that increased BPV could be used for early cardiovascular risk detection but its value is probably lower than that of the BP level.

Short-term BPV has also been associated with a progression of cerebral small vessel disease. In 210 elderly patients, higher levels of BPV in ambulatory monitoring were predictive of more advanced small vessel disease and cognitive decline over a 4-year follow-up in multivariable-adjusted analysis (152).

Short-term BPV measured by noninvasive beat-to-beat variability recordings was more strongly associated with increased intima-media thickness than increased BPV observed in a 24-hour ambulatory monitoring (153). The study sample, however, consisted of only 85 individuals, and in clinical practice, it has not been feasible to assess the beat-to-beat measurements.

One study in 167 newly diagnosed hypertensive individuals, before drug treatment, also found a relation between increased 24-hour ambulatory BPV and left atrial dimension, which is an early cardiac alteration often seen in hypertensive patients (154). Many studies have observed an association between increased short-term BPV and renal damage. In particular, individuals with a non-dipping or reverse dipping pattern in their 24-hour BP profile have a greater risk for development or

progression of microalbuminuria (145,155-158), a reduction in their glomerular filtration rate (159), or poor renal prognosis (160). However, the association between short-term BPV and microalbuminuria seems to be inconsistent even within a single study: in 315 untreated hypertensive patients, only the ARV index showed an association unlike the situation with SD and weighted SD (161).

However, opposite findings of the significance of 24-hour BPV for target organ damage have also been reported. A study in which 305 diabetic hypertensives underwent a 24-hour ABP monitoring, BPV was not associated with echocardiographic parameters of left ventricular hypertrophy or diastolic function (162).

Moreover, changes in BPV over time were not independent predictors of changes in target organ damage, assessed as left ventricular mass index and pulse wave velocity in a study with 286 patients that had uncomplicated hypertension (163). BPV was measured by office measurements performed on 5 visits during a year, home measurements at baseline and 12 months, and 24-hour ambulatory measurements at baseline and 12 months. In that study, only the changes in mean BP levels, but not BPV, were relevant when evaluating changes in target organ damage. Thus, the authors suggested that the clinical significance of BPV was limited.

Furthermore, in 447 hypertensive patients, 24-hour ABP was not associated with left ventricular hypertrophy or diastolic function in controlled or uncontrolled BP (164), and similar observation was made for 24-hour BPV and left ventricular mass and microalbuminuria in 2047 Irish adults in a cross-sectional study (165).

2.4.2 Blood pressure variability and cardiovascular outcomes

Relationship of systolic versus diastolic BPV and cardiovascular outcomes

Most studies on BPV have assessed the relationship between systolic and diastolic BPV with cardiovascular outcomes, although some have used only systolic BPV (166). Some studies have found that diastolic BPV displays an even stronger predicting value for future adverse events than systolic variability (142). Some evidence has been found that systolic BPV has a stronger impact of cardiovascular disease development than its diastolic counterpart (1) which is probably due to the marked significance of the systolic BP level. However, the superiority of systolic or diastolic BPV as a cardiovascular risk factor is difficult to determine because, due to multicollinearity (167), both BPs cannot be included in the same regression model. Thus, systolic and diastolic BPV may be best assessed in separate models.

Long-term blood pressure variability

Table 4 summarizes the results of long-term BPV outcome studies. The hazard ratios for the associations between office BPV and adverse outcomes varied between 1.1 and 2.0.

Table 4. Results from outcome studies regarding office BPV

Cardiovascular outcome of interest	Effect of OBPV on the outcome	Study population	Reference
Stroke	increases	Patients with prior stroke or TIA	(171)
	increases	Elderly	(172)
	increases	Hypertensives	(138)
Coronary heart disease	increases	Elderly	(187)
	increases	Patients with prior stroke or TIA	(186)
Cardiovascular mortality	increases	Elderly	(184,185)
	increases	CKD patients	(179-181)
MACE	increases	Diabetes patients	(112,177-178)
	no effect	Elderly	(194)
	no effect	Mild-to-moderate hypertensives	(192)

OBPV, office blood pressure variability; TIA, transient ischemic attack; CKD, chronic kidney disease; MACE, major adverse cardiovascular events.

Office visit-to-visit BPV has been shown to predict cardiovascular endpoints. During the past two decades, after the initial findings of its significance in the prediction of coronary heart disease events (169), several studies have examined its clinical significance with a focus on fatal and nonfatal cerebrovascular and cardiac events. In a large study on patients with a history of transient ischemic attack or hypertension, increased systolic office BPV clearly predicted the incidence of stroke after adjustment for the BP level (1,36). A similar finding on the association between visit-to-visit BPV and ischemic stroke was made in elderly patients with treated hypertension (170) and in a substudy of the Lifestyle Interventions and Independence for Elders (LIFE) study with 8505 hypertensive patients (135).

Additionally, a Chinese study examined the influence of visit-to-visit BPV on stroke risk in a large sample of 122 636 hypertensive individuals (171). The authors of that study revealed a significant association between increased visit-to-

visit BPV and the risk of stroke. A review also assessed the relationship between office BPV and outcomes in hypertension trials (172). The authors hypothesized that the previously observed association between long-term BPV and increased stroke risk could be explained by a pronounced occurrence of atrial fibrillation in individuals with greater BPV, because atrial fibrillation is a strong risk factor for stroke. However, they found no association between effects of antihypertensive drugs on BPV and effects on new-onset atrial fibrillation.

In addition to cerebrovascular complications, coronary heart disease events also increase with the higher office BPV values (36,173).

The relationship between increased office BPV and incidence of cardiovascular events and deaths has been evident in different populations: among postmenopausal women (174), diabetes patients (119,175,176), patients with chronic kidney disease (177-179), patients with low ejection fraction heart failure (180), hypertensives (181), in well-functioning elderly (182), elderly hypertensives (183), patients who have undergone ischemic stroke (168), rheumatoid arthritis patients (53), patients with stable coronary heart disease (184), and general population (45,166,185).

In a post hoc analysis of the Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) and the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) trials, the impact of visit-to-visit BP on cardiovascular outcomes was evaluated in patients with coronary artery disease and well-controlled BP levels (186). A significant association was found between increased BPV and major cardiovascular events in this patient population.

Visit-to-visit BPV has also been studied in 656 patients at high risk for cardiovascular disease (187). The researchers found that the patients with high systolic BPVs were at 1.5-fold higher risk for adverse events, which remained after adjustment with other cardiovascular risk factors, including the BP level.

A post hoc analysis of another French study with 2157 patients with a previous diagnosis of cardiovascular disease showed an association between increased office visit-to-visit BPV and incident cardiovascular disease (188). In that study, however, there was only marginal additional predictive value gained by taking BPV into account. Systolic BPV was strongly associated with other cardiovascular disease risk factors such as advanced age, the presence of hypertension, and the prevalence of type 2 diabetes. Thus, the investigators concluded that increased office BPV was an integrator of cardiovascular risk factors rather than itself being a robust predictor of adverse events.

Some negative findings on the clinical significance of office BPV have also been reported. In an Italian sample conducted in mild-to-moderate hypertensives, visit-to-visit BPV was not a significant predictor of cardiovascular outcomes (189). A general population study provided similar results that the office BPV was not an indicator of increased cardiovascular risk (4). In addition, a Japanese study in hypertensive coronary artery disease patients indicated that BP control achieved, but not the visit-to-visit variability in BP, correlated with subsequent major adverse cardiac events (190). Moreover, a study examining elderly primary care patients detected no association with increased visit-to-visit BPV (191).

Additionally, in a post hoc analysis of the recent Systolic Blood Pressure Intervention Trial (SPRINT), the researchers assessed the prognostic significance of visit-to-visit BPV for fatal and nonfatal cardiovascular events (192). In their analysis, office BPV did not have significant associations with either the composite endpoint, or with stroke or heart failure.

The significance found in many studies in relation to outcomes may be partly caused by the imperfect adherence of the patients to the antihypertensive treatment or an insufficient dose of medication which may also lead to increased BPV. One previous study has shown that when the percentage of visits with BP values within the reference frames increases, the incidence of cardiovascular adverse events decreases (193).

Mid-term blood pressure variability

The results of mid-term BPV outcome studies are summarized in Table 5. The hazard ratios for the associations between home BPV and adverse outcomes varied between 1.05 and 1.4.

Table 5. Results from outcome studies regarding home BPV.

Cardiovascular outcome of interest	Effect of HBPV on the outcome	Study population	Reference
Stroke morbidity	increases	General population	(2,197,199)
Stroke mortality	increases	General population	(2,197,199)
Cardiac morbidity	increases	General population	(2,197,199)
Cardiac mortality	increases	General population	(2,197,199)

HBPV, home blood pressure variability.

Increased home BPV is associated with cardiac and stroke morbidity and mortality (2,194,195). In a Japanese population study, the risk of cerebral infarction was higher when home BPV was increased, particularly among smokers (196). A study

performed in Belgium, however, found no association of home BPV and cardiovascular outcomes independently of HBP levels (4). In that study, however, HBP was measured by nurses, and not by participants themselves, resulting in a study setting that was different from the other studies.

Short-term blood pressure variability

Table 6 summarizes the results of short-term BPV outcome studies. The hazard ratios for associations between ambulatory BPV and adverse outcomes varied between 1.2 and 2.1.

Table 6. Results from outcome studies regarding ambulatory BPV.

Cardiovascular outcome of interest	Effect of ABPV on the outcome	Study population	Reference
Nonfatal and fatal CV events	increases	Hypertensives	(208)
Nonfatal and fatal CV events	increases	Non-dippers	(209-219)
Adverse CV events	decreases	Systolic HF patients	(221)
Short-term stroke outcomes	no effect	Stroke patients	(222,223)

ABPV, ambulatory blood pressure variability; CV, cardiovascular; HF, heart failure.

The prognostic significance for cardiovascular events of ambulatory BPV has been studied extensively. Consistent evidence demonstrates that short-term BP fluctuations are independent predictors of cardiovascular nonfatal (3,5,197-202) and fatal (3,5,197,203) events. In the International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome, increased ambulatory BPV (204), was predictive of cardiovascular events and mortality but the prediction of outcomes only improved by 0.1 %.

Some evidence also suggests that the predictive value of short-term BPV may be different according to hypertension status; at least one study has indicated that increased short-term BPV predicted cardiovascular mortality during a 20-year follow-up among untreated hypertensives but not in normotensives, independent of BP level (205). Many studies have also shown that nighttime ambulatory BPV has a stronger predictive significance than daytime variability, and it is probably the ability to obtain nighttime BP values that makes ambulatory monitoring an effective method to measure BP and its variability (206-216).

In addition to the association with incidence cardiovascular events in the population, increased short-term BPV has been studied as a possible prognostic risk marker in 100 patients who underwent percutaneous coronary intervention due to stable coronary artery disease (217). The investigators found that increased 24-hour BPV before the procedure was associated with increased risk of stent restenosis.

On the other hand, the results of a retrospective study in 288 systolic heart failure patients were opposite as they paradoxically showed that low systolic BPV was associated with adverse outcomes (218). In that study, the mean follow-up was 4.4 years, BPV was assessed as the average difference between maximum and minimum values in daytime or nighttime ABP values, and cardiac death or heart transplantation were considered as endpoints. According to these findings, the prognostic significance BPV may differ or even be opposite in different patient populations.

The prognostic significance of short-term BPV, assessed by ambulatory, beat-to-beat or casual monitors, in acute stroke, was examined in a systematic review that included 7 studies (219). The authors summarized that increased systolic BPV, assessed early after ischemic or hemorrhagic stroke, is associated with poor functional outcome. However, reverse causality is possible: larger strokes may cause greater BPV, and then the poor prognosis is due to the large damage in brain tissue caused by the stroke itself and BPV may not be crucial. On the other hand, increased BP fluctuations can also have a true role in the pathophysiology of adverse changes after stroke. Cerebral autoregulation is impaired after an acute stroke, and greater BPV may increase cerebral edema or hemorrhagic transformations.

In contrast to long-term outcomes, the short-term BPV does not seem to predict short-term outcomes (219). In addition, a prospective study on 608 ischemic stroke patients, published after the abovementioned review, observed no association between short-term BPV measured during the first 2 to 3 days of hospitalization and in-hospital outcomes (220).

2.5 Effects of antihypertensive treatment on blood pressure variability

Studies that have assessed the effect of antihypertensive treatment, drug and lifestyle intervention, on BPV, have been mainly if not entirely, retrospective analyses of clinical trials that were aimed to reduce BP instead of BPV. This fact has to be taken into account in the interpretation of the study results.

For the evaluation of the effects of antihypertensive drugs on BPV, some specific indexes have been developed. The smoothness index is calculated from the average values of systolic and diastolic BP at baseline and at the end of the treatment period (221,222). A large smoothness index usually indicates a consistent BP reduction and small variability. The treatment-on variability index is computed as the ratio of changes in the 24-hour average BP and the 24-hour SD of BP during antihypertensive treatment (223).

