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To my family

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ABSTRACT

Practical and accurate blood pressure (BP) measurement techniques are needed to ensure adequate diagnostics and treatment of hypertension. Recently, novel monitors have appeared on the market including timer-equipped home monitors and stand-alone noninvasive central BP monitors.

The aim of this study was to clarify how BP measures obtained with these novel measurement methods compare to current measurement methods, and whether they could improve the diagnostics for hypertensive end-organ damage compared with conventional measurements in a cardiovascular substudy (N=290) of the Finnish population-based DILGOM study. Participants underwent 24-hour ambulatory monitoring, office BP measurements, and daytime and night-time home measurements. Hypertensive end-organ damage was assessed with pulse wave velocity (PWV) measurements, carotid intima-media thickness (IMT) and left ventricular mass index (LVMI).

The participants preferred office BP measurement, while ambulatory monitoring was the least acceptable method. Mean night-time BP levels were comparable between ambulatory and home monitoring, and the agreement between the methods in detecting night-time hypertension was substantial. Instead, the agreement in detecting nondipping patterns was weak. Home and ambulatory night-time BP values correlated similarly with end-organ damage, except that there was a slightly stronger correlation between ambulatory systolic BP (SBP) and PWV compared with corresponding home BP. Surprisingly, we found that brachial SBP and pulse pressure were similarly or even more strongly correlated to end-organ damage than the corresponding noninvasive central measures.

To conclude, home night-time monitoring is a convenient, accurate, well-accepted and widely available alternative to ambulatory monitoring in detecting night-time hypertension. In comparison to measurements with conventional office BP, estimated central hemodynamics with a novel stand-alone monitor do not seem to improve the diagnostics of end-organ damage.

KEYWORDS: night-time blood pressure, home blood pressure measurement, central blood pressure, ambulatory monitoring, blood pressure dipping, end-organ damage.

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TIIVISTELMÄ

Kohonneen verenpaineen asianmukaista diagnosointia ja hoitoa tarvitaan käytännöllisiä ja tarkkoja mittausmenetelmiä. Useita uusia mittareita on ilmaantunut markkinoille, mukaan lukien ajastimella varustetut kotimittarit sekä mittarit, joilla pystytään arvioimaan kajoamattomasti sentraalista eli aortan ja suurten suonten verenpainetta.

Väitöskirjan tarkoituksena oli selvittää, miten nämä uudet mittaustavat vertautuvat perinteisiin menetelmiin ja parantavatko ne kohde-elinvaurioiden diagnostiikkaa verrattuna perinteisiin menetelmiin suomalaisessa DILGOM-väestötutkimuksen sydän- ja verisuonitutkimusalaryhmässä (N=290). Tutkimushenkilöille tehtiin verenpaineen vuorokausirekisteröinti, mittaukset vastaanotolla sekä kotona päivä- ja yöaikaan. Verenpaineen pääte-elinvaurioiden arviointiin käytettiin pulssiaallon nopeutta, kaulasuonten intima-media paksuutta ja vasemman kammion massaindeksiä.

Tutkittavat pitivät eniten verenpaineen mittaamisesta vastaanotolla ja vähiten verenpaineen vuorokausirekisteröinnistä. Vuorokausirekisteröinnillä ja kotimittarilla mitatut yölliset verenpainetasot vastasivat hyvin toisiaan ja yhteneväisyys yöllisen kohonneen verenpaineen diagnosoinnissa menetelmien välillä oli huomattavan hyvä. Sitä vastoin verenpaineen poikkeavan päivä-yövaihtelun diagnostinen yhteneväisyys menetelmien välillä oli heikko. Mittausmenetelmästä riippumatta yöllisen verenpaineen yhteys pääte-elinvaurioihin oli samankaltainen lukuun ottamatta pulssiaallon nopeutta, minkä yhteys vuorokausirekisteröinnin kanssa oli hieman kotimittausta vahvempi. Yllättäen olkavarresta mitattu verenpaine oli yhtä hyvin ja osin jopa vahvemmin yhteydessä pääte-elinvaurioihin kuin kajoamattomasti mitattu sentraalinen verenpaine.

Yhteenvetona todetaan, että verenpaineen yöaikainen mittaus kotimittarilla on käytännöllinen, tarkka, miellyttävä ja laajasti saatavilla oleva vaihtoehto verenpaineen vuorokausirekisteröinnille yöaikaisen kohonneen verenpaineen todentamiseen. Kajoamattoman sentraalisen verenpaineen arvioiminen tutkimuksessa käytetyllä helppokäyttöisellä automaattimittarilla ei näytä tuovan lisäetua pääte-elinvaurioiden diagnostiikassa tavanomaiseen vastaanotolla olkavarresta mitattuun verenpaineeseen verrattuna.

AVAINSANAT: yöaikainen verenpaine, kotona mitattu verenpaine, sentraalinen verenpaine, verenpaineen vuorokausirekisteröinti, verenpaineen päivä-yövaihtelu, pääte-elinvaurio.

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Abbreviations

AAMI	Association for the Advancement of Medical Instrumentation
AASK	African American Study of Kidney Disease and Hypertension
ABC-H	Ambulatory Blood Pressure Collaboration in Patients with Hypertension
ACC	American College of Cardiology
AHA	American Heart Association
AOBP	Automated office BP
ANSI	American National Standards Institute
ASE	American Society of Echocardiography
AT	Applanation tonometry
AUC	Area under the curve
BHS	British Hypertension Society
BMI	Body mass index
BP	Blood pressure
CBP	Central blood pressure
CEN	European Committee for Standardization
CI	Confidence interval
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EF	Ejection fraction
ELSA	European Lacidipine Study on Atherosclerosis
ESH	European Society of Hypertension
HDL	High-density lipoprotein
HOT	Hypertension Optimal Treatment
IMT	Intima-media thickness
ISO	International Organization for Standardization
J-HOP	Japan Morning Surge-Home Blood Pressure
J-TOP	Japan Morning Surge-Target Organ Protection
LVH	Left ventricular hypertrophy
LVMI	Left ventricular mass index

MAP	Mean arterial pressure
MAPEC	Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares
NPV	Negative predictive value
OR	Odds ratio
OSA	Obstructive sleep apnea
PAMELA	Pressioni Arteriose Monitorate E Loro
PP	Pulse pressure
PPV	Positive predictive value
PWV	Pulse wave velocity
ROC	Receiver operating characteristic
SAMPLE	Study on Ambulatory Monitoring of Pressure and Lisinopril Evaluation
SBP	Systolic blood pressure
SD	Standard deviation
SHEP	Systolic Hypertension in the Elderly Program
SPRINT	Systolic Blood Pressure Intervention Trial

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Lindroos AS, Jula AM, Puukka PJ, Kantola I, Salomaa V, Juhanoja E, Sivén S, Jousilahti P, Niiranen TJ. Comparison of Acceptability of Traditional and Novel Blood Pressure Measurement Methods. *Am J Hypertens*. 2016 Jun;29(6):679–83.

II Lindroos AS, Johansson JK, Puukka PJ, Kantola I, Salomaa V, Juhanoja EP, Sivén SS, Jousilahti P, Jula AM, Niiranen TJ. The association between home vs. ambulatory night-time blood pressure and end-organ damage in the general population. *J Hypertens*. 2016 Sep;34(9):1730–1737.

III Lindroos AS, Langén VL, Kantola I, Salomaa V, Juhanoja EP, Sivén SS, Jousilahti P, Jula AM, Niiranen TJ. Relation of blood pressure and organ damage: comparison between feasible, noninvasive central hemodynamic measures and conventional brachial measures. *J Hypertens*. 2018 Jun;36(6):1276–1283.

IV Lindroos AS, Kantola I, Salomaa V, Juhanoja EP, Sivén SS, Jousilahti P, Jula AM, Niiranen TJ. Agreement Between Ambulatory and Home Blood Pressure Monitoring in Detecting Nighttime Hypertension and Nondipping Patterns in the General Population. *Am J Hypertens*. 2019 Jul 17;32(8):734–741.

1 Introduction

High blood pressure (BP) i.e. hypertension is the leading risk factor for cardiovascular disease (CVD); in 2016, it was ranked as the leading global risk factor in terms of attributable disability-adjusted life-years for women and the second leading risk factor for men (1). Estimations from population-based studies indicated that 1.39 billion (31.1%) of the world's adult population had hypertension in 2010 when hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or the use of antihypertensive medication (2). Moreover, the prevalence of hypertension is predicted to increase (3). Global hypertension disparities are also on the rise. While from 2000 to 2010 in high-income countries, the prevalence of hypertension decreased by 2.6%, in contrast, a 7.7% increase was reported in low- and middle-income countries (2). To address this issue, the World Health Organization set a global target of a 25% relative reduction in the prevalence of hypertension by 2025, or as a minimum, containment of the hypertension prevalence according to national circumstances (4).

The main reasons for treating hypertension are to prevent end-organ damage, and consequently, cardiovascular, cerebrovascular, or renal disease and eventually, to reduce fatal and nonfatal CVD events. The end-organ damage associated with hypertension includes left ventricular hypertrophy (LVH), chronic kidney disease (CKD), hypertensive retinopathy, increased carotid intima-media thickness (IMT), peripheral arterial disease, increased stiffness of large (conduit) arteries, and brain manifestations including infarctions, microbleeds, and white matter lesions (5).

Currently in clinical practice, BP is measured at the brachial artery by using a conventional mercury sphygmomanometer with a stethoscope, or with an automatic oscillometric BP monitor at the physician's office in either an unattended or attended manner, at home, or with 24-hour ambulatory monitoring. The recent advances in BP monitoring technology include the advent of stand-alone, noninvasive central BP monitors and timer-equipped home monitors. The latter user-friendly devices provide automated triggering of single or multiple night-time BP measurements. Both new measurement techniques have attracted interest after several studies reported that central and night-time BP values are more strongly related to the

cardiovascular risk than either brachial or daytime BP, respectively (6,7). In summary, there is a growing interest in improving risk estimation with these novel monitors. However, it is still unclear whether these novel BP measurement methods offer any clinical benefits over their conventional counterparts.

2 Review of the Literature

2.1 Blood pressure and arterial hemodynamics

2.1.1 Arterial vascular system

BP is the pressure applied by circulating blood on the walls of the vessels which can be divided into two interdependent components: a steady component (mean arterial pressure, MAP) and a pulsatile component (pulse pressure, PP) that fluctuates around MAP peaking at systolic BP (SBP) and nadiring at the diastolic BP (DBP). The large arteries have two functions; to ensure blood flow to the organs and peripheral tissues and to transform a pulsatile flow from the heart into a more steady blood flow. During systole, the left ventricle ejects blood into the aorta. In healthy individuals, the aorta has high compliance, and thus its volume increases in response to a given increase in BP. Then, during diastole, it passively contracts due to its viscoelastic properties and the potential energy stored in the vessel wall turns into kinetic energy pushing the blood from a higher to lower pressure towards the periphery, thus providing continuous perfusion of the organs (8). Propagating blood flow, as well as the BP, decline only slightly in the large or medium-sized arteries, but both parameters fall rapidly as the radius of the vessels decreases in the complex network of small arteries and arterioles (i.e. the resistance vessels). Finally, a very low intraluminal pressure is present in the capillary arteries at the end of the arterial system (Figure 1) (9).

2.1.2 Pulse wave amplification

From the heart towards the periphery, the arteries continuously decrease in diameter and increase in stiffness. When the pulse wave propagates along the arterial system (at a speed of 4–30 m/s), at each discontinuity of the arterial wall (branches, atherosclerotic plaques, and resistance vessels), the incident (forward-travelling) pressure wave may be “reflected” as a retrograde (backward-travelling) pressure wave that travels backward to the heart at the same velocity as the incident wave. Consequently, the observed pressure wave at any given site is the summation of the forward and the reflected wave. As a result of increasing arterial stiffness

and wave reflections, SBP (peak of the waveform) and PP (the difference between SBP and DBP) continuously increase when the pulse wave propagates towards the peripheral arteries. This phenomenon is known as pulse wave amplification (8). Consequently, brachial SBP is higher than SBP measured in the aorta; this has been demonstrated in several studies using intra-arterial catheterization (10–12). In contrast, MAP and DBP remain relatively constant throughout the arteries (10–12). MAP, i.e. the average BP over a cardiac cycle, depends on stroke volume, heart rate, and peripheral resistance, whereas PP depends on the properties of the large arteries and the amplitude and contour of the pressure wave at the point of measurement (8).

The main factors influencing the amplitude and contour of the summation wave of the incident and reflected waves are arterial stiffness, and the amplitude of the wave reflection, which in turn depends on the degree of arterial lumen diameter mismatch and aortic length (8). Moreover, the amplification of SBP and the PP between central and peripheral arteries is not fixed but also vary with age (13,14), posture (10), exercise (11), smoking (13–15), and heart rate (16–21). In a small study conducted with young healthy men, the difference between brachial and central SBP was up to 80 mmHg during exercise (11). Men generally exhibit a larger PP amplification than women (13,14,21). However, the large meta-analysis conducted by Herbert et al. showed that amplification decreases more with age in men than in women, thus the difference between the sexes decreases with age (13). In a large cohort of 10 000 volunteers, the difference between aortic and brachial SBP ranged from approximately nine up to 20 mmHg (14). All in all, it seems that the age-related increase in aortic stiffness and the consequential increase in the forward wave amplitude rather than changes in the wave reflection constitutes most of the increase in SBP and PP evident in advancing age (22).

Finally, different classes of antihypertensive medication seem to have different effects on pulse wave amplification. In a meta-analysis of 24 clinical studies, conventional beta-blockers and diuretics reduced more brachial than central BP. Instead, monotherapy with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, alpha-blockers or spironolactone seemed to reduce both pressures to similar degrees (23).

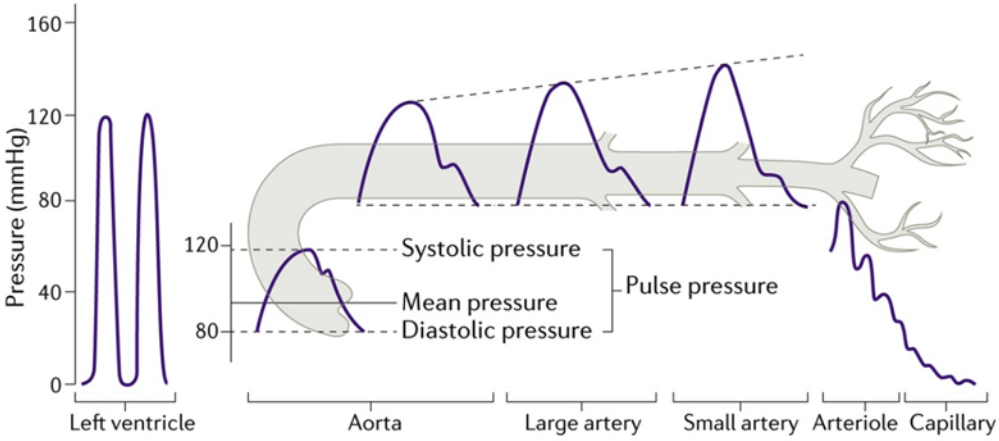

Figure 1. Adapted with permission from Safar, M. E. & Lacolley, P. Disturbance of macro- and microcirculation: relations with pulse pressure and cardiac organ damage. Am. J. Physiol. Heart. Circ. Physiol. 293, H1–H7 (2007), American Physiological Society (9).

2.1.3 Pulse wave velocity and arterial stiffness

The carotid to femoral PWV reflects the viscoelastic properties of the aorta and it is the gold standard method for the assessment of aortic stiffness (24). PWV varies according to structural and transient functional changes in the properties of the arterial wall. Elastase activity increases with age, while elastin synthesis reduces, thus leading to thinning and breakage of elastin of the arterial wall. This results in a decrease in the elastin and collagen ratio leading to arterial stiffening, and consequently to higher PWV. Other causes for vascular structural alterations include some metabolic diseases (chronic kidney disease, diabetes, liver failure, conditions with alterations in calcium metabolism), inflammation, some genetic disorders (Marfan and Ehlers-Danlos syndromes), and hypertension. The main functional factors that affect PWV transiently are alterations in MAP, left ventricular systolic ejection function, and heart rate (8).