2.5.1 Effects of antihypertensive treatment on long-term (office) blood pressure variability

A multicenter randomized controlled trial examined the effects of weight loss and salt reduction on the visit-to-visit BPV in 1820 participants with high-normal diastolic BP (224). They observed that visit-to-visit BPV did not differ between those randomized to the weight loss or salt reduction intervention groups and those randomized to the control groups. These findings suggest that weight loss and salt reduction might not be effective in reducing long-term BPV.

In an analysis originating from the National Health and Nutrition Examination Survey (NHANES), the administration of ACE inhibitors was associated with higher BPV in multivariable models, with no differences in visit-to-visit BPV being observed for the other antihypertensive drug classes (45). The limited sample size made it impossible to perform any head-to-head comparisons of drug classes, ACE inhibitors, beta blockers, calcium channel blockers, and thiazide diuretics.

In a large systematic review of the effects of different drug classes on visit-to-visit BPV, Webb et al. showed that as compared with other drug classes, calcium channel blockers and thiazide-type diuretics reduced systolic BPV (225). In contrast, ACE inhibitors, angiotensin II receptor blockers and beta blockers increased BPV. In this analysis, BPV and the treatment-induced changes were assessed as inter-individual BP variance, which is a surrogate for variability measured within-individual. The authors discussed that their findings of drug-class effects were most likely due to within-individual BPV.

Many other studies have also found that calcium channel blockers may reduce long-term BPV more effectively than other antihypertensive drug classes (226-230).

On the other hand, visit-to-visit BPV did not markedly differ between individuals being administered beta blockers and those taking calcium channel blockers in the European Lacidipine Study on Atherosclerosis (ELSA) (189).

2.5.2 Effects of antihypertensive treatment on mid-term (home) blood pressure variability

Two trials have revealed that an angiotensin II receptor blocker and calcium channel blocker combination reduces home BPV more effectively than a combination of an angiotensin II receptor blocker and a diuretic (231,232). Additionally, one of these studies suggested that the reduction in home BPV achieved was partly due to a reduction in arterial stiffness by this drug combination (231). Different calcium channel blockers, such as lercanidipine and felodipine, seemed to exert a similar effect on BPV (233). Some controversial results have, however, been obtained regarding the different effects of antihypertensive classes on home BPV. For example, an interventional study with 2484 patients randomly allocated to treatment with a calcium channel blocker, an ACE inhibitor, or an angiotensin receptor blocker found no differences in the effects of these drugs on home BPV (234).

In addition to the rather limited results on the effects of drugs on home BPV, data on the use of home BPV as an interventional target is also scarce. In one study, 310 participants received candesartan or a diuretic for 6 months which led to reduced home BPV (137). This reduction was, however, not associated with an improvement in urinary albumin excretion, which questions the role of BPV as an interventional target.

2.5.3 Effects of antihypertensive treatment on short-term (ambulatory) blood pressure variability

A study with a hypertensive population of 40 subjects undergoing hemodialysis therapy revealed that administration of the angiotensin receptor blocker, losartan, decreased nighttime ambulatory BPV more effectively than other conventional antihypertensive medications. The authors assumed that the part of the benefit of losartan therapy in hypertensive hemodialysis patients could be due to decreased pathological cardiovascular remodeling through better control of short-term BPV (235).

A post-hoc analysis in 2983 patients treated with a combination of the calcium channel blocker, benidipine, and either a beta blocker or a thiazide-type diuretic (229). The calcium channel blocker –based treatment in combination with thiazide reduced visit-to-visit variability more than the calcium channel blocker combined with the beta blocker. On the other hand, combination of an angiotensin receptor blocker and a calcium channel blocker reduced short-term BPV more effectively

than a combination of angiotensin receptor blocker and diuretic in another study (236).

In a trial investigating different antihypertensive drugs, Levi-Marpillat et al. showed that in a population of 2780 essential hypertension patients, a treatment based on calcium channel blockers and diuretics in combination or alone had the strongest ambulatory BPV lowering impact compared with other drug classes (237). In general, calcium channel blockers have been shown to reduce BPV in several studies.

A study in metabolic syndrome patients targeted all of the components of the metabolic syndrome (238). The researchers exploited a multidisciplinary approach including dietary intervention and physical training in 44 non-diabetic patients. BPV was assessed with 24-hour ambulatory monitoring. The researchers observed that after the 1-year intervention, short-term BPV had reduced independent of the BP level. Arterial stiffness and metabolic control also improved. Another study in type 2 diabetic hypertensives showed a decrease in 24-hour ambulatory BPV after one-week long salt reduction (239). The participants consumed a diet with the amount of salt restricted to less than 6 g /day. Although the sample was very limited, only 10 patients, the results suggest that BPV can be decreased by salt restriction. These findings support the possible BPV lowering effect of lifestyle interventions.

Presumably, long-acting and short-acting antihypertensive agents may have different effects on BPV. Comparative studies between antihypertensive classes and their impact on BPV seem to be scarce. In a Chinese study with a retrospective design, more than 5000 hypertensive patients were studied. Blood pressure was measured thrice during a clinic visit, and thus the BPV measured was one kind of short-term variability. The authors found out that amlodipine, which has the longest half-life, reduced BPV more effectively than other calcium channel blockers (240).

In addition to lifestyle interventions and antihypertensive drug treatment, renal sympathetic denervation also seems to have BPV reducing effects. Vogiatzakis et al. showed in their review and meta-analysis that catheter-based renal denervation had favorable effects on short-term BPV in resistant hypertensive patients (241).

2.6 Current hypertension guidelines and their shortcomings regarding blood pressure variability

The latest guidelines of the European Society of Hypertension and the European Society of Cardiology, updated in 2018, consider increased office BPV at the same

or different visits as a clinical indication to perform out-of-office BP measurements either with home or ambulatory monitoring (242). The guidelines also mention that ambulatory BP monitoring would be feasible in the assessment of BPV. The guidelines do not, however, address any diagnostic thresholds for BPV, suggesting that further research is required.

In addition to the European guidelines, also the Japanese Society of Hypertension guidelines consider BPV as a significant phenomenon in the measurement of BP (7). These guidelines state that one of the advantages of HBP measurement is that it enables the evaluation of BPV over a long period, e.g. is able to take into account seasonal variability. The Japanese guidelines also point out the significance of different timeframes in the definition of different BP variations: it is possible to assess short-term BPV by ambulatory monitoring, diurnal changes by home or ambulatory monitoring, changes between two consecutive days by home measurement, and finally, long-term changes can be investigated via home or office measurements. They also mention marked home BPV as an indication for ambulatory BP monitoring. The Japanese guidelines also highlight the prognostic significance of different types of BPV. They recommend that to promote the use of BPV as a diagnostic tool in hypertension and in modifying of antihypertensive treatment, the definition of BPV should be clarified and analytical methods for its assessment should be established. Furthermore, possible interventions which could reduce BPV would need additional research.

On the other hand, the Evidence-Based Guideline for the Management of High BP in adults, a report from the panel members appointed to the 8th Joint National Committee and 2017 AHA guidelines (243), as well as the Evidence-Based Finnish Current Care Guidelines of Hypertension, did not mention increased BPV in their recommendations (244,245). The Finnish hypertension guidelines, however, recommend that diagnosis of hypertension should be based on four sitting duplicate blood pressure measurements and confirmed always by self-measurements or ambulatory BP monitoring.

BP levels measured at home seem to predict future adverse cardiovascular outcomes more accurately than office BP (246), and home BP measurement carries several advantages over traditional office BP measurements. Furthermore, its prognostic significance has been recognized in international guidelines (6,7). BP measurements conducted at home are performed in the individual's natural environment and are free from the white-coat effect. In addition, home measurement enables a long-term follow-up of BP values and is generally well accepted by people. Given these advantages, and the proven significance for cardiovascular disease risk prediction, home monitoring could provide a feasible and readily accessible

option for the assessment of BPV. Thus, a standardized measurement protocol would be necessary for the measurement of home BPV.

A pronounced long-term systolic BP variability may also be associated with increased resting heart rate variability, but this phenomenon is not covered in this thesis.

2.7 Summary

BP is a highly variable phenomenon, with the variability being partly physiological and partly pathological.

While BPV, measured as long-term, mid-term or short-term fluctuations of BP values, has been recognized as a potential risk factor for various diseases and subclinical organ damages, its role as an independent risk factor has not been observed consistently in all studies, and conflicting findings have also been reported.

The difficulty in measuring BPV has been highlighted in a systematic review and meta-analysis that examined data from various studies focusing on long-term, mid-term, or short-term variabilities (247). The majority of BPV studies have been conducted in elderly populations which may limit the generalizability of the results to younger individuals. In addition, European and East Asian populations have been overrepresented in these studies. Antihypertensive treatment is a potential confounding factor in BPV and should be taken into account in the analyses.

The variety of different methods used to measure BPV complicates any head-to-head comparison of different studies. Thus, more standardized study methods will be required if we are to elucidate the actual prognostic and clinical value of BPV. In addition, some quantitative analyses will be needed to determine the limits of physiological and pathological BPV.

3 AIMS OF THE STUDY

This thesis was set out to devise a standardized measurement schedule for the measurement of home BPV so that this methodology could be better used in the future to help clinicians perform a cardiovascular disease risk assessment.

The specific goals were:

1. To resolve the agreement between different methods (office, home, and ambulatory BP measurements) of BPV measurement. (Study I)

2. To examine how home BP varies based on the day of the week. (Study II)

3. To determine the optimal number of measurement days for home BPV assessment using an outcome-based approach. (Study III)

4. To define outcome-based reference values for increased home BPV. (Study IV)

4 SUBJECTS AND METHODS

4.1 Study I

4.1.1 Study sample

Two cohorts examined in 1992−1996 were combined to form the study population. The first cohort (population cohort) consisted of 340 individuals aged from 34 to 64 years. The subjects were living in Southwestern Finland and were randomly drawn from the population register. In all, 275 of these individuals agreed to participate in the study. The second cohort (hypertensive cohort) consisted of 252 newly diagnosed untreated hypertensive men and women. The participants in the hypertensive cohort were recruited by internists and general practitioners in Southwestern Finland. The individuals were eligible to participate in the study if they had a mean systolic/diastolic BP of 180 to 220/100 to 120 mmHg of two BP measurements taken in the primary health care system.

We included individuals for whom we had data from at least half of the maximum number of BP measurements, in the analyses. Thus, the exclusion criteria were <24 daytime ambulatory readings, <6 nighttime ambulatory readings, <14 self-measurements performed at home and <4 office measurements performed by a nurse, respectively. After excluding participants with an insufficient number of ambulatory, home, and office BP measurements and those who were taking antihypertensive medication (n=66), the study sample consisted of 461 participants (Figure 3).

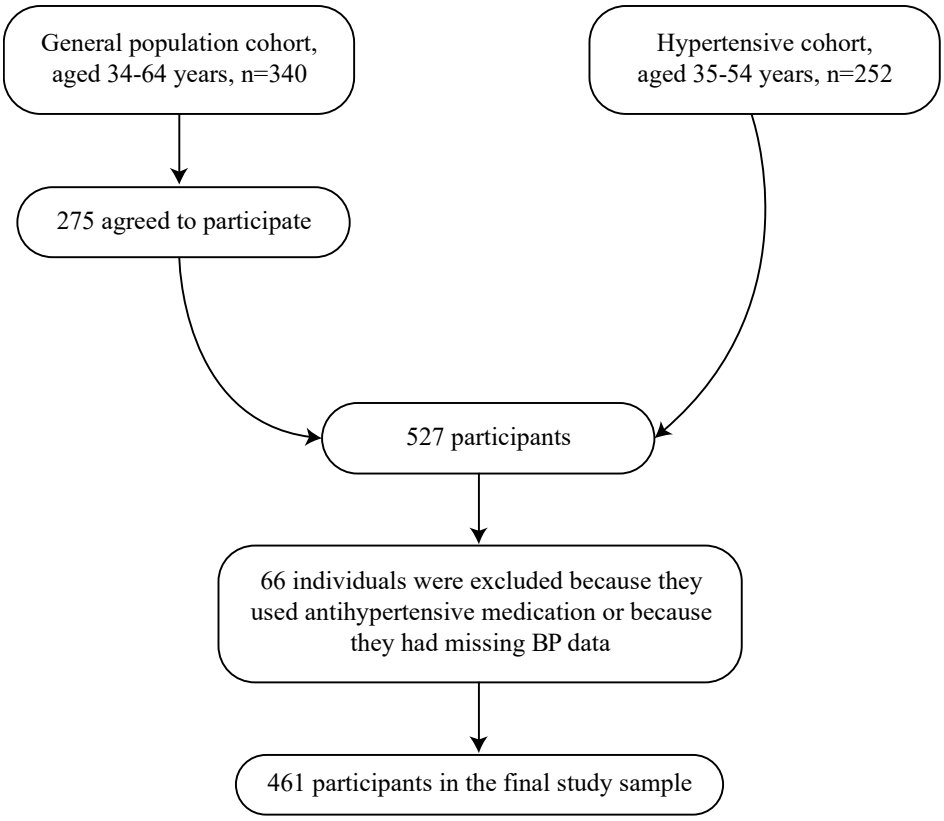

Figure 3. Flowchart for sample selection.