2.1.4 Arterial hemodynamics and cardiovascular risk

The transmural pressure of the vascular wall increases in hypertension leading to increased biosynthesis of collagen, alterations in the endothelial function, smooth muscle cell hypertrophy and hyperplasia. These changes alter the mechanical properties of the arterial wall leading to an increase of arterial stiffness and higher PWV which in turn results in larger forward wave amplitude, an earlier arrival of the reflected wave and the reduction of the buffering effect of the aorta and large arteries. Taken together, SBP, PP and cardiac afterload tend to increase while DBP and subendocardial perfusion decrease. Thus, high values of PP might be an expression

of the loss of the viscoelastic properties of the aorta and large elastic arteries (8). More specifically, increased PP is largely related to stroke volume and ventricular ejection in young individuals, whereas the main contributors to high PP are arterial stiffness and enhanced wave reflections in the elderly (25).

Consistent with the above findings, increases in both PP and PWV have been shown to predict CV morbidity and mortality (6,26,27). In the meta-analysis published by Vlachopoulos et al. in multivariable-adjusted models, a one m/s increase in aortic PWV corresponded to a risk for 14%, 15%, and 15% in total CV events, CV mortality, and all-cause mortality, respectively (6). With respect to PP, data from the Framingham Heart Study showed that the risk of suffering an acute coronary event progressively increased with a rise in brachial PP in people over age 50 (26). A similar finding was reported in a large meta-analysis that pooled the results of the European Working Party on High Blood Pressure in the Elderly trial, the Systolic Hypertension in Europe Trial, and the Systolic Hypertension in China Trial (28). Furthermore, in a large longitudinal French study with over 21 000 men, CV mortality was higher in those whose DBP declined while SBP increased as compared with those whose SBP and DBP increased together (29). Thus, the prognostic significance of different BP parameters seems to vary with age. In the study of Khattar et al. which evaluated 546 hypertensive patients, DBP was the strongest predictor of CVD events and mortality in middle-aged hypertension patients, whereas among the elderly SBP and PP were clearly superior to DBP (30).

There are some studies reporting that clinic brachial PP ≥65 mmHg or mean 24-hour ambulatory PP >53 mmHg seem to predict a poor prognosis (31,32). With respect to aortic PP, values of 50 mmHg or above are claimed to predict CVD outcomes (33). However, according to a recent report from the Framingham Study, a mismatch between PP and arterial stiffness is common; almost 40% of the study participants had either low PP with high PWV or vice versa. However, only those with both elevated central PP and PWV carried an increased CVD risk when compared with those with low values of PP and PWV (34).

2.1.5 Hypertensive end-organ damage

Hypertension imposes a stress upon the cardiac wall. To normalize this wall stress within the myocardial fibers, the size of existing cardiomyocytes increases without the corresponding growth in the vascular supply. This kind of hypertrophy enables the heart to pump more forcefully but at the same time, increases oxygen demand of the heart. Although these changes are primarily physiological compensatory mechanisms, the hypertrophic myocardial cells may eventually lose their capacity to develop adequate tension, leading to left ventricle dilation and a reduced ejection fraction (EF).

Another issue with the hypertrophied heart is impaired diastolic relaxation, which might lead to diastolic heart failure, or more precisely, heart failure with preserved EF. Patients with heart failure with preserved EF compared with those with reduced EF appear to be a different population. Patients with preserved EF are generally older, more often women, often have hypertension and overweight, renal failure, obstructive pulmonary disease, and sleep apnoea, while a history of myocardial infarction is less common (35).

The major coronary arteries run along the epicardial surface of the heart, with the branches invading into the muscular wall and running perpendicularly from the epicardial to endocardial regions. The endocardial region is therefore anatomically further away from the blood and oxygen supply, and consequently, is more susceptible to ischemia. In the case of major LVH, the distance between epi- and endocardium is longer than usual and accompanied by an increased oxygen demand as well as possibly increased intramyocardial pressure, the potential for subendocardial ischemia is increased.

The most common methods for diagnosing LVH are conductance of an electrocardiogram (ECG) and echocardiography. Although the ECG remains the first line method in the detection of LVH in several clinical settings, its main limitation is its low sensitivity; only 43% for Sokolow-Lyon and 27% for Cornell product. However, both methods have shown good specificity (96%). Nonetheless, Sokolow-Lyon may overestimate LVH in tall slim patients. In obese individuals, the Cornell product criterion seems to be superior in the identification of LVH (36).

As expected, the prevalence of LVH by echocardiography is common among hypertensive patients, being found in up to 20–50 % of patients with mild hypertension and up to 90 % of those with severe hypertension (36). LVH is a major independent predictor of CV morbidity and mortality (37–42). Indeed, the Framingham Heart Study data showed that LVH (diagnosed by ECG, x-ray, or echocardiography) was associated with a three-fold increased risk for CVD events and a five to nine-fold elevated risk for sudden cardiac death (43).

The arterial wall comprises three layers: tunica intima, media, and adventitia. The IMT is a composite thickness of the first two layers. Analogously to the development of LVH, high BP levels cause an increase in transmural pressure of the arteries leading to a changed elastin-collagen ratio accompanied by large-artery remodelling characterized by an increase in IMT due to hypertrophy and hyperplasia of smooth muscle cells and alterations in the endothelial function. In addition to high BP, several other factors, such as endothelial cell dysfunction, neurohormonal activation, and vascular inflammation can cause remodelling of arteries.

IMT is measured usually from the common carotid artery. Although the upper limit of normality is age-dependent, a carotid IMT over 0.9 millimetres is considered abnormal (5). In the European Lacidipine Study on Atherosclerosis (ELSA), carotid

IMT increased progressively with the increase in both office and 24-h ambulatory BP (44). More importantly, carotid IMT predicts coronary and cerebral morbidity and mortality (45). In a meta-analysis of general population studies conducted by van den Oord, a 0.1 mm increase in IMT resulted in a 15 % higher risk for myocardial infarction (MI) and a 17% higher risk for stroke. Mean IMT values in the analysed groups were 0.82 and 0.77 millimetres for MI and stroke, respectively (45).

The blood circulation in the kidney is characterized by high blood perfusion, reduced impedance, and reduced vascular resistance. Due to the high SBP or PP, blood overflow can lead to microvascular damage and further to CKD. Hypertension is the second most important risk factor for CKD after diabetes (46) and even prehypertension is associated with an increased risk for the onset of CKD (47). Microalbuminuria (urine albumin between 30–300 mg/24 hours) is an early manifestation of renal damage and might be present even in non-diabetic patients with prehypertension or patients with atherosclerotic vascular disease (48). Moreover, the presence of microalbuminuria increases the CV risk (49). In clinical practice, urinary albumin excretion is often quantified by calculating the albumin: creatinine ratio. A study conducted by Gerstein et al. showed that for every 0.4 mg/mmol increase in albumin: creatinine ratio level, the adjusted hazard of CV event (MI, stroke or CV death) increased by 5.9% (49). Night-time BP seems to be more predictive for the development of CKD than daytime BP (50). Indeed, in a study with young patients with type I diabetes, the increase in systolic night-time BP preceded the development of microalbuminuria (51).

2.2 Diurnal pattern of blood pressure

2.2.1 Normal circadian rhythm of blood pressure

The development of a direct intra-arterial BP measurement in the late 1960s revealed that BP fluctuates continuously. BP is normally highest in the mid-morning and then varies in response to physical activities and emotional states. Furthermore, BP has a typical diurnal pattern with two distinct features – a fall in the BP during sleep i.e. “dipping” and an increase of BP before awakening i.e. “morning surge” (52). Night-time BP is typically approximately 10–20% lower than daytime BP in healthy individuals.

The dipping is presented as percentage (1-average night-time BP/average daytime BP) x100 (%) or as ratio (night-time BP/daytime BP). The established practice has been to classify dipping patterns as follows when ambulatory measurements are used: normal dipping pattern; an average decrease of BP greater than 10% and less than 20%, extreme dipping; greater than 20% fall, nondipping;

decrease greater than 0% and less than 10%. The reverse dipper i.e. riser pattern is defined as dipping less than 0% i.e. higher night-time than daytime BP (**Table 1**).

Table 1. Dipping categories based on night-day BP ratio and percentage

Category	Ratio/Percentage
Extreme dipper	Ratio ≤ 0.8 /≤20%
Dipper	0.8 < Ratio ≤ 0.9/ >10–<20%
Nondipper	0.9 < Ratio ≤ 1.0/ 0–10%
Riser	Ratio > 1.0/ <0%

The circadian rhythm in the BP is determined by several factors including the intrinsic rhythm of central and peripheral clock genes and the sleep-wake pattern (53). The BP fall during sleep is mostly a result of the inactivity, the reduction in sympathetic tone combined with reduced activity of the renin-angiotensin system and increased vagal input to the heart, resulting in decreases in heart rate, cardiac output, and peripheral resistance (54). Accordingly, several studies have reported that norepinephrine and epinephrine levels display circadian variations with a nadir during sleep (55–59).

2.2.2 Night-time hypertension and abnormal dipping pattern

The reported prevalence of night-time ambulatory hypertension is around 30–45% in the general population (60,61), and it is frequently, but not invariably, accompanied by a nondipping profile. In a large Irish population sample, 28% of the 576 patients classified as dippers had night-time hypertension, whereas, of the 229 nondippers, only 49% had night-time hypertension (62). The prevalences of the nondipping pattern (including reverse dippers) in two large general population cohorts from Japan (63) and Denmark (64) were 16% and 28%, respectively. In the prospective Ambulatory Blood Pressure Collaboration in Patients Diagnosed with Hypertension (ABC-H) study that included ten cohorts with a total of 17 312 hypertensive patients, the proportion of extreme dippers in the different cohorts ranged from 4% to 20%, dippers from 27% to 54%, nondippers from 32% to 46% and reverse dippers from 5% to 19% (65). The prevalence is usually higher in the elderly (66) and black people (67,68).

Multiple concomitant mechanisms may be responsible for evoking night-time hypertension and the nondipping pattern in an individual patient. However, the main mechanisms promoting an abnormal circadian rhythm seem to be increase in sympathetic activity, sodium handling in the kidneys and the circulating plasma

volume. In healthy individuals, urinary sodium excretion is highest during daytime and nadirs during sleep (69). When daytime natriuresis declines due to reduced ultrafiltration capacity or enhanced tubular sodium reabsorption, night-time BP increases to compensate for the diminished natriuresis by pressure natriuresis to preserve sodium balance, thus leading to night-time hypertension and the nondipping BP pattern (70–74). A high dietary sodium intake, especially in salt-sensitive individuals (i.e. those whose BP varies notably with changes in their sodium intake) reduces BP dipping (75). Conversely, dietary salt restriction and diuretics reduce particularly night-time BP and may restore the dipping pattern (76,77). Not surprisingly, nondipping is more prevalent in conditions associated with alterations in sodium handling or plasma volume, such as in primary aldosteronism (78–81), Cushing's disease (79) and chronic heart failure (82).

Increased sympathetic activity leads to vasoconstriction, increased cardiac output and increased norepinephrine uptake by tissues, and further, to hypertension and nondipping. Several conditions are associated with increased sympathetic activation including obstructive sleep apnea (OSA), abnormal autonomic nervous system activity (58,83–85) and pheochromocytoma (79). The prevalence of nondipping in ambulatory monitoring has been estimated to be around 48–71% among OSA patients (86–88), and it increases with the severity of OSA (86–89). In the study of Stergiou et al. with 39 patients with suspected OSA, the prevalences of night-time hypertension and nondipping in home monitoring were 45% and 26%, respectively (90). Other conditions associated with night-time hypertension and nondipping, which are at least partly associated with increased sympathetic activity, include diabetes (91–95), metabolic syndrome (81), and obesity (96,97).

Nondipping and hypertension are frequently seen in patients with chronic kidney disease due to impaired sodium excretion, volume overload, and increased sympathetic activation. In the African American Study of Kidney Disease and Hypertension (AASK) trial that included 617 hypertensive participants with a glomerular filtration rate between 20 and 65 mL/min/1.73 m^2, a significant proportion of patients were either nondippers (41%) or reverse dippers (39%) (98). Even among patients with an underlying renal disease with still normal excretory function, nondipping was shown to be significantly more prevalent (53%) as compared with age-, sex- and race-matched controls with essential hypertension (30%) (99).

2.3 Brachial blood pressure measurement

2.3.1 Measurement techniques

BP has traditionally been measured with an auscultatory method using a stethoscope and a mercury sphygmomanometer. Currently, most of the BP monitors are automated oscillometric devices. Irrespective of the measurement technique, they all rely on the determination of the intra-arterial pressure by applying pressure on the brachial artery with an inflatable cuff followed by a slow deflation. In the auscultation method, SBP is the pressure value at which the first Korotkoff sound is heard and DBP is the pressure where the sounds become muffled or disappear. In the oscillometric method, BP estimation is based on recording and analysing the small oscillations in cuff pressure by using a pressure sensor. The point of maximal oscillation corresponds to the MAP (100), while the estimation of SBP and DBP is then carried out with a select oscillometric algorithm. A comprehensive review of the different algorithms was published recently (101).

Several limitations should be considered with respect to oscillometric BP readings. First, model-specific signal processing and algorithms are needed to translate external cuff measurement to the estimated intra-arterial MAP, SBP, and DBP values, and thus differences in BP readings may occur between monitors (102). Second, BP varies with emotional and environmental influences. Within a few heartbeats, the intrinsic physiological oscillations of the BP signal can shift by as much as 20 mmHg (103). Third, the estimation of BP is difficult in some patient populations, such as individuals with obesity, marked arterial stiffness, and atrial fibrillation. In 2017, Picone et al. conducted a meta-analysis of the accuracy of cuff-measured BP against intra-arterial brachial BP in patients with BP ranging from ≥120/80 to <160/100 mmHg. Understandably, there were marked differences between the different devices. Nonetheless, the overall cuff DBP was 5.5 (95% Cl 3.5, 7.5) mmHg higher and SBP 5.7 mmHg (95% Cl 3.5, 8.0) lower than the corresponding invasive BPs at the brachial level (104).

Regardless of the selected measurement method, important methodological considerations of BP measurement include selecting the right cuff size, ensuring a proper measurement position of the patient, and using a validated measurement device. Moreover, BP readings are very sensitive to the position of the body and arm movements (105). Thus, office and home measurements should be taken in the seated position with the arm supported horizontally with the middle of the upper arm at the level of the heart, legs uncrossed with feet relaxed and flat on the floor, whereas ambulatory measurements should be taken with a still and relaxed arm at the level of the heart.

2.3.2 Validation of devices

The validation of BP monitors began after the release of validation standards by the American National Standards Institute (ANSI) together with the US Association for the Advancement of Medical Instrumentation (AAMI) in 1987 (106). Since then, several organizations including the British Hypertension Society (BHS) (107), the German Hypertension League (108), the European Society of Hypertension Working Group on BP Monitoring (ESH) (109,110), the European Committee for Standardization (CEN) (111) and the International Organization for Standardization (ISO) have published their own or collaborative protocols. However, one common goal was to unify the validation process, and therefore, in 2018, the AAMI/ESH/ISO consensus statement was released that proposed a single validation protocol to replace all previous protocols (112).

According to the recent consensus statement, at least 85 subjects with a total of 255 successful measurement pairs (including at least four rounds of observer measurements with an auscultatory method and three measurements with the test device) are required for conducting a BP device validation study. An acceptable device has a mean difference of five mmHg or less between all 255 pairs of test devices versus the observer measurements, and its SD eight mmHg or less for SBP and DBP. In addition, the SD of 85 averaged BP differences must be within a threshold defined by the mean BP difference. Detailed criteria for the differences are reported in the collaboration statement (112). According to the consensus guidelines, separate validation protocols are needed for noninvasive central monitors. Therefore, the consensus statement from an ARTERY Society task force was released in 2017 to provide recommendations regarding the validation of noninvasive central monitors (113). While most of the criteria are in line with the corresponding brachial BP monitor protocol (112), some select differences need to be described. For example, the device accuracy should be tested across a range of heart rates with the proposed range of 60 to 100 beats per minute as heart rate is known to affect the amplification of the pulse wave (17).

Even though there have been several established validation protocols available, formal clinical validation is not mandatory in several countries. Consequently, the evidence suggests that less than 20% of the BP monitors currently on the market have been validated appropriately (114). Fortunately, an up-to-date list of validated monitors can be found on the Internet site of a non-profit organization (the dabl Educational Trust) (115).

2.3.3 Different measurement methods

2.3.3.1 Conventional office measurement

Office BP can be measured manually with a mercury sphygmomanometer and a stethoscope, or more commonly, with an automated oscillometric monitor. In clinical practice, office BP is often measured improperly (116), which usually leads to an overestimation of the BP level. Nonetheless, even when office BP is measured according to recommendations, it might not accurately reflect BP level in everyday life and might be influenced by the so-called white-coat effect (117).

Current ESH 2018 hypertension guidelines recommend that office BP measurements should be taken three times at one to two-minute intervals. However, visits required for diagnosing hypertension depends on the grade of hypertension based on those measurements. If BP is extremely high (grade 3 hypertension) or there is evidence of hypertensive end-organ damage, a single visit is sufficient for the diagnosis of hypertension (5). ESH guidelines have the following abnormal office BP categories: high normal (130–139/85–89 mmHg), grade 1 hypertension (140–159/90–99 mmHg), grade 2 hypertension (160–179/100–109 mmHg), and grade 3 hypertension (≥180/110 mmHg) (5). In contrast, the new 2017 ACC/AHA guidelines consider 130–139/80–89 mmHg already to be stage 1 hypertension (118). Finnish guidelines recommend that office measurements should be taken twice by a nurse at one to two-minute intervals at least in four separate sessions (119). The classification of hypertension is in consensus with ESH 2018 guidelines (5).

2.3.3.2 Automated office measurement

An automated office BP (AOBP) measurement with the BpTrue device was developed to eliminate the white-coat effect from an office measurement (120). The AOBP measurement protocol includes six readings (the first is excluded from the analysis) at one-minute intervals with an automated oscillometric device while the patient is seated alone and undisturbed (121).

It is still not fully accepted how these unattended BP values correspond to conventional office BP values. It has been suggested that the BP levels obtained with unattended office measurement would result in 5–15 mmHg lower values compared with conventional office measurement (121–123) and correspond to mean values of daytime ambulatory or multiple daytime home readings (120), or are even lower than out-of-office values (123).

Myers et al. proposed a CVD risk-derived threshold of 135/85 mmHg for hypertension after a follow-up study with a 3627 community-dwelling elderly participants untreated for hypertension (124). Furthermore, in 2016, Myers et al.

examined the optimal AOBP level in 6183 community-dwelling elderly patients (≥66 years) who were using antihypertensive medication. They found that the nadir of cardiovascular events was as low as at SBP level between 110 to 119 mm Hg (125). The current guidelines from Canada recommend that AOBP ≥130/80 mmHg should be considered as the hypertension threshold for diabetic patients, with ≥135/85 mmHg recommended for non-diabetics (126).

2.3.3.3 Out-of-office measurements

Out-of-office BP measurements i.e. ambulatory and home measurements are valuable in several clinical conditions, such as diagnosing white-coat or masked hypertension, evaluating patients with resistant hypertension, estimating BP control in treated patients, and evaluating symptoms that may be associated with hypotension (5). If office BP varies extensively, an out-of-office BP monitoring can also facilitate the management of hypertension. Select features of ambulatory and home monitoring are presented in **Table 2**.

Until recently in several major guidelines, the diagnosis of hypertension was based on office measurements. In ACC/AHA 2017 and NICE 2016 guidelines, either ambulatory or home monitoring is now recommended to confirm a hypertension diagnosis (118,127), while ESC/ESH 2018 guidelines now recommend out-of-office measurements as an alternative diagnostic method for hypertension if logistically and economically feasible (5). In Finnish guidelines, out-of-office measurements have been recommended since 2002. Currently, they are recommended for patients representing a high normal office BP (130–139/85–89 mmHg) or hypertension (≥140/90 mmHg) (119). Current recommendations also state that ambulatory and home monitoring can be used interchangeably to measure daytime BP in clinical practice (5,118,119,126,127).

Table 2. Features of ambulatory and home monitoring

Feature	Ambulatory BP	Home BP
Prognostic evidence	Good	Good
Identification of white-coat and masked hypertension	Yes*	Yes*
Diurnal rhythm assessment	Yes	No**
Acceptability	Poor/moderate	Good
Cost	Costly	Inexpensive
Availability	Might be limited	Good
BP variability assessment	(Very) short-term	Short- and long-term

*Together with office BP

**Not yet in daily clinical use

Ambulatory blood pressure

Ambulatory monitoring is considered as the gold standard BP measurement method due to a large number of BP values obtained in a single session, the possibility to assess a complete profile of BP during a patient's habitual activities and the BP variability. Finally, it makes it possible to estimate the efficacy of antihypertensive treatment over a 24-hour period and BP load i.e. the percentage of readings exceeding the predefined cut-off value in a given time period (128). However, ambulatory monitoring has also several limitations including high cost, limited availability, discomfort, possible inaccuracies in readings obtained during movement, and limited reproducibility. One obvious drawback is also the need to keep the cuff on the arm during the entire measurement period which usually lasts for 24-hours with the subject having to wear the monitor unit around the waist. In addition, at least two clinic visits are needed to carry out the monitoring.

Ambulatory monitoring is usually carried out over 24 hours with measurements taken at 20 to 60-minute intervals. ESH recommendations for successful monitoring include >70% of the expected measurement obtained, and those successful readings should include ≥20 daytime and ≥7 night-time readings (128). Ambulatory BP values are lower than the corresponding office BP values, and the discrepancy increases even more with aging and when office BP increases (129).

Kikuya et al. proposed 130/80, 140/85, and 120/70 mmHg for diagnostic thresholds for 24-hour, daytime and night-time ambulatory hypertension based on corresponding CVD risk of office BP over 140/90 mmHg (130). Current guidelines differ slightly from those values. Recent ESC/ESH 2018 guidelines consider mean daytime BP ≥135/85 mmHg, 24-hour ≥130/80 mmHg, and night-time BP ≥120/70 mmHg values hypertensive (5). These are in line with Finnish, Canadian and NICE guidelines (119,126,127). In contrast, in the ACC/AHA 2017 guidelines, the corresponding threshold values are ≥130/80, ≥125/75, and ≥110/65 mmHg for mean daytime, 24-hour and night-time BP, respectively (118).

Home daytime blood pressure measurement

Home monitoring is widely used, and it is an especially convenient method in the long-term management of hypertension in a primary care setting (131,132). A large meta-analysis by Cappuccio et al. showed that treatment management with home rather than office BP yielded better achievement of BP targets (133). Home BP measurement might also improve treatment adherence leading to better control of hypertension (134,135). In addition, home monitoring is an inexpensive, easy and accessible method for repeated monitoring, especially for assessing BP control after treatment changes. However, home monitoring may be subject to reporting bias by patients (136–138).

The optimal home measurement protocol has been debated. Johansson et al. examined two cohorts, the first consisting of Finnish general population and the other of recently diagnosed hypertensive patients, and reported that duplicate measurements twice a day during a minimum of four days would be needed to obtain a reliable estimate of a patient's BP level (139). Consequently, Finnish national guidelines recommend obtaining duplicate morning and evening measurements during four to seven days (119). Several other guidelines recommend duplicate measurements being made in the morning and in the evening for seven consecutive days with (126,127) or without (118) discarding the first day's results. ECS/ESH 2018 guidelines recommend taking measurements for a minimum of three consecutive but preferably for six to seven days (5).

In the large Ohasama study, the cardiovascular risk increased when the home BP was above a level of 137/84 mmHg (140). Consequently, an ad hoc committee of the American Society of Hypertension recommended 135/85 mmHg as the upper limit of normal home BP in the late 90s (141). In 2013, Niiranen et al. showed in a large multinational population-based cohort that a mean home BP level of 133.4/82.2 mmHg on home monitoring was reflected in a similar 10-year CVD risk as an office BP value of 140/90 mmHg (142). Today, most of the guidelines consider home BP ≥ 135/85 mmHg as hypertension (5,126,127). With respect to office BP, the new ACC/AHA guidelines recommend a home BP level ≥ 130/80 as the cut-off value for hypertension (118).

Home night-time blood pressure measurement

A home night-time BP monitor was first introduced in 2001 by Chonan et al. (143). Since then, several devices have been developed to obtain home night-time BP measurements (**Table 3**). Of those, the Omron HEM-7252G-HP and HEM-7080-IC monitors have also telemonitoring systems that are able to send night-time home BP values directly from the patient's home to the clinic (144,145).

The studies comparing ambulatory and night-time home BP are presented in **Table 3**. Five studies have provided a direct comparison of night-time BP levels between home and ambulatory monitoring. Of those, two studies with 40 healthy volunteers (146) and 81 hypertensive patients (147) concluded that night-time home and ambulatory monitoring produced similar BP readings. Similarly, in a substudy of the Japan Morning Surge-Target Organ Protection (J-TOP) study with 50 hypertensive patients, night-time home and ambulatory BP readings were comparable at baseline and after a six-month treatment period with antihypertensive drugs (148). In contrast, in a large J-HOP study with 854 hypertensive patients, home night-time BP was slightly (2.6 mmHg, $p<0.001$) higher than ambulatory night-time BP (149). Andreadis et al. reported similar findings in 2016 when they examined

131 untreated hypertensive Greek patients (150). A subpopulation of the latter study with 94 patients showed that a two-night protocol with a total of six night-time BP measurements seemed to be sufficient for the estimation of the BP level (151). However, they showed that the agreement between the home and ambulatory monitoring increased slightly up to eight measurements before it plateaued (151). Finally, a recently published meta-analysis, including with values originating from this thesis, found no difference in the mean BP levels between the two methods (152).

In summary, home night-time monitoring is still a novel technique and thus lacks adequate prognostic evidence. Therefore, the current guidelines do not provide recommendations regarding night-time home BP measurements.

Table 3. Studies comparing 24-hour ambulatory and home night-time blood pressure levels

Author (Year)	Study population	N	Age, y± SD	Home device	Home device program	M. days	M/night	Main findings
Ushio et al (2009) (146)	Healthy volunteers	40	25±5	HEM-5041, Omron	Automated measurement at 1-h intervals	7	6 (1 h intervals)	Ambulatory and home BPs were comparable (105.7/59.1 vs. 107.6/59.3 mmHg).
Ishikawa et al (2012) (149)	Patients with CV risk factors	854	63±11	HEM-5041, Omron	Automated measurement at fixed times	9	3 (2, 3 and 4 a.m.)	Home SBP was slightly higher and DBP lower than corresponding ambulatory BPs (mean difference SBP/DBP: 2.6/-0.7 mmHg)
Stergiou et al (2012) (147)	HT patients	81	58±11	WatchBP N, Microlife	Automated measurement with timer function	3	3 (2, 3, and 4 h after going to bed)	Ambulatory and home BPs were comparable (mean difference SBP/DBP: -0.4/-1.0 mmHg)
Ishikawa et al. (2014) (148)	HT patients	50	59.1±9.5	HEM-5001, Omron	Automated measurement at fixed times	7	9 (3 measurements at 15-s intervals at 2, 3 and 4 a.m.)	Ambulatory and home BPs were comparable at baseline (mean difference SBP/DBP: 0.7/-2.2 mmHg) and after a 6-month antihypertensive treatment (difference: 3.5/-0.5 mmHg)
Andreadis et al (2016) (150)	HT patients	131	52±12	WatchBP N, Microlife	Automated measurement with timer function	3	3 (2, 3, and 4 h after going to bed)	Home SBP was slightly higher than ambulatory SBP (mean difference: 2.6 mmHg). No difference was found between DBPs (mean difference: 1.2 mmHg)

2.3.4 Acceptability of brachial measurement methods

Different measurement methods have their own unique advantages and drawbacks, though all methods might be uncomfortable or even painful for those patients with high BP or obesity due to the high cuff pressure needed to obtain measurements. Most likely due to the more arduous protocol, ambulatory monitoring has lower acceptability than the office (153) and home monitoring (154,155).

Common drawbacks of ambulatory monitoring include discomfort, inconvenience at work and activities, pressure-related side-effects and sleep disturbance. Beltman and colleagues assessed these problems among 129 patients diagnosed with diastolic hypertension. After 24-h ambulatory monitoring, 61% of the patients reported minor sleep disturbances, 14% had bad sleep quality, and 2% could not sleep at all during the monitoring period. In addition, 27% of the patients reported side effects including pain, skin irritation, inconvenience due to the noise emitted by the device, inconvenience at work, and hematoma (153). In the study of Viera et al., 60 American patients with borderline office hypertension underwent two ambulatory monitoring sessions one week apart. After both sessions, several patients complained of side-effects, such as bruising (20.3%), skin irritation (45.8%), and pain (35.5%). In the first session, up to 19.6% reported that monitoring stopped them from falling asleep and 70.2% had been woken up by the monitor. Due to inconvenience during the night, 5.1% and 8.5% of the participants stopped the monitoring in the first and second session, respectively (156). Patients who reported fair or poor health tolerated ambulatory monitoring more poorly in comparison to those individuals in good or excellent health (75% and 22%, respectively) (156).

A few studies have compared the acceptability of 24-h ambulatory and seven-day home monitoring protocols. In the study of McGowan and Padfield conducted in 2010 with 83 patients, 81% of the participants preferred home over ambulatory monitoring because it gave them the possibility to see the results immediately and provided a feeling of being more “in control” without sleep interference and embarrassment in public. The rest of the patients preferred the ambulatory measurement because of the shorter duration of the procedure (154). However, some participants experienced difficulties in adhering to the home measurement schedule, and three patients reported increased feelings of anxiety during the home measurements (154). A few years later in 2014, Nasothimiou and colleagues examined 104 untreated hypertensives and reported that 82% and 63% expressed positive overall opinions about home and ambulatory monitoring, respectively. In addition to better acceptance, 60% of the participants stated that they would prefer home monitoring for their next BP evaluation method, while only 40% of the patients would choose ambulatory monitoring. Finally, only 13% experienced moderate to severe discomfort during home BP monitoring compared with 55% during ambulatory monitoring (155).

In 2002, Little et al. published the first study that extensively compared different measurement methods available in primary care at that time (home daytime measurement, ambulatory monitoring and office BP measurement by a nurse or by a doctor) in a population of newly diagnosed hypertensive patients or hypertensives with poor BP control. They found that home measurement was better accepted than the other methods, and most of the patients rated it as the best method for them (157). In 2016, Wood et al. examined the influence of ethnicity on acceptability in 770 volunteers (481 known to be hypertensive) across the office, home daytime and 24-hour ambulatory monitoring between three ethnic groups. They observed that white British participants were more likely to complete measurement protocols according to schedule and had higher acceptability for each method as compared with South Asian and African Caribbean participants (158). Focus group investigations revealed that the presence of the clinician during office measurements increased anxiety in some patients. On the other hand, some patients perceived office measurements as more accurate because a professional was executing the process and they appreciated the possibility of immediate interpretation of the results and consequent treatment alterations. In agreement with previous studies, they also reported that the main drawback of ambulatory monitoring for the patients was sleep disturbance and inconvenience during the workday. In addition, some patients experienced embarrassment caused by others being aware of the monitoring. However, many patients also viewed it as the most accurate way to measure BP (158).

Only two studies have previously compared novel night-time home and ambulatory monitoring with respect to acceptability and patients' preferences. In the study of Stergiou et al. with 67 Greek patients, 89% reported more night-time sleep disturbance with ambulatory than home monitoring. Although the difference was not statistically significant, 55% of the patients stated that they would prefer home over ambulatory monitoring for their next night-time BP measurement method (147). In addition, a brief report by Ushio et al. with 40 healthy volunteers revealed that the home-night BP measurement was overall more comfortable than ambulatory monitoring. However, no significant difference was found in the quality of sleep. This might at least partly reflect the rather intensive home night-time measurement protocol. Home night-time BP was recorded at one-hour intervals up to six times per night, whereas ambulatory measurements were taken at 30-minute intervals (146).