The study was approved by the ethics committee of the Social Insurance Institution of Finland. All of the study participants gave informed consent.

4.1.2 Blood pressure measurements

We performed the ambulatory BP recording with an auscultatory device (Suntech Accutracker II) which was validated according to the Association for the Advancement of Medical Instrumentation and British Hypertension Society protocols (248). It fulfilled the criteria of the Association for the Advancement of Medical Instrumentation protocol for systolic and diastolic BPs and the criteria of the British Hypertension Society protocol for systolic BP (248). We measured ABP during daytime (10:00 AM − 10:00 PM) at 15-minute intervals and during nighttime (midnight − 6:00 AM) at 30-minute intervals. All readings were used to calculate mean daytime and nighttime BPs. We rejected the readings with a quality failure code and readings with systolic BP < 70 or > 250 mmHg or diastolic BP < 40 or > 150

mmHg. We also excluded those readings in which pulse pressure was not greater than 0.43 x diastolic BP – 18 (249).

The participants self-measured their home BP with a validated automatic oscillometric device (Omron HEM 705 C) (250) after being trained on how to measure BP correctly. They were advised to measure their BP after resting for 15 minutes, of which the last 5 minutes were to be spent with the cuff around the upper arm. BP was measured twice every morning between 6:00 and 9:00 AM and twice every evening between 6:00 and 9:00 PM on 7 consecutive days. Home BP was defined as the average of the four daily measurements in the analysis.

The participants prepared for the office BP measurements in the same way as for the home BP measurements. Office BP was measured by a nurse with a mercury sphygmomanometer twice with a 2-minute interval. For the analyses, office BP was determined as an average of the 4 duplicate BP values taken at 1-week intervals within 3 weeks. During all of the visits used to calculate visit-to-visit BPV, the participants remained untreated for hypertension.

4.1.3 Blood pressure variability indexes

Five different variability indexes – SD, coefficient of variation (CV), MMD, VIM, and ARV – were calculated. CV is the within-participant SD divided by the within-participant average BP. MMD is simply the difference between the highest and lowest BP value in mmHg. VIM is a transformation of SD that is uncorrelated with average levels (1,36,194). ARV is the average of the differences between successive BP measurements (1,3,35).

SD, CV, VIM, and ARV of office BP were assessed as visit-to-visit variability from the average BP values of all four clinic visits. Similarly, SD, CV, VIM, and ARV of home BP were calculated from the seven averages of the four daily BP measurements. MMDs of office and home BP measurement were calculated from the maximum and minimum of all BP readings (8 office and 28 home measurements). SD, CV, MMD, VIM, and ARV of ambulatory BP were calculated from single readings.

4.1.4 Statistical analyses

We compared the continuous baseline variables between cohorts using the t-test, and we used chi-square test for categorical variables, respectively. The distributions of variability indexes were tested for normality. Because most of the indexes

had a skewed distribution, all indexes were log transformed for the statistical analyses. After the logarithmic correction, we calculated the correlations between ambulatory, home, and office BP variability indexes using Pearson's correlation coefficient. We interpreted the correlation coefficients as negligible (r=0.01–0.19), weak positive (r=0.20–0.29), moderate positive (r=0.30–0.39), strong positive (r=0.40–0.69), and very strong positive (r≥0.70) (251).

We also classified the participants whose BP variability exceeded the 90th percentile as having extreme BP variability in order to assess the agreement between ambulatory, home, and office measurements in diagnosing large BP variability. We used κ coefficients when assessing the agreement in diagnoses of extreme variability made with ambulatory, home, and office measurements. The strength of agreement for the κ coefficients was categorized as follows: poor (κ≤0), slight (κ=0.01–0.20), fair (κ=0.21–0.40), moderate (κ=0.41–0.60), substantial (κ=0.61–0.80), and almost perfect (κ=0.81–1.00) (252).

The limit of statistical significance was P<0.05 in Study I. Statistical analyses were performed with SAS software version 9.4 (SAS Institute, Cary, North Carolina, USA).

4.2 Study II

4.2.1 Study sample

Study II is part of the multidisciplinary epidemiological Health 2000 Study, which was performed in Finland between autumn 2000 and spring 2001. The study locations of the Health 2000 Study are shown in Figure 4. The Health 2000 study population consisted of 8028 individuals aged ≥ 30 years who were randomly drawn from the population register to represent the Finnish adult population. In all, 6354 individuals participated in the health examination, and those aged 44−74 years were invited to a HBP measurement substudy, the Finn-Home study. A total of 2103 participants performed BP measurements at home. A detailed description of the recruitment of study participants has been previously published (253). We excluded the 251 participants who had not measured their BP at least once on all days of the week. Thus, the final study sample consisted of 1852 individuals.

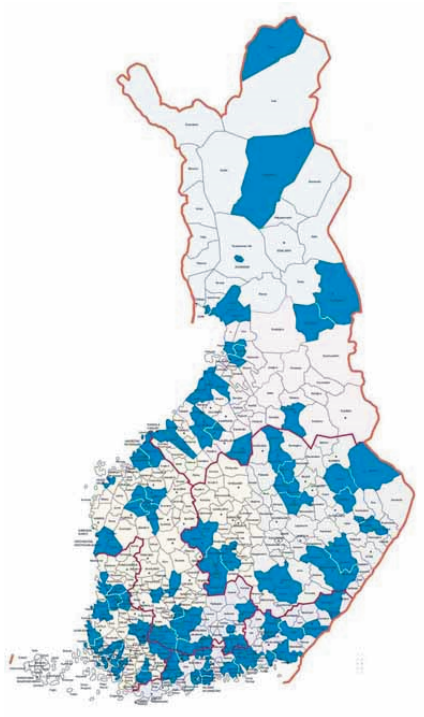

Figure 4. Study locations of Health 2000 Study marked in blue.

4.2.2 Flow of the study

The study protocol of the Health 2000 Study was accepted by the ethical committees of the Finnish National Public Health Institute and Hospital District of Helsinki and Uusimaa, Finland. All of the study participants provided signed informed consent (11). The sample selection for studies II and III is shown in Figure 5.

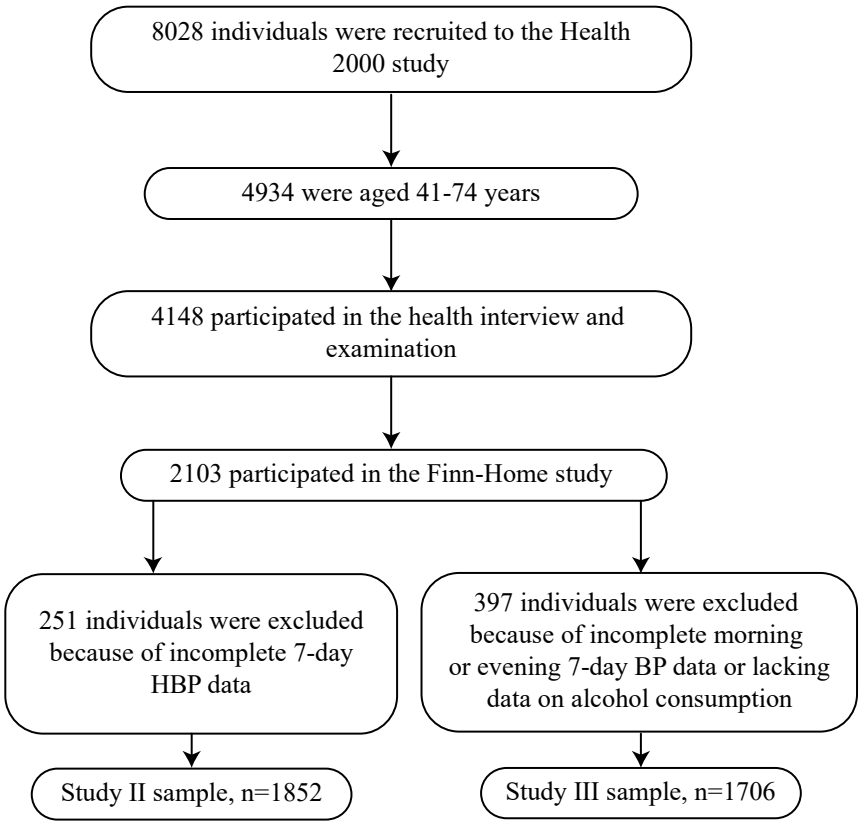

Figure 5. Flowchart for Sample Selection for Studies II and III.

4.2.3 Measurement of home blood pressure and blood pressure variability

Participants self-measured their home BP using an automatic oscillometric device (Omron Model HEM-722 C; Omron Corporation, Tokyo, Japan). The devices were validated in accordance with contemporary guidelines (254-256). Participants were given written instructions and individual advice on how to accurately measure BP. Before measuring BP, the participants were advised to avoid smoking, physical exercise and eating for 1 hour. Before performing the measurements, the participants were asked to sit resting for at least 10 min and during the last 5 min to have the cuff around the upper arm. BP measurements were taken from the non-dominant upper arm. The participants were advised to measure their BP twice in the morning (between 6 and 9 a.m.) and twice in the evening (between 6 and 9 p.m.) on 7 consecutive days. Thus, the maximum number of measurements was 28. The daily BP was defined as the mean of four measurements taken during the day (253).

4.2.4 Definitions

Smoking was defined as daily tobacco use. The men who used over 288 g of pure alcohol per week and the women who used over 192 g were considered to consume alcohol excessively (257). Hypercholesterolemia was defined as use of statins or a fasting serum total cholesterol level of at least 7.0 mmol/l. In our analysis, the definition of diabetes was a fasting serum glucose level of at least 7.0 mmol/l or the use of antidiabetic drugs. The participants were considered as employed if they were working full-time or part-time.

4.2.5 Measurement of ambulatory, home and office blood pressure variability

Five different variability indexes were calculated: SD, CV, MMD, VIM and ARV.

SD, CV, VIM and ARV of office BP were calculated as visit-to-visit BPV from the average BP of the four clinic visits. Similarly, SD, CV, VIM and ARV for home BP were assessed from the seven average values of the four BP measurements performed every day. MMD of office and home BP was calculated from the maximum and minimum values of all BP readings (8 office and 28 home measurements). SD, CV, MMD, VIM and ARV of ambulatory BP were calculated from individual readings.

4.2.6 Statistical analysis

The t test was used to compare the continuous baseline variables between cohorts. For categorical variables, the chi square test was used. We tested the distributions of the variability indexes for normality. Because most of the variability indexes had a skewed distribution, all were log transformed before the statistical analyses. After the correction, correlations between BP variations in ambulatory, home and office measurements were calculated. In these analyses, Pearson's correlation coefficient was used. The following interpretation for the correlation coefficients was used: the correlation was considered negligible if r=0.01−0.19, weak positive if r=0.20−0.29, moderate positive if r=0.30−0.39, strong positive if r=0.40−0.69, and very strong positive if r≥0.70 (251).

The participants were also classified as having lesser or extreme BPV in order to assess the agreement between ambulatory, home and office measurements in the diagnosis of large BPV. If BPV exceeded the 90th percentile, the participant was considered as having extreme variability. Kappa (κ) coefficients were used in assessing the agreement in extreme variability diagnoses made with ABP, HBP, and

OBP measurements. The agreement was considered poor if $\kappa \leq 0$, slight if $\kappa=0.01-0.20$, fair if $\kappa=0.21-0.40$, moderate if $\kappa=0.41-0.60$, substantial if $\kappa=0.61-0.80$ and almost perfect if $\kappa=0.81-1.00$ (252).

P values <0.05 were considered as statistically significant. Statistical analyses were performed with version 9.4 of the SAS software (SAS Institute, Cary, North Carolina, USA).

4.3 Study III

4.3.1 Study sample

In study III, we investigated the Finn-Home cohort, which was used also in Study II, as the study sample. However, some additional exclusions from the population were performed because it was deemed advisable to thoroughly assess the number of measurement days needed, and therefore the participants in Study III had to have a complete number of measurement days available. In all, 397 individuals who had not measured their morning and evening BP on all of the 7 measurement days or had missing alcohol consumption data were excluded. Thus, 1706 participants were included in this analysis. Figure 5 shows the recruitment of the participants.

4.3.2 Measurement of home blood pressure and blood pressure variability

The methodology of HBP measurements in the Finn-Home study is depicted in Chapter 4.3.2 Flow of the Study (Study II).

We defined home systolic/diastolic blood pressure variability as (1) day-to-day variability of daily mean systolic/diastolic blood pressures; (2) morning day-to-day variability of morning mean systolic/diastolic blood pressures; (3) evening day-to-day variability of evening mean systolic/diastolic blood pressures; (4) variability of individual morning, evening, or all-day systolic/diastolic blood pressures, instead of daily means; (5) morning day-to-day variability of first morning systolic/diastolic blood pressure readings of each day; and (6) evening day-to-day variability of first evening systolic/diastolic blood pressure readings of each day. BP variability indexes based on two through seven measurement days were ob-

tained for each participant. We used the coefficient of variation (CV) as the measure of BP variability because standard deviation (SD) would have been strongly dependent of the BP level itself (31).

4.3.3 Outcomes and other definitions

Follow-up data of endpoints were collected until December 31, 2013. In the classification of fatal and nonfatal events, the 10th version of the International Classification of Diseases, Injuries, and Causes of death (ICD-10) was used. To collect mortality data, the National Causes of Death register, which is based on death certificates, was used. The National Hospital Discharge Register that covers all hospitalizations in Finland was utilized when collecting the data on hospitalization due to stroke, heart failure, and coronary heart disease events. Both registers have been validated for diagnoses of coronary heart disease, stroke, and heart failure (258-260). The ICD codes used for these classifications have been previously described in detail (261).

We used a composite endpoint of nonfatal stroke, nonfatal myocardial infarction, hospitalization for heart failure, cardiovascular mortality, and percutaneous or surgical coronary intervention as the primary outcome of the analyses. In case the participant experienced more than one endpoint event, only the first event was considered in the analysis. A previous diagnosis of cardiovascular disease was defined as having at least one previous hospitalization for stroke, angina pectoris, or myocardial infarction.

The participants were considered to have diabetes if they had a fasting serum glucose level ≥7.0 mmol/l or if they were being administered hypoglycemic agents. The definition of hypercholesterolemia was use of statins or a fasting serum total cholesterol level of ≥7.0 mmol/l. Current users of tobacco products were considered as smokers.

Alcohol use was evaluated with a questionnaire. The alcohol amount consumed was transformed to grams of absolute ethanol and expressed as grams per week. 31.0 % of the study sample reported not drinking alcohol. To take this into account, we divided the study participants into 3 groups according to their alcohol use: (1) 0 g/week; (2) 1−280 g/week for men and 1−140 g/week for women; and (3) >280 g/week for men and >140 g/week for women (262).

Questions derived from the Basic Nordic Sleep Questionnaire (263) were used to identify the participants with sleep apnea. The individuals were considered to have sleep apnea if they reported that they had a previous diagnosis of sleep apnea or if

the findings in the questionnaire were indicative of sleep apnea. The questionnaire findings were considered characteristic of sleep apnea if snoring occurred repeatedly (at least 3−5 nights weekly), and, additionally, either of the following was true: (1) the snoring was loud and irregular and occasional respiratory pauses occurred or (2) respiratory pauses occurred during at least 1−2 nights per week.

4.3.4 Statistical analysis

We used Cox proportional hazards regression models to examine the association between home BPV indexes based on 2−7 measurement days and incident cardiovascular events. The models were adjusted for sex, age, BMI, smoking status, diabetes status, hypercholesterolemia, use of antihypertensive medication, history of cardiovascular disease, presence of sleep apnea, alcohol consumption, and mean systolic/diastolic home BP level. Mean BP level was calculated from the corresponding number of measurement days to the variability index.

The Harrell C-statistic was used in assessing the changes in model discrimination when the number of measurement days for the calculation of BPV index and BP mean was increased from 2 to 7. In these comparisons, 3 measurement days were used as the reference because three is the smallest number to assess variability (264). The C statistics were obtained for the whole model, reflecting how the model fit changed when the number of measurement days for both mean BP and BP variability was increased.

We also examined the impact of an increasing number of home BP measurement days on the classification of individuals into those with normal and those with increased BPV. The participants were categorized as having normal or increased morning BPV using previously proposed outcome-based reference values for BPV as described in Study IV (Chapter 5.4) (265). A CV of systolic BP >11.0 was considered as increased morning systolic BPV and a CV of diastolic BP >12.8 was considered as increased morning diastolic BPV. Kappa (κ) coefficients were reported for the intra-individual agreement in classification to high versus low BP variability on consecutive numbers of measurement days (e.g. classification based on measurements on days 1 through 3 versus 1 through 4). The interpretation of the kappa coefficients has been described in Study II (Chapter 4.2.5) (252).

Two-tailed P values <0.05 were considered statistically significant. SAS software version 9.4 (SAS Institute, Cary, North Carolina, USA) was used for statistical analyses.

4.4 Study IV

4.4.1 Study sample

The International Database of Home Blood Pressure in Relation to Cardiovascular Outcome (IDHOCO) consists of random population sample studies which have longitudinal follow-up of both fatal and nonfatal cardiovascular outcomes. The data collection of the IDHOCO and all of its study cohorts have been described in previous publications (266). In our analysis, we considered 6353 participants from Ohasama, Japan; Tsurugaya, Japan; Didima, Greece; and Finland (Finn-Home). The Montevideo cohort of the original IDHOCO consortium was excluded from the present analysis because only 1-day HBP measurements were recorded, and the assessment of day-to-day BPV was therefore impossible. We excluded individuals with missing covariates (n=28) and those with BP measurements performed on <3 days (n=87). After the exclusions, the number of participants included in the analyses was 6238 (2775 from Ohasama, 768 from Tsurugaya, 634 from Didima, and 2061 from Finland). All participants gave their written informed consent, and all IDHOCO study protocols had received ethical approval.

4.4.2 Flow of the study

At an initial health interview at the participant's home, basic background and sociodemographic information, information about health and illnesses, and information about use of medication were gathered by centrally trained interviewers. A physical examination was performed 1 to 6 weeks later at a local health center by centrally trained nurses and doctors. The participant's height and weight were measured. Fasting blood samples for serum lipids and glucose were drawn. At the end of the examination, the participants in the Finn-Home substudy received home BP monitors to measure their home BP during the week after the health interview. A detailed description of the study methodology has been previously published (253,267).

4.4.3 Blood pressure measurements

In all studies included in the IDHOCO, home BP was self-measured in the participants' homes. An automated, oscillometric, upper arm cuff device that had been validated was used. A cuff of appropriate size was utilized. Participants measured their BP in the sitting position (266). home BP was measured only in the morning

in the Tsurugaya cohort, and therefore, in our analysis, day-to-day home BPV was calculated based on the participant's first BP reading of each measurement day taken between 5:00−12:00 AM to minimize the potential effect of different measurement protocols on the results. In the current analyses, BP measurements of the first 3 to 7 days were taken into account. We aimed at retaining only physiologically meaningful BP readings in the analysis to avoid exaggerating BPV. Our exclusion criteria for individual HBP values were systolic BP <70 or >250 mm Hg, diastolic BP <40 or >140 mm Hg, or pulse pressure <10 mm Hg. Consequently, 76 of 90 432 (0.08%) BP readings were discarded. Office BP was measured with an automated device or a standard mercury sphygmomanometer. Office BP values were calculated as the average of the individual's two consecutive readings.

4.4.4 Measurement of home blood pressure variability

In study IV, home BPV was assessed using four different indexes: SD, CV, ARV, and VIM.

CV was used as the main exposure variable because it is less dependent on BP level than SD. CV can be rather easily calculated in clinical practice, and it enables the definition of a universal reference frame.

4.4.5 Definitions

Information on the study participants' medical history, medication intake, and smoking habits were gathered with baseline questionnaires. The participant was considered a smoker if there was any use of tobacco products. BMI was determined as body mass in kilograms divided by the square of the height in metres (kg/m^2). Serum cholesterol and blood glucose were measured by automated enzymatic analysis methods on venous blood samples. Participants were considered as having diabetes mellitus if they self-reported a previous diagnosis of diabetes mellitus, or had a fasting or random blood glucose concentration of at least 7.0 or 11.1 mmol/L, respectively, or if they were being administered antidiabetic drugs. Previous cardiovascular disease was defined as having a cardiac, cerebrovascular, or peripheral vascular disorder (268). Data on serum cholesterol levels were unavailable for the Didima cohort and they were extrapolated by sex and 10-year age strata based on a large population cohort that had been examined in the same area at the same time (269,270).

4.4.6 Outcomes

We determined vital status and incidence of cardiovascular events from the applicable sources of each country as previously described (266). The mortality data were derived from regional registers in the Ohasama and Didima cohorts and national registers in the Finnish and Tsurugaya cohorts, and the data were based on death certificates. Cardiovascular mortality and a composite of all adverse cardiovascular events were used as study end points. Cardiovascular deaths, myocardial infarction, coronary revascularization (surgical or percutaneous), pacemaker implantation, heart failure, and stroke (excluding transient ischemic attack) were included in the cardiovascular events. If the individual experienced more than one event, only the first was considered in the analyses (266).

4.4.7 Statistical analysis

We used Cox proportional hazards regression models to examine the association between home BPV indexes and the risk of cardiovascular events. The regression models were adjusted for mean systolic/diastolic home BP, cohort, and traditional cardiovascular disease risk factors: age, sex, BMI, diabetes mellitus, smoking status, total serum cholesterol level, history of cardiovascular disease, and use of antihypertensive drugs. The possible nonlinearity of the associations was tested by adding a quadratic term of BPV indexes into the models.

The enhancement in model differentiation and reclassification achieved by adding CV of home BP into a Cox model that included the conventional cardiovascular risk factors, were examined with (1) the net reclassification improvement (271), (2) the integrated discrimination improvement (271), and (3) Harrell C statistic (264). The following risk categories were used in the assessment of the net reclassification improvement: <5%, 5% to 10%, 10% to 20%, and >20%.

To define outcome-driven thresholds for increased home BPV, we split the study population into 10 groups by deciles of CV of home BP. We calculated HRs comparing the cardiovascular event risk in each decile versus the average risk of the whole population (272). The threshold for increased BPV was defined as the decile above which cardiovascular event risk was increased. Sensitivity analyses were performed by excluding 1 cohort at a time from the Cox regression analyses. In addition, we examined the association between BPV and cardiovascular outcomes in subgroups by ethnicity, sex, age, use of antihypertensive medication, and prevalent cardiovascular disease. We also tested for interaction to discern whether the relative influence of BPV was different among subpopulations by introducing an

interaction term into the models. In these interaction analyses, we dichotomized the CV of BP with the cutoff level of the 90th percentile.

P value 0.05 was considered the limit of statistical significance. SAS software version 9.4 was used for the statistical analyses (SAS Institute, Cary, NC).

5 RESULTS

5.1 Agreement between ambulatory, home and office blood pressure variability (Study I)

5.1.1 Characteristics of the participants

The characteristics of the study population are shown in Table 7. The sample consisted of 249 men and 212 women, who were aged between 34 to 64 years at the time of recruitment (mean: 47.3±6.9). The participants of the patient cohort were older and had higher BMI, cholesterol, glucose, BP and were more likely to be men than those in the population cohort (Table 7).

Table 7. Characteristics of the participants of study I.

Characteristic	All	Population cohort	Hypertensives	p
n	461	226	235	
Women, %	46	50.9	41.3	*
Age, years	47.3 ± 6.9	48.7 ± 8.3	46.0 ± 4.9	***
BMI	27.0 ± 4.4	26.1 ± 4.2	27.9 ± 4.5	***
Serum total cholesterol	5.7 ± 1.1	5.6 ± 1.1	5.8 ± 1.0	*
Fasting glucose, mmol/l	5.3 ± 0.7	5.2 ± 0.7	5.4 ± 0.8	*
ABP day, mmHg				
Systolic	138.4 ± 18.0	127.4 ± 14.5	149.1 ± 14.3	***
Diastolic	85.1 ± 10.9	77.9 ± 8.3	92.1 ± 8.2	***
ABP night, mmHg				
Systolic	115.4 ± 18.6	105.8 ± 15.6	124.6 ± 16.6	***
Diastolic	68.7 ± 11.2	62.1 ± 9.0	75.1 ± 9.1	***
HBP, mmHg				
Systolic	130.0 ± 17.0	119.6 ± 14.2	140.0 ± 13.0	***
Diastolic	85.2 ± 12.1	76.8 ± 9.4	93.3 ± 8.4	***
OBP, mmHg				
Systolic	132.8 ± 18.0	120.6 ± 14.2	144.6 ± 12.6	***
Diastolic	85.2 ± 12.6	75.4 ± 8.8	94.6 ± 7.4	***
Smoking, %	28	30	26	NS
CVD, %	2.2	4.4	0	**

Data are shown as mean ± SD or percentage. BMI indicates body mass index, ABP indicates ambulatory blood pressure, HBP indicates home blood pressure, OBP indicates office blood pressure, CVD indicates previous cardiovascular disease. Smoking data of one participant was lacking. P values are for the differences between normotensives and hypertensives. * indicates P<0.05, ** indicates P<0.01, *** indicates P<0.001, NS indicates nonsignificant.

5.1.2 Characteristics of blood pressure variability

The mean number of BP measurements obtained in daytime ambulatory, nighttime ambulatory, home and office monitoring was 50.0 ± 4.1, 12.5 ± 1.6, 27.6 ± 1.4 and 7.9 ± 0.4, respectively. Systolic and diastolic ambulatory BPV was greater than office BPV or home BPV (Table 8). The statistical significance for the differences between measurement methods are shown in Table 2/Study I. For example, the CVs of systolic daytime ABP, nighttime ABP, OBP and HBP were 9.8, 8.6, 4.6 and 4.4, respectively.