Overall, the current BP monitoring techniques seem to be rather well-accepted among patients. However, it seems that the acceptability of home BP exceeds that of ambulatory measurement. However, BP monitor technology continues to develop and especially telemonitoring and smartphone applications might become an important part of BP measurements in the future.

2.3.5 Association of brachial blood pressure and nocturnal nondipping with cardiovascular outcomes

2.3.5.1 Association with end-organ damage

Elevated BP values, irrespective of if assessed in the office or home or collected ambulatory, are all significantly associated with hypertensive end-organ damage (5). Several authors have tried to clarify whether BP measured with one of these approaches would be a stronger predictor of end-organ damage than the others and whether absolute BP values or dipping status relate more strongly to end-organ damage.

The large-scale Finn-Home Study showed that home BP associated more strongly than office BP with LVH (159,160), IMT (161), PWV (162) and albuminuria (163). In line with these findings, a 2012 meta-analysis conducted by Bliziotis et al., claimed that home BP was superior to office BP in detecting LVMI (14 studies). However, no significant difference was revealed between home and office BP with carotid IMT (4 studies) or PWV (3 studies) (164). The superiority of the two out-of-office methods remains unclear. However, several studies have shown that home BP is at least as strongly associated as ambulatory BP with end-organ damage including LVH and carotid IMT (165–169).

The prospective study of O'Flynn and colleagues showed that a 10 mmHg increase in night-time SBP resulted in a 40 % increase in the odds of ECG-LVH. In contrast, they found no associations between dipping status and end-organ damage after adjusting for the usual risk factors (62). Similarly, Cuspidi et al. found no difference in LVMI between dippers and nondippers in treated hypertensive patients with or without good BP control among 229 treated hypertensive individuals (170). However, another study conducted by Cuspidi et al. showed that individuals with a reproducible nondipping pattern on two ambulatory monitoring sessions had a higher prevalence of LVH and increased IMT as compared with those with normal dipping pattern on both occasions (171). In a study examining a total of 375 middle-aged hypertensive patients, Ivanovic et al. found that LVH prevalence increased significantly from extreme dippers (5%) to dippers (9%) to nondippers (17%), and reverse dippers (31%) (172). With respect to IMT and the nondipping pattern, a meta-analysis with 13 studies by Cuspidi et al. showed that carotid IMT values were higher and the odds for carotid plaques were 67% higher in nondippers versus dippers (173).

The Japan Morning Surge-Home Blood Pressure (J-HOP) study, which focused on home night-time monitoring of hypertensive patients with well-controlled morning home BP less than 135/85 mmHg, showed that 27 % of them had home night-time SBP over 120 mmHg, and had also more severe end-organ damage than

patients with normal night-time SBP (174). Similar findings have also been reported with ambulatory measurements (175). In a larger population of the J-HOP Study by Ishikawa et al., no associations were found between home or ambulatory nondipping status with LVMI or urinary albumin: creatinine ratio among 594–854 hypertensive patients (149).

2.3.5.2 Association with cardiovascular risk

Office DBP has traditionally been considered as the most important component of BP. A high SBP value was assessed as a benign manifestation of a vigorous heart and DBP as a dangerous manifestation of increased arterial tone. This concept was reinforced from the 1950s to the 1970s in several intervention studies that focused on middle-aged men who had typically combined hypertension instead of isolated systolic hypertension. Furthermore, most of the treatment studies of that time focused solely on DBP. In general, DBP increases with age up to approximately 55 years and tends to decrease after that due to arterial stiffening, whereas SBP increases with age at least up to 80 years in Western populations (5). In the 1980s, reports from Framingham Heart Study (176) started to change the perception of the SBP. Furthermore, in the 1990s, three large intervention studies (Systolic Hypertension in the Elderly Program (SHEP) (177), Syst-Eur (178), and Syst-China (179)) showed that the treatment of isolated systolic hypertension reduced cardiovascular events. Since then, a large-scale meta-analysis conducted in 2002, showed that BP over at least 115/75 mmHg was linearly related to cardiovascular mortality, without any evidence that there would be distinct thresholds (180). Although currently SBP is recognized to be a stronger cardiovascular risk factor than DBP, a very recent publication by Flint et al. using data from 1.3 million adults showed that both SBP and DBP were associated with an increased risk for poor outcome (181). While SBP seemed to have a greater effect on outcomes than DBP, the effect of SBP on outcome was greater at lower DBP values. Moreover, a J-curve relationship was reported between outcome and DBP (181). However, this finding was explained at least in part by age and other variables and by a greater effect of systolic hypertension in persons in the lowest quartile of DBP (181). Several previous studies have found a J-curve relationship between DBP and cardiovascular risk in hypertensive patients (182,183). The HOT (Hypertension Optimal Treatment) study indicated that the J-curve between DBP and CV events might be explained by underlining pathologies such as poor left ventricular function, poor general health and artery stiffness (184).

An automated office BP measurement was used recently in the large-scale Systolic Blood Pressure Intervention Trial (SPRINT) study that compared prospectively two different SBP targets with the aim to reduce CV events;

conventional <140 mmHg against a lower <120 mmHg target (185). More intensive treatment (achieved BP level at one year 121 vs. 136 mmHg) was associated with a 25% reduction in major CV events. However, because the results were based on AOBP values, the conclusions of SPRINT study have been widely challenged. Regardless of the ongoing debate, in its 2017 guidelines, ACC/AHA lowered the office BP level for diagnosing hypertension down to 130/80 mmHg (118).

Ambulatory BP is a stronger predictor of CV morbidity and mortality as compared with office BP irrespective of whether it is the general population (186,187), untreated (188–190), or treated (191,192) hypertensive population which is being examined. Ambulatory night-time BP seems to be a particularly strong predictor for a future CVD event (7,60,186,187,189–197), and even isolated nocturnal hypertension is related to CVD events and mortality (60). In the Ambulatory Blood Pressure Collaboration in Patients with Hypertension (ABC-H) meta-analysis, a 10 mmHg increase in night-time SBP increased the risk for CVD by 13% (7). Similarly, home BP is a stronger predictor than office BP (198,199). However, it remains unclear which of the two out-of-office methods is superior in predicting cardiovascular outcome, (187,200–202). However, in the clinical setting, repeated ambulatory measurements may not be as feasible as home measurements.

Ambulatory nondipping compared with dipping pattern is also a well-established predictor of adverse CV outcomes (63,65,193,195,196,203). However, it seems to be a less significant predictor than absolute night-time BP levels (204). Reverse dipping consistently shows the poorest outcomes among different types of dipping patterns with respect to CVD events and all-cause mortality (63,65,192,194,197,203,205,206). In the ABC-H study, reversed dippers had a 57% higher risk for coronary events as compared with normal dippers (65). However, in several studies, reverse dippers have been older (197,205,207), are more likely to be diabetics (207) or have pre-existing cardiovascular disease (205,207), and have been more frequently using antihypertensive medications (197,205). Thus, the reverse dipping pattern might be a marker rather than a cause of a poorer outcome.

In addition to a diminished decline in BP, an extreme fall of BP might also be harmful, although the results on previous studies have been mixed. Extreme dipping has been associated with myocardial ischemia in patients with hypertensive coronary artery disease (208), and silent cerebrovascular disease (205). However, in the ABC-H study, no significant difference was found between extreme and normal dippers with respect to CVD events or mortality (65).

In the MAPEC (Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares) study with a total of 3344 normotensive and hypertensive individuals, nondippers had a significantly higher cardiovascular event risk than dippers irrespective of BP level. A considerable proportion (21%) of the study population were classified as normotensive nondippers. Interestingly, they had a

similar risk for CVD events than dippers with elevated ambulatory BP irrespective of their antihypertensive treatment status (209). The MAPEC study also showed that the administration of at least one antihypertensive medication at bedtime was able to lower nocturnal BP, help to restore the dipping pattern and, most importantly, reduce cardiovascular events and mortality (210).
The first prospective outcome study using home night-time BP monitoring was published in 2018 (211). In the above study of Kario et al., 2545 Japanese patients with a history of CVD or having its risk factors were followed for somewhat over seven years. In this study population, a ten mmHg increase in home night-time SBP was associated with a 20.1% higher risk for CVD events even after adjustments for several covariates including office and home morning SBPs (211).

2.3.6 Reproducibility of the nocturnal nondipping pattern

Nondipping pattern on ambulatory monitoring has a limited reproducibility over short- and long-term periods in several studies (212–218). In the study conducted by Mochizuki et al., which examined 253 untreated hypertensive patients that underwent two ambulatory monitoring sessions, of those with a dipping pattern in the first night, 28% had a nondipping pattern in the second night. Similarly, 31% of the patients with nondipping pattern in the first night changed to dippers in the second night (212). In the Study on Ambulatory Monitoring of Pressure and Lisinopril Evaluation (SAMPLE) cohort, approximately 35-40% of patients changed their dipping pattern between ambulatory monitoring sessions (217). McGowan with colleagues reported that among 512 untreated patients, the dipping pattern changed in 24% of the patients between two sessions (with a kappa value of 0.29 for the reproducibility). In contrast, when dipping was analysed as a continuous variable, the median absolute change between assessments was only 3.8% (intraclass correlation coefficient 0.60). When these investigators compared the two methods in different time-frames, the continuous dipping showed better reproducibility than the dichotomous dipping pattern (218).

Several factors may explain the relatively low reproducibility of the nondipping pattern. Night-time physical activity based on actigraphy measurements has been shown to reduce noninvasively measured BP dipping (219–222). This may be related to sleep quality, which can have a significant effect on night-time BP levels (221,223). Interestingly, a large study with 1046 patients that investigated the associations between sleep disturbances and the nondipping pattern detected no differences in perceived sleep quality between habitual night and during ambulatory monitoring based on diary data (224). However, sleep disorders reported by cohabitants were more common and the number of awakenings followed by urination was higher in nondippers than in dippers (224).

The results concerning nocturnal urination and sleep disorders have been confirmed by others (225–227).

With respect to daytime BP, lifestyle-related factors, such as day-to-day variations in physical activity, emotional state, caffeine or alcohol consumption or smoking might contribute to the large differences evident in BP values. Indeed, Cavelaars et al. showed that dipping is more common in individuals who are physically active during daytime (228). More specifically, BP increases during dynamic and static exercise, and the increase is more prominent for SBP than DBP (229). Finally, the use of BP medication and the time of administration of drugs might also affect BP dipping (230).

Very little is known about the reproducibility of nondipping and night-time BP based on home monitoring. The Greek study conducted by Stergiou et al. revealed that the agreement of nondipping pattern between three consecutive nights varied from 71 to 73% (147). Both Chonan et al. and Hosohata et al. reported poor reproducibility of night-time home BP, especially when patients experienced different sleep qualities between measurement nights. However, both measurement protocols consisted only of a single measurement taken at two a.m. (143,231).

2.4 Noninvasive central blood pressure

2.4.1 Measurement techniques

The most accurate assessment of central BP (CBP) is to measure it invasively with a high-fidelity pressure transducer placed in the ascending aorta, but clearly, this is not an applicable method for daily clinical practice. Therefore, several noninvasive techniques have been developed to derive central BP from peripheral BP measurements using different algorithms.

The fundamental idea in all noninvasive CBP measurement techniques is to estimate the aortic pressure waveform from a peripheral waveform, which is then calibrated into units of pressure with noninvasive brachial BP values. One of the principal methods to obtain the peripheral pressure waveform is applanation tonometry (AT), where a superficial artery (usually carotid or radial) is slightly flattened against bone or some otherwise stiff structure with a tonometer, and the changes in arterial pressure i.e. pressure waveforms, are recorded by a pressure sensor located in the tip of the tonometer.

The carotid pressure waveform can be used as a surrogate for the aortic pressure wave as pulse wave amplification is no more than two mmHg between the aorta and carotid artery (232). However, AT requires that there is a thin skin layer to avoid cushioning of the pressure pulse, and thus obtaining a carotid pressure waveform reliably might be difficult, especially in obese patients (233). More peripheral

pressure waveforms (usually radial) can be mathematically transformed to central waveforms by using a generalized transfer function (234). Finally, if the second systolic shoulder of the radial waveform is clearly recognizable, it can be used to estimate CBP (235,236). The latter two methods have been shown to provide very similar results (237). However, the latter technique cannot be used if the second shoulder is not clearly present – as is often seen in young adults, patients with tachycardia or systolic heart failure, or during the influence of vasodilatory drugs (238).

Several companies have developed cuff-based devices to obtain operator-independent noninvasive central BP measures (233). These novel cuff-based recording systems, for example, the ARCsolver (239), Centron (240), Vicorder (241), and SphygmoCor XCEL (242) typically utilize a standard BP cuff to obtain volume waveforms from the brachial artery. Then CBP is derived using either a transfer function or taking the second systolic peak of the waveform and applying proprietary algorithms. Recently, Cheng et al. introduced a new type of CBP measurement device, which determines CBP by using parameters from the pulse volume plethysmography derived waveform by applying a multivariate regression equation incorporated in Microlife WatchBP Office Central monitor (243).

In summary, there is growing interest in the development of noninvasive central BP monitors, of which upper arm cuff-based devices seem to be especially appealing for clinical use. However, the variety of techniques and the different signal processing steps significantly reduce the inter-study comparability of BP values derived with these novel devices.

2.4.2 Estimation of aortic pressures from peripheral pulse waveforms

Estimated dimensionless pulse waveforms need to be calibrated with peripheral BP measures if one intends to obtain central values. Two widely used strategies are to calibrate the pulse wave by brachial SBP and DBP or MAP and DBP. However, a recent meta-analysis by Papaioannou et al. concluded that calibration with MAP and DBP rather than SBP and DBP seemed to relate more accurately to invasively obtained central BP values (244).

Several issues should be considered with respect to CBP values obtained noninvasively. First, when a transfer function-derived pulse wave is calibrated with brachial pressures, the pulse wave amplification between radial and brachial measurement sites is not accounted for, although the amplification is much larger than the aorta-to-brachial pressure amplification (21,245). Second, with respect to AT, the measurement is highly operator-dependent and good quality measurements might be difficult to obtain in some individuals. Third, the oscillometric monitors

used to calibrate waveforms tend to underestimate brachial SBP and overestimate DBP (104). Thus, calibration of the transfer function-derived waveform with oscillometric versus invasive brachial BP seems to lead to an underestimation of central SBP. Finally, the CBP values obtained are not interchangeable since they are device and technique-dependent (246).

Although CBP values between techniques are not necessarily comparable, some investigators have proposed diagnostic thresholds for CBP measures. For example, Cheng and colleagues examined a 1272 patient cohort with a median follow-up of 15 years by using MAP and DBP calibrated carotid pulse waveform and estimated that 130/90 mmHg would be a suitable threshold for hypertension, while CBP under 110/80 mmHg seemed to be optimal (247).

2.4.3 Association of central blood pressure with cardiovascular outcomes

2.4.3.1 Association with end-organ damage

Large arteries and organs, such as the heart, brain, and kidneys are exposed to central rather than brachial pressure. Thus, it is logical to assume that central pressure contributes more than brachial pressure to the risk of end-organ damage. In agreement with this paradigm, a recent comparative meta-analysis published by Kollias et al. in 2016, showed that central BP rather than brachial SBP was slightly better associated with LVMI, and carotid IMT (248). However, in several investigations (249–255), central measures as compared with the corresponding brachial measures were equally or less strongly related to end-organ damage yielding relatively small absolute differences in the correlations between systolic BPs and end-organ damage (0.04 for both LVMI and IMT) (248). Similarly, the absolute differences in the correlations for central and brachial PPs with end-organ damage were small (0.05 and 0.07 for LVMI and IMT, respectively). CBP was measured by using applanation tonometry (either carotid or radial) in all these studies (248). No previous study has investigated the associations with end-organ damage between peripheral and central BP measured by using a noninvasive central stand-alone Microlife device (243).

2.4.3.2 Association with cardiovascular risk

The incremental prognostic value of central over conventional office BP remains unclear. Several individual prospective studies have shown central hemodynamic measures to associate more strongly than brachial BP measures with cardiovascular outcomes (249,255–258). However, Vlachopoulos et al. failed to demonstrate any

prognostic superiority for central SBP or central PP over the corresponding brachial measures in a meta-analysis conducted in 2010 (259). However, the prognostic value of central PP over brachial PP did approach statistical significance; the relative risk of a clinical event for a ten mmHg increase in PP was 1.318 for central vs. 1.188 for brachial PP (p=0.057 for the difference) (259). Data from the Framingham Heart Study showed that transfer function-derived central measures did not improve the CVD risk assessment after the risk was adjusted with conventional risk factors including brachial BP (260). Since all of the studies mentioned above have used noninvasive methods for assessing central hemodynamic measures, differences in these measurement methods and calibration measures might be the reason for these partly conflicting results.

2.5 Summary

SBP and PP are not constant throughout the vascular system but typically increase from central to the more peripheral arteries due to pressure wave amplification. Thus, central hemodynamics represent more accurately the conditions affecting the organs and large arteries than the corresponding peripheral values. In line with this paradigm, some prospective studies have indicated that noninvasively measured central hemodynamic measures display stronger associations with cardiovascular outcomes than the corresponding brachial measures (249,255–258) Nonetheless, a recent meta-analysis failed to detect any prognostic superiority of central over brachial measures in predicting the cardiovascular outcome (259). Moreover, the variety of different methods used to obtain noninvasive central BP complicates direct comparisons between different studies. Recently, a novel stand-alone monitor to obtain noninvasive central BP measures was released (243). So far, no published studies have examined whether central BP values obtained with this monitor are more strongly related to hypertensive end-organ damage than corresponding brachial measures.

BP is characterized by a circadian rhythm, with a clear decline in BP often being present during sleep. Several studies have shown that both night-time hypertension and a blunted fall in BP i.e. nondipping pattern are cardiovascular risk factors independent of ambulatory daytime BP (7,65). Thus, accurate and clinically feasible measurement methods are needed to assess night-time BP in clinical practice. Until recently, 24-hour ambulatory monitoring has been the only method available to assess night-time BP. However, ambulatory monitoring often causes discomfort, inconvenience at work and other activities and may lead to disturbed sleep (153). Consequently, ambulatory monitoring has been shown to have lower acceptability than both office (153) and home daytime monitoring (154,155). To date, select timer-equipped home monitors have been introduced to the market to offer a more comfortable and feasible alternative to ambulatory monitoring.

Preliminary data, although obtained mostly from hypertensive populations, show that these novel home monitors produce comparable (146,147) or slightly higher (149,150) night-time BP values than ambulatory monitoring. Moreover, two Japanese studies suggested that home night-time BP might be even more closely associated with hypertensive end-organ damage than ambulatory night-time BP (148,149). Nonetheless, in both studies, the number of home night-time measurements exceeded that of ambulatory assessments. So far, only two Greek studies have reported substantial diagnostic agreement in detecting night-time hypertension (150), and nondipping patterns (147,150) between the two methods. However, both studies have examined only hypertensive patients, and thus the results might not be generalizable to other populations.

BP measurement is widely used as a screening tool and in the management of hypertension. Thus, it is essential that patients are willing to adopt these BP measurement protocols. Studies concerning acceptability are rather scarce. Among the currently used methods, ambulatory monitoring seems to be the least accepted (153,154,157). However, BP monitor technology has developed significantly over the past two decades, and therefore the acceptability of BP monitors (especially ambulatory) might have altered significantly.

Thus far, there are no publications comparing the agreement of BP values and the diagnostic agreement in the detection of night-time hypertension and nondipping patterns between home and ambulatory monitoring in a general population setting with a feasible two-night measurement protocol. Furthermore, no previous studies have compared the acceptability of the novel home night-time measurement approach against the conventional BP measurement methods.

3 Aims

This thesis was designed to investigate novel BP measurement methods in a general Finnish population.

The specific aims were:

1. To investigate which method of BP measurement is preferred by patients (I).
2. To compare BP levels and their associations with end-organ damage between ambulatory monitoring and a timer-equipped home monitor (II).
3. To assess whether non-invasively estimated central BP assessed with a stand-alone device is more strongly associated with end-organ damage than conventional brachial BP (III).
4. To investigate the diagnostic agreement of ambulatory and home night-time monitoring in the detection of night-time hypertension and the nondipping BP pattern (IV).

4 Materials and Methods

4.1 Study sample

The study sample is based on a subsample of The National FINRISK 2007 Study cohort, a random sample of 10,000 Finns aged 25 to 74 years drawn from five geographical areas of Finland. A total of 6,258 individuals participated in the health examination between January and March 2007. To gather more precise information on the clustering of cardiovascular risk factors, all participants of the FINRISK 2007 study were invited to participate in the DIetary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome (DILGOM) study between April and June 2007. The DILGOM study aimed to assess how nutrition, diet, lifestyle, psychosocial factors, environment, and genetics are linked to obesity and metabolic syndrome. A total of 5,024 individuals out of all those invited participated, and of those, 1037 were examined in the south-western Finland area. Of these participants, 500 (50 men and 50 women from each 10-year cohort) were randomly invited to participate in a cardiovascular substudy, and 493 agreed to participate.

In the spring of 2014, after a seven-year follow-up, the DILGOM participants living in southwestern Finland and the Helsinki area were invited for a re-examination via mail. Invitations were sent to 1,783 persons still alive and 1,314 individuals participated in the health examination. In addition, all 453 of those still living participants of the cardiovascular substudy were invited to a re-examination and a total of 290 persons responded positively. This population sample was used as the base population for studies I–IV. All participants gave written informed consent. The study was approved by the Ethics Committee of the Hospital District of Southwest Finland.

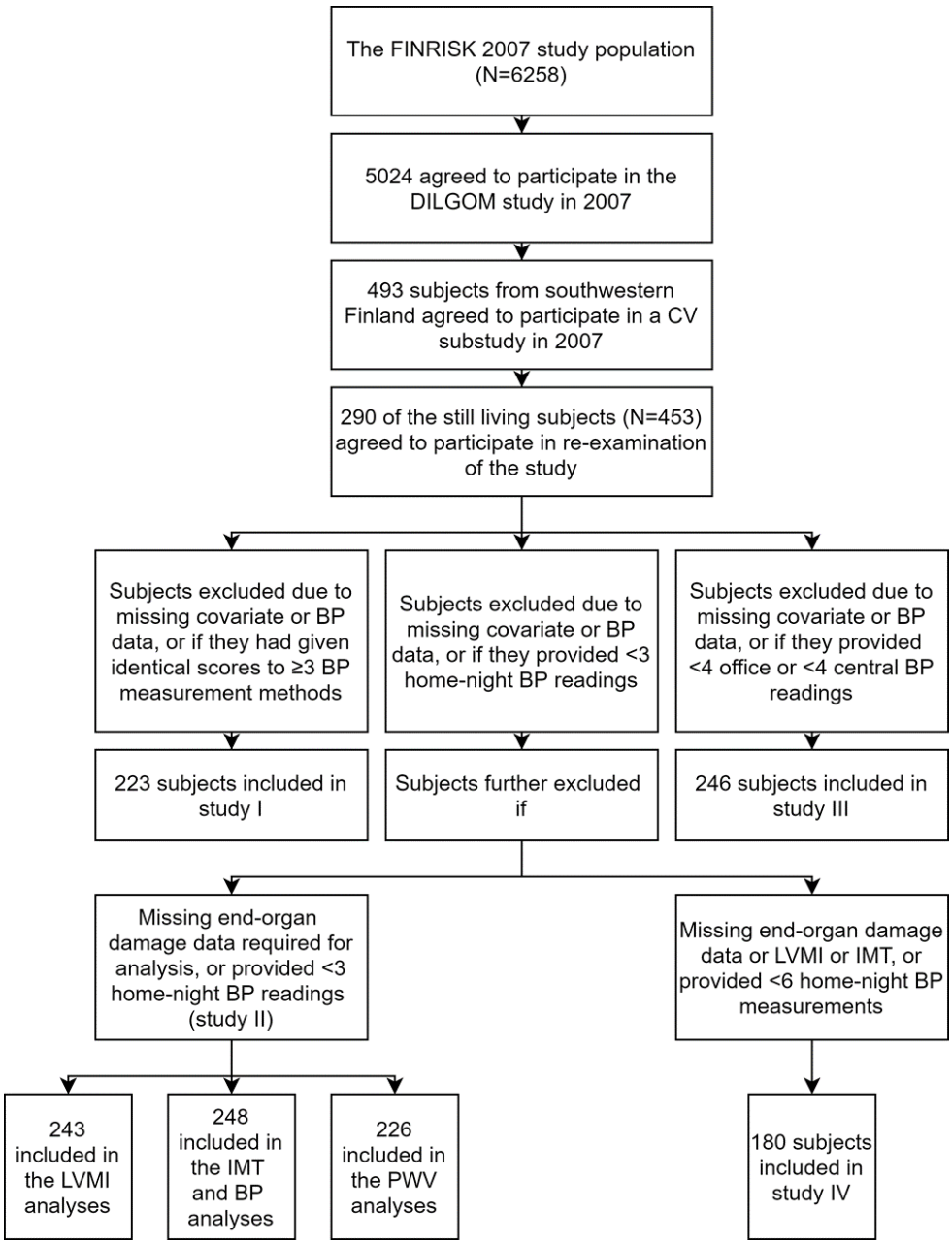

Figure 2. A flow chart illustrating the exclusion criteria of participants from studies I–IV. Detailed exclusion criteria for each study are presented in the text below.

Study I

Participants who had missing laboratory or health examination data (n=6) or BP data (n=39) or those who have not completed the questionnaire (n=58) were excluded from the analyses. In addition, if the participant had given identical scores to three or more BP measurement methods (n=10), it was interpreted as careless responding, and thus excluded from the analyses, resulting in a final sample of 223 participants.

Study II

Participants with missing information for any confounding covariates (n=6) used in the multivariable-adjusted linear models or those who had not provided ambulatory BP (n=14) or night-time home BP readings (n=26) were excluded from all the analyses. After the exclusions, participants were analysed in three groups according to the available end-organ damage data. Participants with missing PWV (n=31) or LVMI (n=5) data were excluded from these analyses. After exclusions, the final study populations for the PWV, LVMI and IMT analyses consisted of 226, 243 and 248 participants, respectively. Night-time home and ambulatory BP levels were compared in participants of the IMT group.

Study III

Participants who had missing laboratory or health examination data (n=6) or missing data for end-organ damage (n=34) or had fewer than four central or brachial measurements (n=10) were excluded from the study. After removing participants with one or more exclusion criteria, the study population consisted of 246 participants.

Study IV

Participants who had not performed ≥20 valid daytime (n=20) or ≥7 night-time ambulatory BP (n=16) or ≥6 night-time home BP readings (n=94) or had missing information (n=6) on confounding covariates or incomplete end-organ (n=5) data were excluded from analyses resulting in a study sample of 180 participants.

4.2 Flow of the study

All participants underwent four study visits between April and December 2014. Participants received questionnaires for information on sociodemographic factors, health and illnesses, use of medications, and lifestyle with the study invitation letter. On the first visit, participants returned the questionnaires. The participants' height,

weight, waist and hip circumferences were measured by centrally trained nurses, and fasting blood samples for serum lipids and plasma glucose were drawn. In addition, office brachial BP was measured twice by a nurse. After each conventional brachial BP recording, central BP and pulse pressure were automatically measured.

On the second visit, participants underwent end-organ damage examinations for LVMI, PWV and carotid IMT. At the end of the second study visit, 24-hour ambulatory BP monitoring was initiated. In addition, the participants were asked to empty their bladder and then collect their urine for the following 24 hours for the determination of 24-hour urine albumin, and for this purpose they received a urine collection container. On the following day, the participants returned the ambulatory monitor and the urine container, underwent similar office and central BP measurements as on the previous day, and received a Microlife WatchBP Home N automatic oscillometric monitor with oral and written instructions on how to measure both daytime and night-time home BP correctly.

The participants returned the home monitors approximately one week later. After the home measurement period, the participants filled in an acceptance questionnaire consisting of 13 items and ranked their most preferred measurement method. The participants received oral and written feedback of all the examinations from a physician.

4.3 Blood pressure measurements

4.3.1 Office brachial and stand-alone central blood pressure measurements

We measured both office brachial and stand-alone noninvasive central BP measurements twice at one-minute intervals on two occasions after a three-minute rest in a sitting position from the participant's right arm with an appropriately sized rigid cuff using an oscillometric Microlife WatchBP Office Central device (Microlife AG, Widnau, Switzerland) (243,261). After conventional oscillometric brachial SBP and DBP measurements, the device automatically deflates cuff pressure to 60 mmHg (or to DBP if it is less than 60 mmHg) for approximately 30 seconds. During this time, the device records 20–30 brachial pressure waveforms using pulse volume plethysmography. Multiple brachial pressure waveforms are then averaged and calibrated to brachial SBP and DBP. Finally, certain parameters from the pulse waveform analysis are used in a validated multivariate regression equation incorporated in the software to determine central SBP and PP (262). We calculated brachial PP as the difference between SBP and DBP. We averaged all brachial and central BP measurements to yield a single brachial and central value per patient.

4.3.2 Ambulatory blood pressure monitoring

We obtained 24-hour ambulatory BP monitoring from the non-dominant arm of the participant using a Microlife WatchBP O3 device (Microlife AG, Widnau, Switzerland) (263). One minute before each BP measurement, the device issued a warning signal and the participant was then instructed to stop walking and preferably sit down and keep the arm motionless and relaxed. We obtained measurements at 20-minute intervals during the daytime (from 07:00 to 22:00) and at 30-minute intervals during the night-time (from 22:00 to 07:00) on a weekday. We asked participants to report their actual time when they went to bed and woke-up and used this time period to calculate the actual daytime and night-time BPs. We calculated night-time ambulatory BP dipping percent as (daytime-night-time BP)/daytime BPx100, separately for SBP and DBP.

4.3.3 Home blood pressure measurements

Participants measured their home BP with a validated oscillometric Microlife WatchBP Home N device (Microlife AG, Widnau, Switzerland) (264) in a sitting position after a three-minute rest at one-minute intervals. Daytime home BP was measured twice in the morning (between 0600 and 0900 h) and twice in the evening (between 1800 and 2100 h) on seven consecutive days. During the last two nights of the home monitoring period, participants activated the home night-time monitoring mode of the monitor by taking a pre-sleep BP measurement immediately before going to sleep. Thereafter, the device took three automated BP measurements at 60-minute intervals, starting two hours after the initial pre-sleep BP measurement. We averaged all daytime and night-time readings (except for the pre-sleep activation BP measurement) to yield a single daytime and night-time home BP value, respectively. The night-time home BP dipping percent was calculated as (daytime-night-time BP)/daytime BPx100, separately for SBP and DBP.

4.4 Laboratory analyses

We obtained venous blood samples after a minimum of four-hour fast from a vein in the arm, with the subject in the sitting position at the Population Studies Unit (Turku, Finland). After sample processing, we froze the samples to -70 °C on site and later transported them to the accredited in-house laboratory of the National Institute for Health and Welfare (Helsinki, Finland) for the laboratory testing. We measured serum total cholesterol, high-density lipoprotein, triglycerides, and plasma glucose with enzymatic assays using Architect c8200 analyser (Abbott Laboratories, Abbott Park, Illinois, USA). We calculated low-density lipoprotein (LDL) cholesterol with the Friedewald formula. We measured urine albumin with an immunoturbidimetric

assay with the same equipment. In our relatively healthy study population, the prevalence of microalbuminuria was low (11 participants had microalbuminuria) and therefore we decided to omit this parameter from the analyses.

4.5 Acceptability questionnaire (I)

We used a translated and slightly modified version (question 6 was slightly altered) of the questionnaire introduced and validated by Little et al. to obtain readily comparable results (157). The questionnaire consisted of 13 questions, of which nine questions (questions 1–5, 7–10) assessed potential inconveniences associated with the BP measurement including measurement-induced anxiety, discomfort, uncertainty and the disturbance of home life, everyday activities, sleep, and work. The rest of the questions (questions 6, 11–13) evaluated participants' BP awareness and their estimation of the accuracy, efficiency, and controllability of each measurement method. All questions are shown in Article I, Table 1.