Table 8. Blood pressure variability in study I.

	ABP (day)		HBP		OBP	
Index	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
SD	13.6±4.5	10.0±4.3	5.7±2.7	4.0±1.7	6.2±3.3	4.4±2.2
CV	9.8±2.9	11.9±3.6	4.4±1.8	4.7±1.9	4.6±2.4	5.2±2.6
MMD	67.8±26.7	49.5±16.4	34.6±12.5	24.1±9.1	16.8±7.9	12.3±5.2
VIM	13.6±4.0	10.0±3.0	5.7±2.3	4.0±1.7	6.2±3.2	4.4±2.2
ARV	11.3±3.7	8.7±3.1	5.6±2.6	4.0±1.9	7.1±4.0	4.9±2.7

Data are shown as mean ± SD. ABP indicates ambulatory blood pressure, HBP indicates home blood pressure, and OBP indicates office blood pressure. SD indicates standard deviation, CV indicates coefficient of variation, MMD indicates maximum-minimum difference, VIM indicates variability independent of the mean, and ARV indicates average real variability.

5.1.3 Correlation of blood pressure variabilities measured by different methods

Systolic ambulatory, home, and office BPV indexes were significantly (P<0.05) correlated with each other with the exception of nighttime ambulatory-home CV (r=0.08, P=0.11) and nighttime ambulatory-home VIM (r=0.07, P=0.13) (Table 9).

In general, however, the relationships were weak or negligible, with the correlation coefficients varying between 0.07−0.26. The correlations were mainly weak between the three measurement methods irrespective of which variability index was used. The lowest correlation between the methods was found for CV and VIM (r=0.08−0.18), while the correlations were somewhat higher, but still weak, for SD, MMD and ARV (r=0.17−0.26). The scatter-plots between CV of BP in daytime ambulatory-home, daytime ambulatory-office, and office-home measurements, when assessed by CV are shown in Figure 1/Study I.

Table 9. Correlations between systolic ambulatory, home, and office BPV.

BPV Index		ABP (day)	HBP
SD	HBP	0.25***	-
	OBP	0.22***	0.23***
CV	HBP	0.10*	-
	OBP	0.13**	0.14**
MMD	HBP	0.25***	-
	OBP	0.22***	0.24***
VIM	HBP	0.09*	-
	OBP	0.13**	0.13**
ARV	HBP	0.21***	-
	OBP	0.17***	0.16***

Data are shown as Pearson's correlation coefficients. Blood pressure variability indexes were log-transformed before the analysis. BPV indicates blood pressure variability, SD indicates standard deviation, CV indicates coefficient of variation, MMD indicates maximum-minimum difference, VIM indicates variability independent of the mean, and ARV indicates average real variability. * indicates P<0.05, ** indicates P<0.01, and *** indicates P<0.001.

For diastolic BPV (Supplemental Table 1/Study I), the inter-method correlations were significant (P<0.05), with the exception of daytime ambulatory-office CV (r=0.03, P=0.52), daytime ambulatory-office ARV (r=0.08, P=0.08), and daytime ambulatory-office VIM (r=0.05, P=0.32). In general, the correlations between different measurement methods were weaker in diastolic than systolic BP, although the relationships in diastolic also varied between negligible and weak (r=0.03−0.23).

Subgroup analyses were performed for cohort, sex, age, and BMI. In these analyses, we used CV as the variability index for daytime ambulatory, home, and office BP (Supplemental Table 3/Study I). The correlations were mainly weak, and 13 of

the 24 correlation coefficients were non-significant (P>0.05) in the subgroup comparisons. Only in the normal-weight versus overweight comparison, was a consistent trend observed that lean persons displayed lower correlation coefficients than the obese persons.

5.1.4 Agreement of different methods on diagnosis of increased blood pressure variability

Table 4/Study I and Supplemental Table 2/Study I present the agreement in diagnoses of the greatest variability (the 46 participants above the 90th percentile) between systolic and diastolic ABP, OBP, and HBP. The agreement between the three methods in diagnosing extreme systolic and diastolic variability varied from poor to slight. The kappa coefficients varied from -0.01 for systolic nighttime ambulatory-home VIM to 0.20 which was determined for systolic nighttime ambulatory-home MMD. Figure 2/Study I shows the agreement in diagnoses of extreme BPV between different measurement methods. Only one individual for systolic and three for diastolic were diagnosed as having extreme BPV with all three measurement methods. Between two methods, agreement was reached in 24 individuals in systolic BP and 17 individuals in diastolic BP.

5.1.5 Correlation between different blood pressure variability indexes

Within each measurement method, the correlations between the variability indexes ranged from 0.63 to 0.9998. The highest correlations between indexes were observed in office BPV and the lowest in home BPV.

5.2 The impact of the day of the week on home blood pressure (Study II)

5.2.1 Baseline Characteristics

The characteristics of the participants are shown in Table 10.

Table 10. Characteristics of the participants of study II.

Characteristic	Mean
Age, years	56.4 ± 8.5
Body mass index, kg/m^2	27.4 ± 4.5
Systolic HBP, mmHg	
Based on 3 days	130.9 ± 19.3
Based on 7 days	129.5 ± 18.5
Diastolic HBP, mmHg	
Based on 3 days	80.7 ± 9.5
Based on 7 days	80.1 ± 9.2
Alcohol consumption, g/week	75.9 ± 145.9
Excessive alcohol consumption, %	6.5
Smoking, %	18.9
Women, %	54.4
Antihypertensive drugs, %	22.3
Hypercholesterolemia, %	29.4
Diabetes mellitus, %	6.7
Employed, %	53.3

Data are shown as mean ± SD or percentage. HBP, home blood pressure.

5.2.2 Seven-day blood pressure trend

Systolic and diastolic BP profiles according to the initial day of the week of the measurements are shown in Figure 1/Study II. In general, during the 7-day measurement period, systolic and diastolic BP decreased. The decrease was most marked during the first 3 to 4 days. However, a small increase or plateauing in both systolic and diastolic BP was observed from Sunday to Monday in all curves (Figure 1/Study II). Thus, the 7-day average BP values were slightly lower than the 3-day values irrespective of the initial day of the week of the measurement period as is shown on the left side of Table 12. P values were <0.002 for all comparisons with the exception of the difference between 7-day and 3-day diastolic BP measurements initiated on Saturday, P= 0.15).

5.2.3 Differences between blood pressure means according to the initial day of measurement

Table 11 presents the mean 3- and 7-day HBP values according to the initial day of the week of the measurements. No significant overall differences were found in mean systolic/diastolic BP values when the measurement was initiated on various days of the week.

Table 11. Average blood pressure values by initial day of the week of measurement.

	Blood pressure			
	Systolic		Diastolic	
Day	3-day	7-day	3-day	7-day
Monday	130.5±18.5	128.8±17.8	80.8±9.1	79.9±8.7
Tuesday	129.8±19.0	128.7±17.9	80.6±9.7	80.0±9.3
Wednesday	133.9±18.4	132.5±18.0	81.7±8.8	81.0±8.7
Thursday	130.1±18.9	129.0±18.0	80.6±10.2	80.1±10.1
Friday	129.8±19.4	128.3±18.7	80.3±9.4	79.6±8.9
Saturday	131.0±22.2	130.1±21.6	80.4±10.1	80.1±9.8
Sunday	131.4±20.5	129.6±19.2	80.2±9.4	79.3±9.1
p	0.15	0.11	0.66	0.55

Data are shown as mean ± SD. P values are for ANOVA. 428 participants initiated their blood pressure measurements on Monday, 322 on Tuesday, 296 on Wednesday, 268 on Thursday, 223 on Friday, 156 on Saturday and 159 on Sunday.

5.2.4 Weekday-weekend blood pressure differences

The daily BP values, irrespective of the initial day of measurement, were also examined (Table 12). Small but significant within-subject BP differences were observed from one day of the week to the next ($P<0.001$ for systolic and diastolic). Weekday-weekend BP differences, with the weekend defined as a 3-day measurement period from Friday to Sunday in accordance with the guidelines, were also analyzed (Table 12). BP was marginally lower during the weekend than the weekdays (129.2 ± 18.8/79.8 ± 9.4 vs. 129.8 ± 18.7/80.3 ± 9.3mmHg; $P<0.001$). The highest BP values were measured on Monday, 130.4 ± 19.8/80.6 ± 9.9mmHg on average.

Table 12. Average blood pressure irrespective of the initial day of the week of measurement.

	Blood pressure					
	Systolic			Diastolic		
Day	One-day*	Mon-Thu vs. Fri-Sun**	Sat-Sun vs. Mon**	One-day*	Mon-Thu vs. Fri-Sun**	Sat-Sun vs. Mon**
Mon	130.4±19.8		130.4±19.8	80.6±9.9		80.6±9.9
Tue	130.0±19.7	129.8±18.7		80.4±9.9	80.3±9.3	
Wed	129.5±19.4			80.1±9.8		
Thu	129.2±19.7			80.0± 9.8		
Fri	129.4±19.7			80.0±9.9		
Sat	128.7±19.2	129.2±18.8	129.0±18.9	79.5±9.8	79.8±9.4	79.6±9.6
Sun	129.3±19.7			79.8±10.0		
p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Data are shown as mean ± SD. P values are for ANOVA* or paired t-test**. 428 participants initiated their blood pressure measurements on Monday, 322 on Tuesday, 296 on Wednesday, 268 on Thursday, 223 on Friday, 156 on Saturday and 159 on Sunday.

The difference between weekend and weekday BP was also examined in subgroups of sex, age, employment, alcohol consumption, smoking, and use of antihypertensive medication (Table 3/Study II). Higher systolic and diastolic BP values were obtained during weekdays, especially on Mondays than during the weekend in all subgroups. In the subgroup analyses, the only significant difference between groups was observed in the employed versus the unemployed. Among the employed, the diastolic BP decrease from weekdays to weekend was significantly greater than among the unemployed (0.8 vs. 0.3mmHg; P =0.01). Additionally, the systolic/diastolic BP surge was more substantial from Saturday–Sunday to Monday among the employed than among the unemployed (1.8/1.3 vs. 0.8/0.7 mmHg; P= 0.02/0.01).

5.3 The number of measurement days needed to reliably assess home blood pressure variability (Study III)

5.3.1 Characteristics of the study population

Characteristics of the participants are reported in Table 13.

Table 13. Baseline characteristics of study III participants.

Characteristic	
n	1706
Age, years	56.5 ± 8.5
Men, %	45.7
Body mass index, kg/m^2	27.3 ± 4.4
Smokers, %	18.4
Diabetes, %	6.3
Use of antihypertensive drugs, %	22.8
Hypercholesterolemia, %	29.6
CVD history, %	7.7
Probable sleep apnea, %	10.7
Alcohol use, g/week	74.6 ± 142.0
Alcohol use as a categorical variable	
Non-users %	31
Moderate users, %	60.7
Excessive users, %	8.3

Data are shown as mean ± SD or percentage. CVD, cardiovascular disease.

5.3.2 Association between home blood pressure variability and adverse cardiovascular outcomes; sufficient number of measurement days based on prognostic data

The mean follow-up time was 11.8±3.1 years. During that time frame, 216 adverse cardiovascular events occurred. Table 14 shows that systolic morning day-to-day home BPV, when assessed from 3 through 7 measurement days, had a significant association with incident cardiovascular events. In contrast, diastolic morning day-to-day home BPV was associated with incident cardiovascular events only when the whole measurement period of 7 days was included. Figure 2/Study III presents

the relationship between morning systolic and diastolic day-to-day home BPV calculated from 3, 5, and 7 measurement days. On the other hand, systolic day-to-day home BPV, calculated from the averages of 4 daily BP values (2 in the morning and 2 in the evening), did not display any significant association with the incidence of cardiovascular events (Table 2/Study III), whereas diastolic day-to-day variability calculated from the averages of 4 daily BP values of all 7 days was predictive of events. Evening day-to-day home BPV assessed based on 2 through 7 measurement days was not predictive of future cardiovascular events (Table 3/Study III). The model C statistic did not significantly improve when the number of measurement days was increased to more than 3 (Table 2/Study III).

Table 14. Relation of home blood pressure variability (based on daily average blood pressures) and cardiovascular events.

	Number of measurement days for morning blood pressure				
BP parameter	3	4	5	6	7
Syst					
Mean SD	129.0±20.0	128.3±19.7	127.9±19.5	127.6±19.3	127.4±19.1
CV SD	5.6±3.6	5.9±3.3	6.0±3.1	6.1±2.9	6.1±2.8
HR for Mean	1.019***	1.019***	1.020***	1.020***	1.021***
HR for CV	1.039*	1.057**	1.051*	1.063**	1.057*
C statistic	0.737 (ref)	0.738	0.737	0.737	0.737
Diast					
Mean SD	80.7±10.0	80.3±9.9	80.2±9.8	80.0±9.7	79.9±9.6
CV SD	5.0±3.5	5.3±3.1	5.3±2.9	5.5±2.8	5.5±2.7
HR for Mean	1.038***	1.039***	1.042***	1.043***	1.045***
HR for CV	1.033	1.037	1.031	1.042	1.058*
C statistic	0.738 (ref)	0.738	0.739	0.739	0.742

BP, blood pressure; HR, hazard ratio; SD, standard deviation; CV, coefficient of variation. Confidence intervals for the hazard ratios are shown in Table 2/Study III. All Cox models were adjusted for age, sex, smoking, diabetes, antihypertensive medication, hypercholesterolemia, history of cardiovascular disease, body mass index, sleep apnea, alcohol consumption, and mean systolic or diastolic home blood pressure. 216 cardiovascular events occurred during follow-up. *P<0.05; **P<0.01; ***P<0.001.

When BPV indexes were based on individual measurements, instead of daily or morning BP averages, the results were fairly similar (Table 4/Study III). Systolic

morning BPV based on 3 through 7 measurement days was a predictor of cardiovascular events. In contrast, diastolic morning BPV was significantly associated with events only when based on measurements of all 7 days. The model C statistic did not significantly improve when the number of measurement days was increased to more than 3. Systolic day-to-day BPV based on both morning and evening readings was inconsistently associated with cardiovascular events when variability indexes were formed based on readings from 3, 4, and 6 days. On the contrary, diastolic BPV indexes based on BP values of 6 and 7 measurement days were a significant predictor of outcomes. A significant association between evening BP variability and cardiovascular outcomes was only observed when 7-day diastolic BP variability based on individual measurements was used as the exposure variable (Table 3/study III).

The analyses were also performed using BP variability indexes that were calculated based on only the first measurements of every morning and evening. BP levels of the first measurements were, in general, higher than the average levels of the two consecutive readings, and BP variability was also higher (Table 5/Study III). The hazard ratios for cardiovascular events were, in general, slightly higher when BP variability was based on the average of two BP values than in those analyses based on only the first BP reading.

5.3.3 Classification of participants according to the level of home blood pressure variability

When examining the influence of increasing the number of measurement days on the reclassification of the participants into normal or increased BPV category, we found that 9−12 % had increased systolic BPV and 4−6 % had increased diastolic BPV, depending on the number of measurement days used in the analysis (Table 6/Study III). Agreement between consecutive measurement days in classification improved with the increasing number of measurement days. Substantial agreement was reached after the fourth measurement day (κ=0.69 for systolic and κ=0.68 for diastolic), and excellent agreement was reached (κ = 0.85 for systolic and κ = 0.84 for diastolic) after the sixth measurement day.

5.4 Outcome-driven thresholds for increased home blood pressure variability (Study IV)

5.4.1 Characteristics of the participants

Baseline characteristics of the study participants are shown in Table 15 and home BPV in table 16. The sample of the Study IV included 3543 Asians and 2695 Europeans. BP measurements were available for 6.8±0.7 days in Ohasama, 6.3±1.3 days in Tsurugaya, 3.0±0.0 days in Didima, and 6.8±0.6 days in Finland.

Table 15. Characteristics of study IV participants overall and by cohort.

Characteristic	Overall	Cohort			
		Ohasama	Tsurugaya	Didima	Finn-Home
n	6238	2775	768	634	2061
Age, years	60.0±12.9	59.2±12.7	75.3±4.6	54.1±17.7	57.1±8.5
Women, n (%)	3518(56.4)	1629(58.7)	410(53.4)	372(58.7)	1107(53.7)
Smokers, n (%)	1317(21.1)	586(21.1)	96(12.5)	159(25.1)	476(23.1)
BP lowering medication use, n (%)	1385(22.2)	510(18.4)	319(41.5)	92(14.5)	464(22.5)
BMI, kg/m^2	25.2±4.1	23.4±2.9	23.9±3.3	27.0±4.3	27.4±4.5
Serum total cholesterol, mmol/l	5.4±1.1	5.0±0.9	5.3±0.9	5.1±0.4	6.1±1.1
Diabetes, n (%)	528(8.5)	252(9.1)	119(15.5)	29(4.6)	128(6.2)
CVD history	640(10.3)	211(7.6)	125(16.3)	58(9.2)	246(11.9)

Data are presented as mean ± SD or n (percentage). BMI, body mass index; CVD, cardiovascular disease.

Table 16. Home blood pressure variability in study IV participants.

BP parameter	Overall	Cohort			
		Ohasama	Tsurugaya	Didima	Finn-Home
Systolic					
Mean, mmHg	128.7±19.0	125.3±15.8	141.1±20.2	125.5±21.0	129.5±19.9
SD	8.8±4.4	8.4±4.0	9.6±4.9	8.8±5.8	9.1±4.3
CV	6.8±3.3	6.7±3.0	6.8±3.3	7.0±4.5	7.0±3.1
VIM	8.8±4.2	8.4±3.8	9.6±4.7	8.8±5.7	9.1±4.0
ARV	9.8±5.4	9.3±4.9	10.4±5.6	10.9±7.7	9.7±4.8
Diastolic					
Mean, mmHg	77.3±10.4	75.3±10.2	77.5±10.4	74.6±9.9	80.8±10.0
SD	5.7±3.2	6.3±3.0	5.2±2.9	5.5±4.5	5.2±2.8
CV	7.5±4.1	8.4±4.1	6.8±3.6	7.4±5.6	6.4±3.4

VIM	5.7±3.1	6.3±3.0	5.2±2.8	5.5±4.2	5.2±2.8
ARV	6.3±3.9	6.9±3.6	5.7±3.3	7.0±6.3	5.6±3.1

BP, blood pressure; SD, standard deviation; CV, coefficient of variation; VIM, variability independent of the mean; ARV, average real variability.

5.4.2 Effect of increased home blood pressure variability on occurrence of cardiovascular events

The mean follow-up was 8.3 years in the Study IV and during the follow-up, 304 deaths due to a cardiovascular cause and 715 cardiovascular events occurred. The four systolic and diastolic home BPV indexes, SD, CV, VIM and ARV, were all associated with deaths of any cause, cardiovascular deaths, cardiovascular events, and strokes in multivariable-adjusted Cox regression models (Table 17). In Cox models including systolic or diastolic SD of BP or systolic VIM or ARV of BP, no association was found between BPV and cardiac events; the other variability indexes, however, were related to cardiac events. The quadratic terms formed of the variability indexes, were not statistically significant ($P \geq 0.06$, data not shown) when included in the models to test for possible nonlinearity. Additionally, in a subset of 5980 individuals with office BP data available, adding systolic/diastolic office BP average as a covariate into the models did not substantially alter the results (Table S1/Study IV in the Data Supplement). The association between certain variability indexes and cardiac events became nonsignificant due to the smaller sample size.

Table 17. Cardiovascular event risk per 1-SD increase in home BPV.

BPV index	Outcome	Systolic BP HR (95% CI)	Diastolic BP HR (95% CI)
SD	All-cause mortality	1.13(1.06−1.20)***	1.14(1.07−1.22)****
	CVD mortality	1.15(1.04−1.28)**	1.21(1.10−1.33)****
	CVD events	1.12(1.04−1.19)**	1.12(1.05−1.20)***
	Cardiac events	1.10(0.98−1.23)NS	1.11(0.99−1.24)NS
	Stroke events	1.14(1.04−1.25)**	1.13(1.03−1.24)*
CV	All-cause mortality	1.13(1.06−1.21)***	1.15(1.08−1.22)****
	CVD mortality	1.17(1.06−1.30)**	1.22(1.11−1.34)****
	CVD events	1.13(1.05−1.21)***	1.14(1.07−1.23)***
	Cardiac events	1.12(1.003−1.26)*	1.13(1.004−1.27)*
	Stroke events	1.14(1.04−1.25)**	1.14(1.04−1.26)**
VIM	All-cause mortality	1.13(1.06−1.21)***	1.14(1.07−1.21)****
	CVD mortality	1.17(1.05−1.30)**	1.21(1.10−1.33)****
	CVD events	1.13(1.05−1.21)***	1.13(1.05−1.21)***
	Cardiac events	1.12(0.999−1.25)NS	1.12(1.003−1.26)*
	Stroke events	1.14(1.04−1.26)**	1.12(1.02−1.23)*
ARV	All-cause mortality	1.13(1.06−1.20)***	1.14(1.07−1.21)****
	CVD mortality	1.13(1.02−1.25)*	1.20(1.10−1.31)****
	CVD events	1.10(1.02−1.17)*	1.12(1.05−1.20)***
	Cardiac events	1.09(0.98−1.23)NS	1.12(1.003−1.25)*
	Stroke events	1.11(1.01−1.23)*	1.11(1.01−1.22)*

BPV, blood pressure variability; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; SD, standard deviation; CV, coefficient of variation; VIM, variability independent of the mean; ARV, average real variability. During the follow-up, 832 deaths of any cause, 304 cardiovascular deaths, 715 cardiovascular events, 243 cardiac events, and 399 stroke events occurred. Hazard ratios are estimated from adjusted Cox models (adjusted for cohort, sex, age, body mass index, smoking status, diabetes status, use of antihypertensive medication, total serum cholesterol, history of cardiovascular disease, and mean systolic/diastolic home blood pressure). * indicates P<0.05, ** indicates P<0.01, *** indicates P<0.001, **** indicates P<0.0001; NS, nonsignificant.

The C statistic for cardiovascular events increased by 0.003/0.002 (P=0.02/0.18) and the C statistic for cardiovascular mortality by 0.003/0.004 (P=0.02/0.01) when CV of systolic/diastolic BP was added into the Cox regression models that in-

cluded the traditional cardiovascular risk factors. Changes in integrated discrimination improvement and net reclassification improvement were not statistically significant (Table 3/Study IV).

5.4.3 Thresholds for increased blood pressure variability based on prognostic data

Table 18, and Table 4/Study IV and Figure/Study IV show risk of cardiovascular disease by deciles of CV. Among the participants whose BPV exceeded the 90th percentile (systolic CV>11.0 or diastolic CV>12.8), the risk of cardiovascular mortality and events was significantly greater than the overall risk for the whole study population. The lowest cardiovascular disease risk was observed when BPV was in its third or fourth decile. Having a CV of BP above the 90th percentile was associated with cardiovascular events in most subgroups by age, sex, ethnicity, prevalent cardiovascular disease, and use of antihypertensive medication. No significant interactions were observed between these factors and BPV (Table 5/Study IV).

Table 18. Relation between home blood pressure variability divided into deciles and cardiovascular deaths.

	CV range		Cardiovascular death, HR (95 % CI)	
Decile of CV	Systolic	Diastolic	Systolic	Diastolic
1	0−3.3	0−3.3	1.04 (0.73−1.50)	0.86 (0.56−1.32)
2	3.4−4.3	3.4−4.2	1.26 (0.90−1.77)	1.29 (0.88−1.90)
3	4.4−5.0	4.3−5.0	0.55 (0.33−0.90)*	0.74 (0.47−1.15)
4	5.1−5.6	5.1−5.8	0.92 (0.62−1.37)	0.54 (0.33−0.87)*
5	5.7−6.3	5.9−6.6	0.93 (0.64−1.36)	1.33 (0.96−1.86)
6	6.4−7.1	6.7−7.5	1.05 (0.75−1.48)	0.76 (0.52−1.09)
7	7.2−8.0	7.6−8.6	1.03 (0.74−1.44)	1.24 (0.89−1.72)
8	8.1−9.1	8.7−10.2	1.04 (0.74−1.46)	0.86 (0.60−1.24)
9	9.2−10.9	10.3−12.7	0.86 (0.62−1.19)	1.15 (0.85−1.56)
10	11.0−37.7	12.8−43.3	1.66 (1.27−2.17)**	1.84 (1.42−2.37)**

CV, coefficient of variation; HR, hazard ratio, CI, confidence interval. The risk of events in each group, defined by deciles of home blood pressure variability, was assessed with multivariable-adjusted Cox models while using the overall risk in the whole population as reference. The models were adjusted for cohort, sex, age, body mass index, smoking status, diabetes status, use of antihypertensive medication, total serum cholesterol, history of cardiovascular disease, and average systolic/ diastolic home blood pressure. *P<0.05, ** P<0.001.

5.4.4 Participants with increased blood pressure variability

The risk of cardiovascular diseases was increased only in the highest decile of CV of HBP, and therefore, we compared these individuals with those who had a lower BPV (Table S2/Study IV). Individuals with the highest systolic/diastolic BPV were more likely to be older (P<0.0001/0.01), to be women (P<0.0001/<0.0001) and to have a cardiovascular disease history (P=0.001/0.002). In addition, individuals in the 10th decile of diastolic BPV had lower serum total cholesterol (P<0.0001), BMI (P<0.0001), and systolic (P=0.0002) and diastolic BP (P<0.0001). The participants of the Didima substudy were over-represented in the 10th decile of systolic BPV, whereas those of Ohasama and Didima substudies were over-represented in the 10th decile of diastolic BPV (Table S2/study IV).