4.6 Pulse wave velocity measurement (II)

We obtained arterial tonometry measures after the participant had rested in a supine position for five minutes. A trained nurse recorded pulse waves from the right common carotid and femoral arteries sequentially by using a high-fidelity SPT-301 applanation tonometer (Millar Instruments, Houston, Texas, USA). We then analysed the results with the SphygmoCor PVx device with MM3 module (Atcor Medical, Sydney, Australia). We estimated the transit time of the pulse wave between carotid and femoral sites by subtracting the time delays between the feet of two waveforms in relation to the R-wave of the simultaneously recorded ECG. We measured the straight distance from the carotid recording site to the suprasternal notch and subtracted it from the straight distance from the femoral recording site to the suprasternal notch to obtain the distance between recording sites. We acquired PWV measurements twice and used the average of two measurements in statistical analyses.

4.7 Carotid intima-media thickness measurement (II-IV)

We performed IMT measurements with a Vivid E9 device with an 11L-D linear-array transducer (GE Healthcare, Little Chalfont, UK). We acquired the measurements in Doppler colour flow-controlled B-mode from the far wall of right common carotid artery from the lateral view at the end of diastole according to the American Society of Echocardiography (ASE) consensus statement (265). We

performed the measurements twice from three cardiac cycles and used the mean of six measurements in the statistical analyses. One clinical physiologist performed all of the measurements in the current study.

4.8 Echocardiography (II-IV)

We defined left ventricular mass by using echocardiographic measurements. We performed in 2D-mode controlled M-mode echocardiography with a Vivid E9 device equipped with a M5S-D transducer (GE Healthcare, Little Chalfont, UK) after a ten-minute rest according to ASE recommendations (266). One experienced clinical physiologist performed all ultrasonographic examinations and off-line measurements from digitally stored ultrasound images. Measurements were taken from three cardiac cycles and then averaged for statistical analyses. We used the Cube formula to calculate left ventricular mass and indexed it for body surface area as recommended by ASE (266).

4.9 Definitions

We defined night-time hypertension as a night-time SBP ≥120 mmHg or DBP ≥70 mmHg for both home and ambulatory monitoring. As recommended by ESH guidelines, we defined nondipping as a reduction in the mean night-time SBP or DBP <10 % compared with daytime values (5). We calculated non-high-density lipoprotein cholesterol (non-HDL-C) as total cholesterol minus HDL-C. We defined diabetes as a fasting plasma glucose level ≥7.0 mmol/l or treatment with antidiabetic drugs (oral hypoglycaemic agents, insulin injections or both). We defined smoking as self-reported daily use of cigarettes. We defined previous CVD event as having self-reported history of previous myocardial infarction or stroke. For categorical analyses, we dichotomized the LVH based on LVMI values with the cut-off level of 95 g/m^2 and 115 g/m^2 for women and men, respectively (266). In the IMT analyses, we divided the study population into ten-year strata and defined increased IMT as IMT over 75th percentile of each stratum to adjust the high correlation between age and IMT (267).

4.10 Statistical analyses

We performed the computations with SAS software version 9.4 (SAS Institute, Cary, NC, USA). We tested normality with Shapiro-Wilk or Kolmogorov-Smirnov tests. LVMI, PWV, and IMT data were log-transformed to obtain a normal distribution for the statistical analyses. We verified the equality of variances with Levene's or with folded F-test. We compared the differences in the characteristics of the participants

by using the Student's t-test for independent samples for continuous variables and Fisher's exact test for categorical variables. All multivariable-adjusted logistic or linear regression models included age, sex, BMI, diabetes, current smoking, non-HDL-C, antihypertensive medication, and a history of MI or stroke as covariates. We considered a two-sided P-value under 0.05 to be statistically significant.

Study I

We calculated Cronbach's alpha for each method to test the internal consistency. We reversed the scores for positive items (questions 6, 11–13) and calculated mean item scores for each measurement method, with a lower score indicating better acceptability. Then we performed repeated measures analysis of variance with post hoc Bonferroni corrections to compare mean item scores. Finally, we compared the pairwise differences in the ranking for the most preferred method with McNemar's test.

Study II

We compared mean ambulatory and home night-time BP levels with paired t-test and evaluated the agreement between night-time home and ambulatory mean SBP and DBPs with intraclass correlation coefficients and Bland–Altman plots. We calculated Pearson's correlation coefficients for the bivariate associations of daytime and night-time BP measures with end-organ damage (LVMI, IMT and PWV), and compared the correlation coefficients with the method described by Dunn and Clark (268). Then we assessed the independent associations between all measures of end-organ damage and BP measures (one measure in the model at a time) with multivariable-adjusted linear regression models.

Study III

We calculated Pearson's correlation coefficients for the bivariate associations of central and brachial BP measures (SBP and PP) with end-organ damage (LVMI and IMT). We compared the differences in the correlations with the method described by Clark and Dunn (268). We performed separate unadjusted and multivariable-adjusted logistic regression analyses to assess the effect of a 10 mmHg increase of each BP measure on the risk of LVH and increased IMT. Furthermore, we assessed the discriminatory power of each BP measure for LVH and increased IMT by using receiver operating characteristic (ROC) curve analysis and compared the difference between areas under the curves (AUC) by using the method introduced by DeLong, DeLong, and Clarke-Pearson (269).

Study IV

We used Kappa (κ) coefficients to assess the diagnostic agreement in diagnoses of the hypertension phenotype (hypertension/normotension and nondipping/dipping) obtained with ambulatory and home monitoring, and between two consecutive home monitoring nights. We calculated the measures of diagnostic performance for home monitoring (sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV)) against the ambulatory measurement. We tested the agreement of dipping percentages as continuous variable with a paired t-test and Bland-Altman plots. Then we used pooled or unequal variances t-test to compare the severity of end-organ damage between dipping categories and BP status determined with ambulatory and home monitoring. We used logistic regression to calculate odds ratios for LVH and increased IMT for nondippers versus dippers and normotensive versus hypertensive participants.

5 Results

5.1 Acceptability of different BP measuring methods (I)

The sample of Study I included 223 participants (mean age 57.0 years; 54.7% women). Mean BP values for different methods are presented in **Table 4**. Median, interquartile range and mean scores for individual questions and mean item scores are showed in Article I, Table 1. More than every fourth participant (26.9%) were taking antihypertensive medication, 7.1% had diabetes, and 5.3% had a history of previous CVD event.

Mean item scores representing the acceptability of BP measurement differed overall and between all of the between-method comparisons ($p<0.001$ for all). The mean item score was the highest for ambulatory monitoring (3.11±0.93) indicating that it was considered the least preferred method. For the rest of the methods, mean item scores decreased from home night-time (2.74±0.81) to home (2.20±0.70) to office (1.95±0.63) measurement. The largest between-method differences of the individual questions were observed in comfort of use and disturbance to home life or everyday activities ($p<0.001$). Moreover, ambulatory monitoring was reported to be more disturbing for work than night-time home monitoring ($p< 0.001$). Overall, 73.1%, 31.8%, 1.3%, and 2.2% of the participants rated office, home, home-night, and ambulatory measurements as the most preferred method, respectively. The differences in preference between all the methods were statistically significant ($p<0.0001$), except for between home night-time and ambulatory measurement ($p=0.48$, Article I, Table 1).

Table 4. Characteristics of study participants

Number of participants	223
Women, n (%)	54.7
Age, y	57.0 (12.9)
Systolic blood pressure, mmHg	
Home daytime	126.3 (13.3)
Home night-time	113.3 (12.2)
Office	130.7 (16.0)
24-h ambulatory	122.7(11.5)
Diastolic blood pressure, mmHg	
Home daytime	76.7 (8.0)
Home night-time	65.2 (7.6)
Office	78.0 (9.1)
24-h ambulatory	73.4 (7.7)
Diabetes mellitus, %	7.1
Current smokers, %	3.1
History of cardiovascular disease event, %	5.3
Antihypertensive medication use, %	26.9

Data are presented as mean (SD) or as percentage.

5.2 Agreement between night-time home and ambulatory monitoring (II and IV)

5.2.1 Blood pressure level (II)

The BP analysis group of Study II included 248 participants (mean age 58.0 years; 55.2% women). The characteristics of participants are presented in Article II, Table 1. The mean number of BP measurements obtained by daytime home, night-time home, daytime ambulatory and night-time ambulatory monitoring were 13.2±2.0, 5.6±1.3, 42.8±6.3, and 16.6±3.5, respectively. Mean night-time BPs were 113.0±12.6/65.2±7.8 mmHg for home and 112.3±12.5/65.0±7.9 mmHg for ambulatory monitoring, respectively. No significant differences were observed between mean night-time home and ambulatory BPs (SBP: 0.7 mmHg±7.6, p=0.16 and DBP: 0.2 mmHg±6.0, p=0.62, Article II, Figure 1). The intraclass correlation coefficients between night-time home and ambulatory SBP/DBPs were 0.81/0.71 ($p<0.0001$ for both), indicating a good agreement between the methods. Furthermore, in the Bland-Altman plots, no systematic differences between the methods were detected in night-time SBP or DBPs (Article II, Figure 2). However,

large individual differences between the two methods were observed. Thus, the 95% limits of agreement for SBP and DBP were -15.3 to 15.3 and -12.0 to 12.0 mmHg, respectively (Article II, Figure 2).

5.2.2 Association of BP measures with hypertensive end-organ damage (II)

The subsamples based on available end-organ damage consisted of 243, 248, and 226 participants for LVMI, IMT and PWV analysis, respectively. The characteristics of the participants for each analysis group are presented in Article II, Table 1. In the LVMI group (mean age 57.8 years; 55.6% women), mean LVMI was 84.1±17.6 (range 53.5–153.6) g/m^2 in women and 100.2±20.8 (range 64.8–163.4) g/m^2 in men. Overall, 20.7% of women and 19.4% of men met the criteria for LVH (266). In the IMT group (mean age 58.0 years; 55.2% women), mean IMT was 0.75±0.18 (range 0.44–1.74) mm in women and 0.79±0.18 (range 0.51–1.39) in men. The mean PWV in the PWV group (mean age 57.2 years; 55.8% women) was 7.8±1.8 (range 4.5–12.8) m/s in men and 7.2±1.8 (range 4.6–15.6) m/s in women.

Pearson's correlation coefficients between end-organ damage markers and BPs are reported in **Table 5**. We found positive relationships between all daytime and night-time SBPs with LVMI, PWV, and IMT ($p<0.0001$ for all). Both daytime home ($r=0.32$, $p<0.0001$) and ambulatory ($r=0.20$, $p<0.01$) DBPs were significantly related to LVMI, but only home and not ambulatory DBP was significantly associated with PWV (home DBP: $r=0.22$, $p<0.001$). We found no statistically significant relationship between IMT and daytime home or ambulatory DBPs ($p\geq0.08$ for both). All night-time DBPs were significantly correlated with all end-organ damage markers ($p\leq0.01$ for all).

Daytime home SBP and DBP values correlated more strongly than daytime ambulatory BPs with all measures of end-organ damage ($p\leq0.02$ for the differences in all comparisons, **Table 5**). In contrast, home and ambulatory night-time SBP and DBP correlated equally strongly with LVMI and IMT ($p\geq0.11$ for the differences in all comparisons). However, the correlation coefficients for PWV and ambulatory vs home SBP differed slightly in favour of ambulatory SBP (r =0.57 vs. 0.50, $p=0.03$, **Table 5**). The scatterplots for the correlations between night-time SBPs and PWV, LVMI, and IMT are shown in Article II, Figure 3.

Table 5. Correlation coefficients for home or ambulatory blood pressure and end-organ damage

	Daytime blood pressure					
	Systolic			Diastolic		
	Home	Ambulatory	P for difference	Home	Ambulatory	P for difference
LVMI	0.52	0.43	0.02	0.32	0.20	0.003
PWV	0.54	0.36	<0.0001	0.22	0.0007	<0.0001
IMT	0.44	0.28	<0.0001	0.11	-0.09	<0.0001
	Night-time blood pressure					
	Systolic			Diastolic		
	Home	Ambulatory	P for difference	Home	Ambulatory	P for difference
LVMI	0.46	0.46	0.91	0.32	0.35	0.46
PWV	0.50	0.57	0.03	0.30	0.37	0.17
IMT	0.37	0.43	0.11	0.17	0.23	0.23

Values indicate Pearson's correlation coefficients. All correlations were statistically significant except for diastolic home or ambulatory daytime BP and IMT. Differences between the correlation coefficients were compared with the method described by Dunn and Clark (268).

Multivariable-adjusted linear regression analyses were conducted with LVMI, PWV or IMT as the dependent variable to examine the independent associations between BPs and end-organ damage (**Table 6**). Only one BP parameter was included as an independent variable in the model at a time due to collinearity issues as indicated by the variance inflation factors ranging from 3.8 to 12.3 between BP parameters. In addition to the BP parameter, all the models included sex, age, BMI, smoking status, history of cardiovascular disease, diabetes, non-HDL cholesterol and antihypertensive medication use as covariates. All daytime and night-time BPs were positively associated with LVMI and PWV ($p \leq 0.007$ for all). Moreover, daytime and night-time SBPs and night-time ambulatory DBP were associated with increased IMT ($p \leq 0.03$ for all). However, daytime home DBP, night-time home DBP or daytime ambulatory DBP were not independently associated with IMT ($p > 0.13$ for all). The adjusted coefficients of determination (Adj. R^2) of all models for LVMI, PWV or IMT that included night-time ambulatory or home SBP/DBP, were within 1–2% indicating that there were comparable associations with end-organ damage between the methods. Although small variations were seen depending on the BP parameter in the model, these determinants explained approximately 34–40%, 49–56% and 46–49% of the variance in LVMI, PWV and IMT values, respectively.

Table 6. Multivariable-adjusted linear regression models for hypertensive end-organ damage

	Left ventricular hypertrophy			Pulse wave velocity			Intima-media thickness		
	t-value	P-value	Model Adj R^2	t-value	P-value	Model Adj R^2	t-value	P-value	Model Adj R^2
Daytime SBP									
Home	5.76	<0.0001	0.40	4.79	<0.0001	0.52	2.59	0.01	0.48
Ambulatory	5.47	<0.0001	0.40	4.83	<0.0001	0.52	3.05	0.003	0.48
Daytime DBP									
Home	3.08	0.002	0.34	2.98	0.003	0.49	0.49	0.63	0.46
Ambulatory	3.43	0.0007	0.35	2.95	0.004	0.49	0.79	0.43	0.47
Night-time SBP									
Home	5.16	<0.0001	0.39	5.82	<0.0001	0.54	3.31	0.001	0.49
Ambulatory	4.74	<0.0001	0.38	6.67	<0.0001	0.56	3.78	0.0002	0.49
Night-time DBP									
Home	3.04	0.003	0.34	3.96	0.0001	0.51	1.52	0.13	0.47
Ambulatory	2.74	0.007	0.34	4.70	<0.0001	0.52	2.15	0.03	0.47

Multivariable-adjusted linear models were adjusted for age, sex, body mass index, smoking status, history of cardiovascular event, diabetes, non-HDL cholesterol and antihypertensive treatment. P-value was <0.001 for adjusted R^2 in all the models. SBP, systolic blood pressure; DBP, diastolic blood pressure.

5.2.3 Diagnostic agreement between home and ambulatory monitoring in detecting BP patterns (IV)

The sample of Study IV consisted of 180 participants (mean age 57.1 years; 62.2% women). The characteristics of the study participants are presented in Article IV, Table 1. The mean number of daytime measurements for ambulatory and home monitoring were 45.7±6.1 and 13.3±2.1, respectively. With respect to night-time BP, the mean numbers for ambulatory and home BP measurements were 16.8±3.0 and 6±0, respectively. As expected, participants classified as nondippers had significantly higher night-time systolic/diastolic ambulatory (118.9±12.9 vs. 107.5±9.5/68.2±7.8 vs. 62.6±6.9 mmHg) and home BPs (home systolic/diastolic: 115.6±12.1 vs. 107.5±10.9/66.1±7.6 vs. 62.2±6.6 mmHg) than dippers ($p<0.001$ for all comparisons).