5.4.5 Sensitivity analyses

In sensitivity analyses, excluding one cohort at a time did not significantly change the results (Tables S3/Study IV and S4/Study IV). In addition, we also repeated the main analyses of relations between BPV, assessed either as continuous or categorical variable (Tables 2/Study IV and 4/Study IV), by including only individuals with at least 7 days of BP measurements, which was possible in the Ohasama, Tsurugaya, and Finnish cohorts because of the sufficient number of measurement days (Tables S5/Study IV and S6/Study IV), and by including only the first 3 days of measurement in all cohorts (Tables S7/Study IV and S8/Study IV). Including in the analyses only those participants with the full 7 measurement days available did not markedly alter our results, but for 3-day BPV, no association with stroke was found (Table S7/Study IV).

6 DISCUSSION

6.1 Agreement between ambulatory, home and office blood pressure variability (Study I)

In Study I, BP variabilities measured with ambulatory, home, and office methods, were only weakly correlated each other, irrespective of which variability index was used. Slightly higher correlations between the three methods were observed for variability indexes SD, MMD and ARV than for VIM and CV. Additionally, the agreement on diagnoses of extreme variability between different measurement methods is poor.

There are few earlier studies that have compared ambulatory, home, and office BPV. As far as we are aware, no previous study has compared all three methods simultaneously. Imai et al. compared home and ambulatory BPV among a Japanese unselected population. They used SD and CV as variability indexes. The relationships between systolic/diastolic morning home and ambulatory BPV were fairly weak (r=0.21−0.31/0.07−0.14) in their untreated participants as was also the case in our study (27). The Ohasama investigators also found that the correlations between variability indexes were stronger in individuals who were not treated with antihypertensive drugs than in their treated counterparts. Another study carried out by Wei et al. with 256 untreated Chinese also investigated the relationships between beat-to-beat, ambulatory, and home measurements using ARV, MMD and VIM as BPV indexes (273). In that study, the correlation coefficients for systolic home and ambulatory BPV were marginally weaker than those obtained in our population: 0.15 for ARV, 0.17 for MMD and 0.13 for VIM, compared with 0.26, 0.28 and 0.18 in our study (Table 3/Study I). In another study by Muntner et al., the correlations between office visit-to-visit variability and ambulatory variability (SD and ARV were studied in 174 individuals. The correlation coefficients were low: 0.17/-0.13 between ARV of day-night and office visit-to-visit variability and 0.25/0.02 between SD of day-night and office visit-to-visit variability (274).

One abstract published by Nasothimiou et al., compared of BPV as assessed with home, office and ambulatory measurements (275). In this study with 144 untreated hypertensives, a significant association was observed between SD of home and ambulatory BP measurements. The correlation coefficients were 0.40/0.30 between home and 24-hour ambulatory BP SD and 0.35/0.23 and 0.42/0.35 between home vs. awake ambulatory and home vs. asleep ambulatory SD, indicating somewhat stronger inter-method correlations than in the other studies mentioned above.

BPV has been studied actively after being recognized as an independent risk factor for adverse cardiovascular events (1,2,80). However, in most studies that have examined BPV, the type of variability has not been taken into account. The results of the Study I show only weak associations between different measurement methods of BPV, which reinforces the hypothesis that BPV is a complex phenomenon with short- and long-term variability probably having somewhat different backgrounds. These weak associations were also replicated in the subgroups according to cohort, sex, age, and BMI.

Shorter-term changes of BP are caused by physiological factors such as elasticity of arteries, sympathetic nervous system activity, emotional stress, and humoral factors like angiotensin and nitric oxide (276). These shorter-term fluctuations can be detected by ambulatory monitoring in which the intervals between consecutive measurements are relatively short. An individual's BP values are higher at work than at home among both normotensive and hypertensive office employees (277). Cavelaars et al. observed that in hypertensive persons, the effect of physical activity on systolic/diastolic BP was 11.6/7.0 mmHg when the activity was increased from very low to a moderate level. This reaction was more pronounced in older and overweight subjects (278). The emotional state also affects shorter-term BPV; anxiety and anger are associated with greater (279,280) whereas happiness is associated with lesser BPV (280).

Weakened baroreflex function and increased large artery stiffness and decreased compliance have been shown to be responsible for long-term BPV (281,282). Office and home BP measurements, with longer intervals between consecutive readings, are probably not able to capture all the underlying cardiovascular control mechanisms. Long-term BPV, assessed with office and home measurements, can also be explained by behavioral changes.

Several determinants of day-to-day home BPV have been recognized. Increased SD and CV of home BP were associated with female gender, older age, alcohol use, and higher systolic BP level in an unselected Japanese population (67). In the Finn-Home study with Finnish participants, older age, excessive alcohol consumption, and a higher BP level were associated with greater day-to-day BPV (66). Regarding office BPV, the related factors seem to be partly the same as for home BPV. Office visit-to-visit variability of systolic BP was associated with female gender, age, diabetes and peripheral vascular disease in the Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA) study. Its effect on stroke risk was most marked at young ages (1). In another study, the National Health and Nutrition Examination Survey (NHANES), an association was observed between increased systolic office BPV and older age, higher total cholesterol levels, diabetes, elevated CRP, reduced eGFR (estimated glomerular

filtration rate), albuminuria, physical inactivity, a history of myocardial infarction or stroke, use of antihypertensive medication, mean pulse pressure, and mean systolic BP (45). It seems that BP level and advanced age are the most pronounced determinants of increased BPV.

In addition to the poor agreement between different BPV measurement methods, there are also other challenges. First, the repeatability of measurements is often poor with all measurement methods used to assess BPV (283). Moreover, the rather small number of home and office measurements obtained can impair the reliability of these methods in the assessment of BPV. One challenge is also the greater amplitude of ambulatory variability; for instance, this strongly depends on physical activity or inactivity throughout the day. In addition, reference values for normal and abnormal BPV are lacking.

6.2 The impact of the day of the week on home blood pressure

According to the results of Study II, a 7-day home BP measurement period can be initiated on any given day of the week. However, a 3-day measurement, which is the minimum number of measurement days accepted by the guidelines, may be influenced by the measurements conducted on the initial day of the week. This is especially true among employed individuals. BP seems to be lower during weekends than on weekdays, irrespective of the initial day of the 7-day home BP monitoring.

As far as we are aware, no trials assessing how the day of the week affects home BP have been published before. The BP difference between workdays and non-workdays was examined with repeated home BP measurement in a Japanese study with 700 participants (284). No clinically significant differences were observed between the BP levels of workdays and non-workdays. The same observation emerging from our Study II was made also by the authors of the Japanese study i.e. that home BP typically declines during repeated home measurements.

Some studies have examined the impact of the day of the week on office BP. In a study examining reproducibility of office visit-to-visit BPV, Howard et al. found that the day of the week of the measurement was not a significant determinant of the BP values (285). In that study, 25 % of the participants had their first BPs measured on the same days of the week. The BPV of these individuals did not significantly differ from those whose BP was measured on various days of the week. Analyses among elderly and among working-age patients provided similar results. However, the study participants were individuals who had experienced a

minor ischemic stroke or transient ischemic attack, and therefore, the results may not be generalizable to other populations.

Home-measured BP tends to decline during a multiple-day monitoring period, an observation reinforced in our study. The decrease of home BP was slight but significant in a previous analysis of the Finn-Home study. Most of the decrease occurred between the first two days of measurement (267). Moreover, Stergiou et al. have shown that in hypertensive persons, BP values on the first day of home monitoring are the highest and most unstable. Therefore, they recommended discarding these first day readings (286). In a third study performed by Hond et al. in a hypertensive population, the first day BP readings were higher than those measured on the following days. Thus, their results were consistent with other studies (41). These results emphasize the possible need to discard the measurements taken on the first day, if the BP level is significantly higher on the first than on the other days (287).

Some confounding factors need to be considered in the assessment of the BP profile or day-to-day variations in BP during a week. In both normotensive and hypertensive individuals, BP measured at work has been shown to be higher than BP evaluated at home (277). As shown in this study, BP is also higher on working days than during leisure time in employed persons. The lower level of physical and mental stress during the weekends than during weekdays is probably the explanation for this finding. Moreover, different sleep quality between weekdays and weekends might, at least to some extent, explain these results, because sleep deprivation is associated with increased BP (288). Additionally, people may have time to comply more accurately with the recommended 10 minutes of rest prior to the measurements during the weekend. Thus, BP readings could be lower in the weekends, because BP values have been shown to decline up to 12/4 mmHg during a rest of 16 minutes in the sitting position (289). Excessive alcohol consumption is also a determinant for higher systolic/diastolic home BPV (66). Day-to-day variations in alcohol amounts consumed may therefore explain the differences in BP levels measured on different days of the week (290). Among people of working age, this phenomenon might be even more pronounced, because they presumably use alcohol more than the elderly and probably consume more alcohol during the weekends than on weekdays. In addition to the variation in alcohol consumption according the day of the week, food intake also tends to vary during the week. In a Finnish study, consumption of energy and meat products has been shown to be highest on Saturday and Sunday, which could affect the BP profile because of the different amounts of salt consumed. However, even though the salt and alcohol intakes are higher during weekends, the BP lowering effects of leisure time seem to be greater than the BP increasing effects of nutrients, as reinforced by our study.

The day-to-day variations in BP were rather small in our representative adult population. However, a slight trend of a BP surge on Mondays seems to occur. Murakami et al. studied the BP variations during a week in 135 community-dwelling participants with ambulatory BP monitoring. They observed that the morning BP surge, i.e. a peak in BP early in the morning, was greatest on Mondays (291). The clinical relevance of this "Monday surge" is unclear. However, many studies have observed an increase in the incidence of cardiovascular events on Mondays and in the morning (292-295). The BP peak detected on Monday could explain this phenomenon to some extent (296).

6.3 The number of measurement days needed to reliably assess home blood pressure variability

The results of the population-based Study III suggest that 3 measurement days, with BP measured two times on one occasion in the morning, are sufficient for estimating the increased cardiovascular risk related to systolic day-to-day home BPV. After increasing the number of measurement days from three to seven, only marginally stronger associations was detected between home BP variability and cardiovascular outcomes. In contrast, 7 measurement days may well be required for the assessment of diastolic BPV. The relationships between diastolic home BP variability, evening home BP variability, all-day BP variability, and variability based on the first measurements of the measurement occasions and cardiovascular disease were non-significant or remained significant only after the 6th day of measurement.

As far as we are aware, studies examining the optimal number of BP readings or measurement days needed to assess home BPV are scarce or non-existent. Kikuya et al. briefly mention in a home BP study that 10 home measurements could be sufficient for estimating home BPV. This finding was, however, based on the cross-sectional analysis in a small sample of 153 individuals. In that sample, the 10-day SD of home BP was not significantly different from the 30-day SD (194). Home BP measurement is generally well accepted by the patients and makes it possible to obtain a great number of readings. Patient compliance, however, tends to decrease with a larger number of measurements (297). Thus, the requirement that there should be 10 measurement days for assessing home BPV may prove challenging in a real-life setting.

According to the results of Study III, only slight improvement occurred in the predictive significance of morning systolic day-to-day home BPV when more than 3 measurement days were included in the variability indexes. In contrast, when assessing the significance of diastolic morning day-to-day BPV as a cardiovascular

risk factor, 7 measurement days may be needed. Our observations are in line with the findings of previous studies that have investigated the optimal number of measurement days for assessing home BP level, instead of home BPV. The prognostic value of home BP has been shown to increase with an increasing number of measurements in the Didima (42) and Finn-Home (297) studies. Most of this increase, however, occurred during the first 3 measurement days. On the other hand, in the Ohasama study, no threshold for the number of home BP measurements needed in stroke risk assessment could be found, and thus the investigators have suggested that as many measurements as possible should be obtained (298). Data from Study III and other outcome-based studies suggest that a 7-day measurement period of systolic and diastolic BP, or a period of at least 3 days for systolic BP, is sufficient for a thorough image of an individual's home BP level and home BPV.

The association to cardiovascular outcomes was greater with morning day-to-day home BPV than with BPV assessed from evening readings or based on individual measurements. Previous studies have yielded similar results (2). The observation that morning day-to-day BPV was the most predictive for outcomes could result from the more pronounced incidence of cardiovascular events that take place during the morning than during the evening (299,300). Additionally, morning BPV rather than evening BPV may be a better indicator of some factors that correlate with an increased cardiovascular risk, such as excessive alcohol use (301), sleep loss (302), or obstructive sleep apnea (303). Study III findings therefore suggest that morning home BP measurements should be preferable when assessing home BPV and the cardiovascular risk related with it.