Detailed results for the binary classification tests (sensitivity, specificity, predictive values, and agreement) for home monitoring in detecting ambulatory night-time hypertension and nondipping pattern are presented in Article IV, Tables 2 and 3. The results for the diagnostic agreement of home monitoring in detecting systolic and/or diastolic ambulatory night-time hypertension and nondipping are shown in **Table 7**. The diagnostic agreement between the methods was good for night-time hypertension (agreement 80%, sensitivity 70%, specificity 86%, $\kappa=0.56$, $p<0.001$, **Table 7**). A total of 63 (35.0%) and 61 (33.9%) of the participants had night-time hypertension based on ambulatory or home monitoring, respectively. In contrast, the diagnostic agreement for detecting nondipping patterns was weak (agreement 54%, sensitivity 68%, specificity 46%, $\kappa=0.12$, $p=0.09$, **Table 7**). Based on ambulatory monitoring, 71 (39.4%) participants were classified as nondippers as compared with 107 (59.4%) who were detected with home monitoring. However, when nondipping was analysed as a continuous variable, mean ambulatory SBP dipping exceeded home SBP dipping by 1.7% (11.5% vs. 9.8%, $p=0.004$). In contrast, no difference was seen in the magnitude of DBP dipping between the two methods (difference: 0.7%, $p=0.33$). Although the mean difference in systolic dipping between the methods was small, we observed large individual-level differences in dipping percentages between the methods (Article IV, Figure 1).

Table 7. Diagnostic agreement between home and ambulatory monitoring in detecting night-time hypertension and nondipping patterns (N=180)

	Ambulatory monitoring (N=180)									
Subjects with home NT/HT	Hypertension (N=63)		Normotension (N=117)		Agreement (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	κ (P-value)
	True positive	False negative	False positive	True negative						
119/61	44	19	17	100	80	70	86	72	84	0.56 (<0.001)
Subjects with home D/ND pattern	Nondipping pattern (N=71)		Dipping pattern (N=109)		Agreement (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	κ (P-value)
	True positive	False negative	False positive	True negative						
73/107	48	23	59	50	54	68	46	45	69	0.12 (0.09)

Night-time hypertension defined as night-time systolic BP ≥ 120 and/or diastolic BP ≥ 70 mmHg. Nondipping was defined as (1-night-time BP/daytime BP) x100 (%) <10 %. Systolic and/or diastolic hypertension/nondipping pattern on home monitoring was compared with ambulatory systolic and/or diastolic hypertension/nondipping pattern. Diagnostic agreement was evaluated with kappa statistics. NT, normotension; HT, hypertension; PPV, positive predictive value; NPV, negative predictive value; D, dipper; ND, nondipper.

5.2.4 Association of night-time blood pressure patterns with end-organ damage (IV)

Participants with night-time hypertension had significantly greater LVMI and IMT values than normotensives, irrespective of the measurement method (**Table 8**). Likewise, ambulatory nondippers had significantly thicker carotid IMT than dippers ($p<0.001$ for all, **Table 9**). In contrast, ambulatory nondippers had greater LVMI values than dippers only when systolic and diastolic dipping were analysed separately (systolic: 94.2 vs. 87.1 g/m2, $p=0.046$; diastolic: 95.2 vs 87.7 g/m2, $p=0.04$; systolic or diastolic: 93.0 vs. 87.5 g/m2, $p=0.12$, **Table 9**). We discovered no differences in LVMI or IMT values between dipping categories based on home monitoring (**Table 9)**.

To investigate further the associations between end-organ damage and BP patterns, we conducted logistic models for LVH and IMT. The odds of LVH were greater in ambulatory systolic and diastolic nondippers compared with corresponding dippers (ambulatory systolic: OR 2.19, $p=0.04$; ambulatory diastolic: OR 2.55, $p=0.02$). However, after adjustment for other risk factors, these associations also lost their statistical significance ($p\geq0.70$ for both, Article IV, Supplemental Table 2). In our study, home nondipping patterns did not associate with prevalent LVH. Furthermore, we failed to associate the nondipping pattern with increased IMT, irrespective of the measurement method (Article IV, Supplemental Table 2).

Table 8. Comparison of the severity of end-organ damage between night-time normotensive/hypertensive participants (N=180)

		LVMI, g/m²			IMT, mm		
	No. with NT/HT	NT	HT	*P-value*	NT	HT	*P-value*
Ambulatory SBP	131/49	85.4 (16.6)	101.1 (20.8)	<0.001	0.71 (0.14)	0.85 (0.18)	<0.001
Ambulatory DBP	139/41	87.2 (17.7)	98.0 (21.6)	0.002	0.73 (0.16)	0.82 (0.17)	0.002
Ambulatory SBP/DBP	117/63	84.9 (15.9)	98.6 (21.5)	<0.001	0.71 (0.14)	0.82 (0.17)	<0.001
Home SBP	133/47	86.4 (17.3)	99.0 (21.2)	<0.001	0.72 (0.15)	0.83 (0.18)	<0.001
Home DBP	136/44	87.5 (18.0)	96.5 (21.2)	0.008	0.73 (0.16)	0.79 (0.17)	0.03
Home SBP/DBP	119/61	85.5 (16.4)	97.9 (21.5)	<0.001	0.72 (0.15)	0.81 (0.17)	<0.001

P-values are for the between-group difference in log-transformed LVMI or IMT. SBP, systolic blood pressure; DBP, diastolic blood pressure; NT, normotensive; HT, hypertensive; LVMI, left ventricular mass index; IMT, intima-media thickness. LVMI data are presented as g/m², and IMT as millimeters.

Table 9. Comparison of the severity of end-organ damage between dippers/nondippers (N=180)

		LVMI, g/m²			IMT, mm		
	No. with D/ND pattern	Dipper	Nondipper	*P-value*	Dipper	Nondipper	*P-value*
Ambulatory SBP	115/65	87.1 (16.3)	94.2 (22.8)	0.046	0.71 (0.14)	0.82 (0.18)	<0.001
Ambulatory DBP	133/47	87.7 (17.1)	95.2 (23.5)	0.04	0.71 (0.15)	0.85 (0.16)	<0.001
Ambulatory SBP/DBP	109/71	87.5 (16.4)	93.0 (22.4)	0.12	0.70 (0.13)	0.82 (0.18)	<0.001
Home SBP	77/103	91.4 (19.2)	88.4 (19.1)	0.26	0.77 (0.15)	0.73 (0.17)	0.09
Home DBP	134/46	89.4 (18.3)	90.5 (21.6)	0.87	0.74 (0.15)	0.77 (0.19)	0.36
Home SBP/DBP	73/107	91.5 (19.3)	88.4 (19.1)	0.25	0.76 (0.15)	0.74 (0.17)	0.21

P-values are for the between-group difference in log-transformed LVMI or IMT. SBP, systolic blood pressure; DBP, diastolic blood pressure; D, dipper; ND, nondipper; LVMI, left ventricular mass index; IMT, intima-media thickness. LVMI data are presented as g/m², and IMT as millimeters.

5.2.5 Reproducibility of home nondipping and night-time hypertension status (IV)

Among the 180 patients with available data on all six night-time home BP measurements, only moderate reproducibility of the nondipping pattern was found between two consecutive nights (agreement 69%, κ=0.37, p<0.001). On the first measurement night, 102 participants were classified as nondippers based on either SBP or DBP values. Of those, 29 (28%) changed from the nondipper to the dipper pattern on the second night. Correspondingly, of the 78 who demonstrated a dipper pattern on the first night, 27 (35%) displayed the nondipping pattern on the second night. Instead, night-time hypertension status showed substantial reproducibility between the two measurement nights (agreement 83%, κ=0.62, p<0.001).

5.2.1 Office versus noninvasive stand-alone central blood pressure in detecting end-organ damage (III)

The characteristics of the whole study population and of the different subpopulations based on LVH and IMT statuses are shown in Article IV, Table 1 and **Table 10**, respectively. The sample of Study III included 246 participants (mean age 57.2 years; 55.3% women). In the whole population, mean central SBP was surprisingly 1.2 mmHg higher than corresponding brachial SBP (p=0.0008), and mean central PP was 5.5 mmHg higher than brachial PP (p<0.0001). Participants with LVH had higher mean age, plasma glucose, SBP, PP, and IMT values than those without LVH (**Table 10**). In addition, individuals with LVH compared to those with normal LVMI had higher prevalence of diabetes and were more likely to take antihypertensive medication (**Table 10**). Those participants with increased IMT had significantly higher levels of serum cholesterol, SBP, and PP than those with normal IMT (**Table 10**).

All central and brachial SBPs and PPs were positively correlated with LVMI and IMT (p<0.001 for all, **Table 11**). Central and brachial SBPs correlated equally well with LVMI (p=0.19 for difference) and IMT (p=0.60 for difference). Brachial PP, however, correlated significantly better than central PP with both LVMI (p=0.03 for difference) and IMT (p=0.04 for difference). The scatter plots for correlations of hemodynamic measures with LVMI and IMT are shown in Article III, Figure 1.

Table 10. Characteristics of participants according to end-organ damage status

Characteristics	Without LVH (n=197)	LVH (n=49)	*P* value	Normal IMT (n=186)	Increased IMT (n=60)	*P* value
Age, years	54.8 (12.0)	66.8 (10.2)	<0.001	56.8 (12.6)	58.3 (12.5)	0.44
Women, %	54.8	57.1	0.77	57.5	48.3	0.21
Body mass index, kg/m^2	26.4 (4.6)	27.5 (3.9)	0.14	26.6 (4.6)	26.9 (4.1)	0.58
Serum cholesterol, mmol/l	5.3 (0.9)	5.3 (1.0)	0.80	5.2 (0.9)	5.6 (0.9)	0.002
HDL cholesterol, mmol/l	1.5 (0.4)	1.4 (0.4)	0.21	1.5 (0.4)	1.5 (0.4)	0.71
Fasting plasma glucose, mmol/l	5.8 (0.6)	6.1 (0.7)	0.02	5.9 (0.6)	5.9 (0.7)	0.69
Mean central systolic BP, mmHg	128.1 (13.2)	141.0 (15.2)	<0.001	129.2 (13.8)	135.3 (15.8)	0.004
Mean central PP, mmHg	55.1 (11.8)	66.0 (15.0)	<0.001	56.0 (12.6)	61.2 (14.3)	0.008
Mean brachial systolic BP, mmHg	126.9 (14.2)	139.1 (15.5)	<0.001	127.8 (14.5)	134.1 (16.4)	0.005
Mean brachial PP, mmHg	50.0 (10.5)	59.2 (11.7)	<0.001	50.6 (10.6)	55.9 (12.7)	0.002
LVMI, Women, g/m^2	77.0 (10.3)	106.7 (11.6)	<0.001	82.2 (15.2)	86.4 (18.6)	0.22
LVMI, Men, g/m^2	92.7 (12.2)	134.9 (16.8)	<0.001	99.1 (21.5)	105.0 (20.0)	0.19
IMT, mm	0.7 (0.2)	0.9 (0.2)	<0.001	0.7 (0.1)	1.0 (0.2)	<0.001
Diabetes mellitus, (%)	7.1	18.4	0.02	10.2	6.7	0.61
Current smoker, (%)	8.6	8.2	0.99	8.1	10.0	0.64
History of CVD event, (%)	2.0	8.2	0.052	3.8	1.7	0.68
Antihypertensive medication use, (%)	21.3	44.9	0.0008	27.4	21.7	0.38

Values are mean (SD) for continuous variables or percentage for categorical variables. LVH, left ventricular hypertrophy; IMT, intima-media thickness; HDL, high-density lipoprotein; BP, blood pressure; PP, pulse pressure; LVMI, left ventricular mass index; CVD, cardiovascular disease defined as myocardial infarction or stroke.

Table 11. Correlation coefficients for central or brachial BP measures and end-organ damage

	Systolic Blood Pressure			Pulse Pressure		
Organ damage	Central	Brachial	*P* for difference	Central	Brachial	*P* for difference
LVMI	0.40*	0.42*	0.19	0.27*	0.34*	0.03
IMT	0.33*	0.32*	0.60	0.35*	0.40*	0.04

Data are shown as Pearson's correlation coefficients. LVMI and IMT were log-transformed before the analysis. Correlation coefficients were compared using a method described by Dunn and Clark. LVMI, left ventricular mass index; IMT, intima-media thickness. *p<0.001.

In the unadjusted and multivariable-adjusted models, all BP measures were significantly associated with prevalent LVH and increased IMT (**Table 12**). In the multivariable-adjusted models, a 10-mmHg increase in central SBP, brachial SBP, central PP, and brachial PP was related to 68%, 59%, 49%, and 52% greater odds of LVH, respectively (**Table 12**). Correspondingly, a 10-mmHg increase in central SBP, brachial SBP, central PP, and brachial PP was related to 31%, 29%, 35%, and 56% greater odds of increased IMT, respectively (**Table 12)**. However, the ROC curve analysis (Article IV, Figure 2) showed that models with central SBP and PP carried similar discriminatory powers for LVH and increased IMT as corresponding brachial BP measures (p≥0.16 for all AUC comparisons, Article III, Figure 2).

Table 12. The odds ratios (with 95% confidence intervals) for prevalent end-organ damage per 10-mmHg increase in different BP measures

	Univariable models			
	LVH		Increased IMT	
BP Parameter	OR (95% CI)	P value	OR (95% CI)	P value
Central SBP	1.86 (1.46–2.36)	<0.001	1.33 (1.09–1.62)	0.005
Central PP	1.86 (1.43–2.40)	<0.001	1.34 (1.07–1.66)	0.009
Brachial SBP	1.69 (1.36–2.11)	<0.001	1.31 (1.08–1.59)	0.006
Brachial PP	2.02 (1.50–2.73)	<0.001	1.49 (1.15–1.93)	0.002
	Multivariable-adjusted models			
	LVH		Increased IMT	
BP Parameter	OR (95% CI)	P value	OR (95% CI)	P value
Central SBP	1.68 (1.27–2.22)	<0.001	1.31 (1.04–1.67)	0.02
Central PP	1.49 (1.11–2.00)	0.007	1.35 (1.04–1.74)	0.02
Brachial SBP	1.59 (1.22–2.09)	<0.001	1.29 (1.02–1.62)	0.03
Brachial PP	1.52 (1.07–2.15)	0.02	1.56 (1.13–2.16)	0.007

Each hemodynamic measure was evaluated in a separate model. Multivariable-adjusted models include sex, age, BMI, smoking, history of CVD event, diabetes, non-HDL, and use of antihypertensive medication as covariates. LVMI, left ventricular mass index; IMT, intima-media thickness; SBP, systolic blood pressure; PP, pulse pressure.

6 Discussion

6.1 Acceptability of different BP measuring methods (I)

Study I revealed that in a general Finnish population sample, the acceptability of BP measurement methods increased from ambulatory monitoring to home night-time to home daytime to office measurement. Especially ambulatory but also home night-time measurement caused greater disturbances to sleep, more discomfort, and increased anxiety as compared with daytime home or office measurement, thus leading to lower acceptance.

Little et al. carried out the first extensive investigation on the acceptability and preferences between different methods in 2002 by comparing home daytime BP measurement, ambulatory monitoring, office measurement by a nurse or a doctor, and self-measurement at the office. They reported that home and office measurements by a nurse were two of the most acceptable methods while the acceptability of ambulatory BP monitoring was the lowest (157). In addition, these investigators stated that home monitoring was the most preferred method in contrast to the preference for office BP measurement listed by our participants. This discrepancy might be at least partly explained by the differences in the study populations. While our study cohort was derived from the general population, Little et al. evaluated only patients with hypertension (157).

Shortly after our study was published, the report of Wood et al. used also the questionnaire introduced by Little and colleagues to compare the acceptability of office, home daytime and ambulatory monitoring between white British, South Asian and African Caribbean study populations with a total of 770 participants. In accordance with our results, the acceptability increased from ambulatory to office to home measurement across all ethnicities. Interestingly, white British participants had higher acceptability for each method as compared with South Asian and African Caribbean participants, although statistical significance was reached only when ambulatory monitoring was compared between British and South Asian participants (158). The mean acceptability scores in our study compared to the study of Little and that of Wood for ambulatory monitoring were quite similar (3.11, 2.8–3.1, and 3.88, respectively). Interestingly, the largest difference was between two study

populations from the UK (2.8 versus 3.88). Similarly, the mean scores for home daytime measurement varied only slightly from 2.0 to 2.67, whereas a larger variation was seen between office measurement (1.95 to 3.45) across these three studies (157,158,270).