6.4 Outcome-driven thresholds for increased home blood pressure variability

Many of the diagnostic thresholds used in clinical medicine to define disease are arbitrary. However, these thresholds are necessary to allow clinicians to separate normal and abnormal findings from each other. As far as we are aware, no thresholds have previously been proposed for increased home BPV. The sample of Study IV is large, international, and population-based. The results reinforce the ability of increased home BPV to have a predicting role cardiovascular disease. The results of Study IV also suggest that cardiovascular risk is pronounced when systolic CV of day-to-day HBP is ≥11.0 or diastolic CV ≥12.8. Nonetheless, the incremental predictive value in risk prediction achieved by adding BPV to a regression model with conventional cardiovascular disease risk factors is modest; it seems that the BP level is still more crucial than BPV in assessment of cardiovascular risk.

The need to standardize the concept of normal or increased BPV has already been noted in some hypertension guidelines. However, until now, no cutoff points have been available for this categorization (6,7). The results of Study IV could help clinicians identify those individuals who may be at an increased cardiovascular disease risk. Our proposed thresholds still apply only to home-measured day-to-day BPV, and definition of thresholds for other methods of BPV measurements, the ambulatory and office monitoring, needs further research. In addition, a major difficulty hindering the widespread use of BPV in clinical practice is that we do not know the optimal way to manage patients with increased BPV. BPV could possibly be reduced through lifestyle interventions. For example, heavy alcohol use increases BPV, and probably by reducing the alcohol use, BPV would also diminish (304). In addition to lifestyle factors, certain antihypertensive medications, used as monotherapies or combinations, could be more effective than others to reduce BPV. Calcium channel blockers were shown to reduce office visit-to-visit BPV in the Anglo-Scandinavian Cardiac Outcomes Trial, whereas an opposite effect was found for β-blockers (36). Moreover, amlodipine and indapamide were reported to lower ambulatory BPV more than candesartan in the Natrilix SR versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients study (305). In contrast, Asayama et al. (234) observed no difference between the effects of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers on home BPV. It seems that a long-acting calcium channel blocker, amlodipine, reduces BPV more effectively than short-acting calcium channel blockers (240). Clearly, clinical trials will be needed to determine whether reducing BPV provides any incremental cardiovascular protection over BP reduction.

Long-term visit-to-visit variability of office BP, mid-term variability of home BP, and short-term variability of 24-hour ambulatory BP are predictors of both stroke (1,170,194,200) and cardiovascular events (3,5,306). The quadratic term for BPV indexes were not statistically significant in the Cox models in Study IV ($P \geq 0.06$). Nonetheless, our results suggest that the association between BPV and cardiovascular outcomes may not be completely linear. In Study IV, the risk of cardiovascular events increased only in the highest decile of BPV, although it was inconsistently lower in the third and fourth deciles. These findings also emphasize the need for thresholds for BPV.

Another new finding emerging from Study IV was that BPV was consistently related with different cardiovascular end points. According to the Ohasama cohort, home BPV was a predictor of stroke, but no significant association was found for cardiac events (194). A study based on the Finn-Home cohort, in turn, provided opposite results (2). These inconsistencies are most likely explained by the differ-

ent incidences of cardiovascular event subtypes. In Europe, the incidence of coronary heart disease is markedly higher than in Asia, whereas the opposite is true for strokes (307,308). In the large sample of Asians and Europeans in Study IV, increased BPV was related with both cardiac and stroke morbidity.

Several determinants have been previously found for increased home BPV. In the Ohasama and Finn-Home populations, high home BP level, old age, and excessive alcohol use were associated with increased day-to-day BPV (66,67). Addtitionally, the Ohasama investigators have shown that low heart rate, elevated home heart rate variability, female sex, and a lack of antihypertensive treatment are determinants of increased home BPV (67). Previously, antihypertensive drugs have been considered as an important driver of the relation between BPV and cardiovascular outcomes (70). Thus, the effects of antihypertensive medications are a relevant aspect when assessing the determinants of BPV. In the large individual-level meta-analysis conducted in Study IV, increased BPV was associated with cardiovascular disease occurrence in both treated and untreated individuals, and no between-group interaction was observed. Additionally, we detected a correlation between increased BPV and increased cardiovascular disease risk in both sexes, in younger and older, in those with and those without prevalent cardiovascular disease, and among Asians and Europeans. These findings suggest that home BPV is a cardiovascular disease risk factor in nearly all populations.

Home self-measurement of BP is a reliable method for BPV because it provides a large number of BP values that are free from the white-coat effect. There are still a few details that should be taken into account in the interpretation of home BPV. For instance, home BP may be somewhat higher during workdays than during weekends among employed individuals (277). These within-week fluctuations in BP may be caused by differences between weekdays and weekends sleep quality (288), alcohol consumption (290) and salt intake (309).

Moreover, diurnal BP patterns seem to be different between various cultures. In Japanese studies, home-measured morning BP has been observed to be higher than evening home BP (37-40), whereas in Europe, the findings have been opposite (41-44). In certain circumstances, however, such as in patients with obstructive sleep apnea, excessive alcohol use, or prevalent cardiovascular disease, this association between morning and evening BP may be reversed (310).

6.5 Study limitations

6.5.1 Study I

Study I has several limitations. First, since it exploited a cross-sectional design, we could not observe the longitudinal consequences of BPV, which could facilitate interpretation of the results. Second, because no clear cut off points for normal and increase BPV had been previously reported, the limit of extreme BPV was determined arbitrarily in Study I. Third, the physical activity of the participants, which could have influenced especially the results of ambulatory monitoring, was not systematically assessed. Fourth, the participants were young and had severe hypertension, which could impair the generalizability of the study.

6.5.2 Study II

The initial limitation of Study II is that ambulatory BP monitoring was not performed. This could have provided important information of the individuals' daily BP profiles. On the other hand, a 7-day ambulatory BP monitoring would not be feasible in practice. Second, the alcohol consumption was not documented on an exact daily accuracy, which means that the variables used only represent the total alcohol amount consumed. The binge drinking habit, however, usually occurs on weekends and could therefore be an important determinant of increased home BPV. Third, the home BP monitors used in Study II did not have a memory function. Thus, the reliability of the BP values was dependent on the integrity of the participants who self-recorded their readings.

6.5.3 Study III

The possible limitations should be considered in the interpretation of the results of Study III. First, individuals probably adhere to a BP measurement schedule more meticulously in a study setting than in a clinical setting (311). Moreover, people are likely to under-report their BP values, which should always be taken into consideration if individuals self-record their BP (312). Thus, our results are best applicable to individuals who have received guidance on how to accurately measure their BP and who adhere to these instructions. Second, the Study III sample only consisted of Finnish participants, and thus it is unclear how generalizable the results would be to other ethnicities. Third, the home BP monitors used in Study III were not memory equipped. Therefore, the reliability of the BP values obtained

depended on the participants' integrity. Fourth, home BP was measured in the non-dominant arm, although the current home BP measurement guidelines recommend that BP should be measured in the arm with highest BP values (287).

6.5.4 Study IV

Study IV has some limitations. First, the impact of alcohol use, which affects BPV, could not be evaluated (304,313). Second, the home BP measurement protocols were different between the sub-studies. We therefore attempted to minimize the influence of these differences by only using the first measurement of each day in the analysis. Third, data on serum cholesterol levels were lacking in the Didima cohort and we had to extrapolate them from another similar Greek population study (273). Fourth, the validation of cardiovascular outcomes was non-consistent across the subpopulations as some relied on registers whereas others were based on data collected from the participants, their relatives, and the treating physicians. Fifth, the study population consists only of Asian and European individuals, and the results may not be generalizable to other populations. Sixth, the reliability of the results could have improved by split sample validation. However, because the study sample is already split into ten groups, further splitting of the samples would have resulted in excessively small sizes of deciles and the number of events per decile. Additionally, we performed sensitivity analyses by excluding one cohort at a time. A different number of measurement days in the analysis was also tested to increase the validity of our results.

7 CONCLUSIONS

The aims of this thesis were to provide some insights into the optimal methods and schedule for the measurement of BPV, focusing especially on home BPV.

Based on Study I, the agreement between office, home, and ambulatory BPV is poor. BPV measured by different methods seems to reflect different physiological or pathological phenomena. The method of BPV measurement type of variability of interest should be taken into account when investigating an individual's BPV.

According to the findings of Study II, a 7-day home BP measurement period can be started on any given day of the week. However, if the shorter 3-day measurement period is performed, it is recommended to bear in mind that BP readings tend to be at their lowest during the weekend and at their highest at the beginning of the week, especially among the employed. A longer evaluation most likely indicates more reliably the individual's "true" BP level. In our study a 7-day measurement has proven to be more informative than a 3-day measurement because of the lower and more stable BP average obtained.

The results of study III reinforce the proposal that the assessment of BPV is beneficial in cardiovascular risk assessment. HBP measured twice in the morning on at least 3 days for systolic BP and at least 7 days for diastolic BP seems to be sufficient for home BPV assessment in relation to cardiovascular morbidity and mortality in a general population. Nonetheless, the longer duration, i.e. 7 days of systolic and diastolic BP measurements, are needed to minimize patient reclassification into categories of normal and elevated BPV and to ensure the prognostic accuracy.

Home BPV is associated with an increased cardiovascular risk in the general population. In study IV, we observed that a CV of >11.0 for systolic and >12.8 for diastolic morning day-to-day HBP seems to be independently associated with an increased cardiovascular event risk. Clinicians should consider searching for underlying factors, such as excessive alcohol consumption or obstructive sleep apnea, if a patient's home BPV exceeds these thresholds. Further research will be required to clarify the generalizability of these thresholds as well as determining the optimal way to manage individuals with increased BPV. Our findings might, however, help physicians identify individuals with pronounced BPV who may be at an increased risk of cardiovascular disease.

ACKNOWLEDGEMENTS

This series of studies was performed in the Department of Health, National Institute for Health and Welfare and in the Deparment of Medicine, University of Turku. These studies were supported by grants from Urmas Pekkala Foundation, The Paulo Foundation, The Yrjö Jahnsson Foundation, Turku University Foundation, Finnish Cultural Foundation, and The Hospital District of Southwest Finland. These grants are gratefully acknowledged.

I express my deepest gratitude to my supervisor, Docent Teemu Niiranen. Without your continuous and constructive guidance and you being available at all times, I would not have finished this thesis. You have helped me to grow as a researcher and to take responsibility of my work.

Similarly, I wish to thank my other supervisor, Research Professor Antti Jula for all of the discussions that have provided me with new insights into human physiology and epidemiological methodology. Your valuable comments have improved my work numerous times.

I am also extremely grateful to my third supervisor, Docent Jouni Johansson, for always being supportive and friendly towards me. During difficult days, it has been especially crucial.

Pauli Puukka has helpfully directed me to understand the biostatistical phenomena necessary in these studies. Professor Ilkka Kantola is thanked for being a great mentor and Docent Kaj Metsärinne for being a member of the steering group of this thesis.

I want to express my gratitude to Docent Tuula Tikkanen and Docent Hannu Vanhanen who have reviewed this thesis despite their busy schedules. Your comments were constructive and improved the quality of this thesis. Dr. Ewen MacDonald is thanked for the careful linguistic revision of this thesis. I am honoured and grateful to Professor Pirjo Mustonen for accepting the invitation to be my opponent.

Additionally, I want to express my gratitude to all of the participants in the studies and the staff working on the studies. I also thank the IDHOCO consortium and Health 2000 Collaboration. Annika, Arttu, Sam, Ville, Hanna-Maria, Sirpa, and other co-workers, thank you for peer support and cheerful moments.

I also worked as a clinician while completing this thesis. I would like to thank all the senior doctors and other colleagues who have helped and guided me at my work, in Turku City Hospital, Division of Medicine, Turku University Hospital,

Turku Health Centre, Turku Region Joint Emergency Services, and Oncologic Outpatient Clinic and Oncology Ward 1, Turku University Hospital.

I thank all my friends for being there for me. Especially *Porukka* – Hilla, Ilona, Kaisa, Noora, Selmi and Vilma, you are thanked for long-lasting friendships and support in every situation. My godparents are thanked for relaxing moments and discussions. Jouko and Raili, thank you for your support. Antti, Aino, Anna, Marika, Maria, Sirkka, Robert and the Aaltonen family: thank you for your friendship. Laura Tommola, thank you for everything. I also want to thank my previous teachers.

I also owe my gratitude to the Koivuset-Halmiset family. Thank you Mirja and Kari and the others for accepting me as a member of your warm family. Santeri, thank you for being like a brother for me.

I want to express my deepest gratitude to my parents Sirkka and Jukka for encouraging me in my life and for their love and support. My dearest brothers Mammu and Sisu, my heartfelt appreciation goes to you! Thank you for growing up with me and always being there for me. You mean everything to me.

Finally, my warmest thanks belong to you, Sakke. I love you more than anything. Thank you for being there for me.

Turku, November 2018
Eeva Juhanoja

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Annales Universitatis Turkuensis

UNIVERSITY OF TURKU

Painosalama Oy, Turku , Finland 2018

ISBN 978-951-29-7513-6 (PRINT)
ISBN 978-951-29-7514-3 (PDF)
ISSN 0355-9483 (Print) ISSN 2343-3213 (Online)