In our study, office measurement was the most preferred method as opposed to home monitoring in two other reports. This might at least partly be explained by the differences in the study populations. Between 63% to 100% of the populations examined in the studies conducted in both the UK and the US had been previously diagnosed with hypertension, whereas in our study, only 27% of the sample were using antihypertension medication. Furthermore, we used a rather arduous seven-day measurement protocol for home daytime measurements in contrast to a four-day protocol, which seems to be enough to allow the assessment of home BP (139). We suspect that a less demanding protocol might have been better accepted. Interestingly, focus group interviews in the study of Wood et al. revealed that some patients perceive office measurements as more accurate because a professional is performing the measurement, and they appreciate the possibility for the prompt interpretation of the results (158). It is possible that this kind of reasoning was also prevalent in our study sample.

In accordance with our findings, both Little and Wood reported that the main drawback of ambulatory monitoring for the patients was sleep disturbance and inconvenience during the work-day (157,158). In another study of 83 patients by McGowan and Padfield, 81% of the participants preferred home measurement to ambulatory measurement because it caused less interference with sleep and less embarrassment in public and furthermore, it gave the possibility to assess the results immediately and provided a feeling of being more “in control.” The rest of the patients preferred the ambulatory measurement because of the shorter duration of the procedure (154).

Two studies have previously compared the acceptability and preference between night-time home and ambulatory monitoring. In the study conducted in Greece by Stergiou et al. with 67 patients, 89% reported more night-time sleep disturbance during ambulatory than with home monitoring. More patients also preferred home over ambulatory monitoring (55% versus 45%) for their next night-time BP measurement method, however, the difference was not statistically significant (147). In addition, the brief report of Ushio et al. with 40 healthy volunteers revealed that home-night BP measurement was overall more comfortable than ambulatory monitoring. However, no significant difference was reported in the quality of sleep although home night-time measurements were taken six times at one-hour intervals during the night over several nights, whereas ambulatory measurements were taken at 30-minute intervals for one night (146).

In conclusion, both home and ambulatory night-time monitoring seem to be relatively well accepted by patients. However, both home daytime and night-time monitoring seemed to be more acceptable to patients than 24-hour ambulatory monitoring.

6.2 Agreement between night-time home and ambulatory monitoring (II and IV)

6.2.1 BP level (II)

In study II, we observed no difference in the mean BP levels or systematic bias between night-time home and ambulatory BPs in a general population sample. In accord with our findings, two small cross-sectional studies with 40 healthy volunteers (146) and 81 hypertensive patients (147) have reported that night-time home monitoring produces similar BP values than ambulatory monitoring. Furthermore, in the Japan Morning Surge-Target Organ Protection (J-TOP) study with 50 hypertensive patients that was designed to assess the changes in home and ambulatory BP patterns induced by antihypertensive medication, night-time home and ambulatory BP readings were similar at baseline and after a six-month treatment period with antihypertensive medication (148). In contrast, home systolic night-time BP has been slightly (2.6 mmHg) higher than ambulatory BP in two studies conducted in Greece (150) and Japan (149) with 131 and 854 hypertensive patients, respectively.

The previous slightly conflicting results may be explained by the differences in measurement protocols in these studies with the number of measurement nights ranging from three to nine, and with a varying number of measurements per night. Moreover, in three of the previous studies, the number of night-time home measurements actually exceeded the number of ambulatory measurements (146,148,149). In our study with 248 participants, we demonstrated that mean night-time home BP, measured three times per night on two nights, was similar to mean night-time ambulatory BP. Furthermore, our Bland-Altman plots did not reveal any systematic differences between these two methods. However, we observed large individual-level disparities in some participants. Differences in the quality of sleep during measurement nights, which has been shown to affect both night-time home and ambulatory BPs, may explain at least partly these disparities. All in all, a very recently published meta-analysis with the present study included found no difference in the mean BP levels between the home and ambulatory monitoring (152).

6.2.2 Association of BP measures with hypertensive end-organ damage (II)

In study II, we observed that the associations between night-time home and ambulatory BP with hypertensive end-organ damage indicators were comparable, except for the slightly stronger association between ambulatory SBP and PWV.

In line with our findings, in a Greek study with 131 hypertensive patients, night-time home BP (measured on three nights) and night-time ambulatory BP had similar correlations with LVMI and carotid IMT (150). In contrast, a Japanese study with 854 patients conducted by Ishikawa et al. found that night-time home SBP was actually more strongly associated with LVMI and the urine albumin: creatinine ratio than night-time ambulatory SBP (149). In a smaller study also by Ishikawa et al. with 41 patients, antihypertensive medication-induced reduction in LVMI was significantly associated with reduction of night-time home SBP, but not with reduction of ambulatory SBP (148). However, in latter two studies, night-time home BP was measured on an average of seven to nine nights.

After the publication of Article II, Kollias et al. studied the optimal home night-time protocol for the estimation of nocturnal BP level and prediction of end-organ damage in a sample of 94 hypertensive patients. They concluded that a two-night protocol with six readings is the minimum number for assessing night-time BP compared with ambulatory monitoring, and produces comparable relation to end-organ damage, thus replicating our findings (151). Overall, the results of previous studies suggest that an extended measurement protocol with a large number of night-time home measurements taken on numerous nights can result in improved diagnostic accuracy of prevalent end-organ damage. However, this type of night-time home measurement protocol would not likely to be feasible for most patients in everyday clinical practice. In favour of home monitoring, we also observed that daytime home BPs displayed stronger correlations with all measures of end-organ damage compared with daytime ambulatory BPs. This finding was also supported by previous findings by Ishikawa et al. (149).

In conclusion, based on the results of this and other studies, measurement of night-time home BP with a timer-equipped home device using a feasible two-night measurement protocol can be promoted as an alternative method for ambulatory monitoring. However, more prospective data on the clinical utility of night-time home BP for predicting adverse cardiovascular outcomes are needed until it can be widely endorsed.

6.2.3 Diagnostic agreement between home and ambulatory monitoring in detecting BP patterns (IV)

According to the results of Study IV, ambulatory and home monitoring can be used as alternative methods to detect night-time hypertension. In contrast, home monitoring tended to classify more participants as nondippers than dippers compared with ambulatory monitoring.

We observed that ambulatory SBP dipping was 1.7 percentage points greater than home SBP dipping. Consequently, a markedly larger number of systolic nondippers was found based on home instead of ambulatory monitoring (59% vs 39%). In line with our findings, similar trends were seen in the studies of Stergiou et al. (22% home vs 16% ambulatory nondippers) (147) and Andreadis et al. (24% vs 12%) (150). In concordance with these findings, in the study of Ushio et al., the average night-time SBP fall was 5.3% and 14.7% on home and ambulatory monitoring, respectively (146). Furthermore, in the J-TOP study, ambulatory systolic dipping exceeded home dipping by 3.6% (148). In all previous studies, except for the J-TOP study and the study by Ushio et al., a markedly lower number of home than ambulatory measurements were performed. In our study, the prevalence of nondippers was quite high when compared to two large general population cohorts from Japan (63) and Denmark (64) reporting 16% and 28% of the population being nondippers or reverse dippers on ambulatory monitoring, respectively. The reasons for the high number of nondippers on both home and ambulatory monitoring in this study are unclear. However, in a recent study conducted by Fujiwara et al. where they compared the effect of two treatment regimens on morning BP surge based on home monitoring, the prevalence of nondipping was quite high in both treatment groups (46 to 48.5%). However, their cohort consisted of patients with morning hypertension (271).

Only a few previous studies have compared the diagnostic agreement in detecting nondipping and night-time hypertension between ambulatory and home monitoring. Two Greek studies reported a substantial diagnostic agreement in detecting a nondipping pattern between home and ambulatory monitoring in hypertensive cohorts with 81 and 131 patients (147,150). However, the kappa coefficients only ranged from fair to moderate (0.20–0.31) in both studies (147,150). Furthermore, in a 94-patient subsample of the latter study including patients with a total of nine measurements taken successively across three nights, Kollias et al. observed a slightly better agreement between ambulatory and home monitoring for detecting the nondipping pattern (agreement 84%, κ=0.40). However, the agreement did not significantly increase after the fourth measurement (151). With respect to night-time hypertension, Kollias et al. reported a subsequent agreement between the methods (agreement 78%, κ=0.51), which was similar to our findings. In contrast to the nondipping pattern, the diagnostic agreement in detecting night-time

hypertension improved up to eight measurements before it plateaued (151). Thus, in line with our results, Kollias et al. reported a more robust diagnostic agreement between the two methods in detecting night-time hypertension than the nondipping pattern. They proposed a minimum of six measurements as a requirement for the assessment of night-time home BP (151).

Although the diagnostic agreement in detecting nondipping pattern in our study was suboptimal between ambulatory and home monitoring, it does not automatically indicate that the home monitoring device used in this study was inaccurate. Several factors might affect the reproducibility of estimating the BP nondipping pattern in this and previous studies. Both home and ambulatory monitoring have imperfect reproducibilities, as discussed previously in Chapter 2.3.6. Moreover, small and clinically irrelevant BP differences near the diagnostic dipping threshold might have led to contradicting dipping categories within the same individual. In both methods, night-time BP is measured in the same supine position with minimal physical activity. In contrast, daytime measurement conditions vary greatly between ambulatory and home BP measurements. Although intensive training is discouraged during ambulatory monitoring, physical activity cannot be completely avoided during ambulatory monitoring and thus it differs from home measurements, which are obtained in the sitting position after an adequate resting period. In addition, a random measurement error and natural biological fluctuation of BP might lead to the large within-patient variability in BP. Because the measurements were taken on different nights, the varying sleep quality might have affected BP values, as has been shown previously (223). Finally, antihypertensive medication and the time of drug administration might affect the dipping status (230). However, the difference in night-time BP values between home and ambulatory BP monitoring could not be explained by these kinds of pharmacodynamic effects, because both BP measures were taken at a similar time of day.

6.2.4 Association of night-time blood pressure patterns with end-organ damage (IV)

We demonstrated that participants with night-time hypertension had greater LVMI and IMT values than normotensive participants, regardless of the measurement method. Similarly, Andreadis et al. found a positive, although statistically insignificant, trend toward greater LVMI and IMT values among patients with night-time home hypertension as compared with their normotensive counterparts (150).

We found that nondippers had higher SBP and DBP values than dippers irrespective of the measurement method. In contrast, both Cuspidi et al. and Jiri et al. reported 48-hour ambulatory SBP and DBP values to be comparable between dippers and nondippers. Nevertheless, nondippers had higher LVMI than their

dipping counterparts in these studies (171,272–274). Similar findings have been reported in studies investigating normotensive (275), isolated hypertensive (276) and essential hypertensive (277–281) patients cohorts. However, in a larger study examining 854 patients reported by Ishikawa et al., nondipping was not related to end-organ damage in either the home or ambulatory BP monitoring (149). In the small study of Albert et al. with 73 normotensive overweight men, carotid IMT increased with decreasing systolic and diastolic dipping percent (282). In our study, nondippers had higher values of LMVI and IMT than dippers only when dipping was defined using ambulatory instead of home monitoring. In addition, the initial categorical analyses revealed a significant association between ambulatory systolic and diastolic nondipping pattern and LVH. However, after adjusting for classic risk factors, neither of these parameters remained statistically significant.

Our inability to detect a significant relationship between the home nondipping pattern and end-organ damage might be attributable to our relatively small study sample derived from the general population. In our population, BP levels were relatively low and there were only small absolute night-time drops in systolic and diastolic home BPs BP values. Moreover, end-organ damage is less common in the general than in the hypertensive population. Nonetheless, it is the actual BP level rather than the categorical dipping status irrespective of the monitoring method which seems to identify more reliably those participants with more severe end-organ damage.

6.2.5 Reproducibility of home nondipping pattern and night-time hypertension status (IV)

In Study IV, we found that the reproducibility of home night-time BP was only moderate between two consecutive nights. There are rather few previous studies that have examined the reproducibility of the nondipping pattern assessed by home monitoring. The study of Stergiou and colleagues only briefly mentions that agreement of nondipping pattern between three consecutive measurement nights varied from 71 to 73% (147), which is very similar to the values in our study (69%).

In contrast, the reproducibility of night-time hypertension diagnosis was good between the first and second home monitoring nights. Two studies have previously examined the reproducibility of night-time home BP. In both studies, the reproducibility of night-time BP was poor, especially when patients experienced different qualities of sleep between measurement nights. In the study of Hosohata, the absolute differences between two night-time monitorings were greater than 10 mmHg in 46.9% and 26.0% of the patients for SBP and DBP, respectively (231). However, in both studies, BP was only measured once at two a.m. over two or ten nights (143,231).

6.3 Office versus noninvasive stand-alone central BP in detecting end-organ damage (III)

In Study III, we detected positive associations between higher continuous levels of central SBP and PP and an adverse end-organ damage status. However, the corresponding associations were essentially similar for brachial SBP and even stronger for brachial PP. Furthermore, central SBP and PP carried comparable discriminatory powers to detect LVH or increased IMT than the corresponding brachial measures.

As far as we are aware, no previous study has used the stand-alone Microlife WatchBP Central monitor in a similar research setting. As shown by Narayan et al., noninvasive central BP estimation is device-dependent, making comparisons with previous studies somewhat problematic (246). Probably due to these methodological issues, the results from previous studies assessing the associations between LVMI and central versus peripheral hemodynamic measures are somewhat mixed. In line with our findings, several studies have reported similar or weaker correlations between central than peripheral SBP with LMVI (249–253). In contrast, others have found a stronger association between central SBP and LVMI than with peripheral SBP (255,283–289). However, only two of these studies included statistical testing for the difference between the correlations (255,289). With regard to IMT, some studies have reported a stronger relationship between IMT and central SBP than with brachial SBP (257,289–291), while others have not (254,255).

We found brachial PP to associate more strongly with both IMT and LVMI than was achieved with the noninvasively calculated central PP. Furthermore, calculated central PP did not have a significant incremental predictive value in the diagnosis of LVH or increased IMT as compared with conventional office measures. In regards to previous findings, some studies have found central PP to associate more strongly to IMT and LVMI than brachial PP (250,255,257,285,289,292), while others have not (249,251,253,293).

There are marked differences in previous studies that complicate any direct comparison between the results. Among the most obvious differences are the technique used to determine the pulse waveform and the BP measure used to calibrate the pulse wave and the BP measurement device. In addition, differences in study populations (age, cardiovascular risks, etc.) should be considered when results are applied in a clinical setting.

Interestingly, we observed that mean SBP and PP values obtained with the stand-alone noninvasive central BP monitor were higher than conventional office SBP. This contradicts the paradigm that brachial SBP and PP should be higher than the corresponding central values due to pulse wave amplification. Although the monitor used in this study was successively validated against an invasive BP measurement, the validation report itself showed numerically higher mean noninvasive central BP

values as compared with their brachial counterparts (141 vs. 138 mmHg and 69 vs. 76 mmHg, respectively. Moreover, the algorithm does not necessarily generate reliable values across all patients, especially when the measurements are not taken in the supine position in which it was validated (243). Indeed, several studies have shown that average SBP is higher when measured in the supine rather than the sitting position (294–297). SBP has been reported to be eight mmHg lower in the sitting versus the supine position, even with the cuff level at the right atrium during both measurements (295). With respect to DBP, it is approximately five mmHg higher in a sitting than in a supine position (298). In addition, in the Microlife WatchBP Office central device, the estimated central waveforms are calibrated to brachial SBP and DBP, even though the current recommendation is to use MAP and DBP (113).

In our study sample, central BP measures did not improve the diagnostic accuracy for left ventricular hypertrophy or carotid IMT over brachial measures. Our findings were somewhat at odds with previous results. However, these discrepancies might be related to the major differences in the studies and the properties of the monitor itself.

6.4 Limitations of the study

Despite its strengths such as comprehensive examinations for cardiovascular risk factors and detailed data on hypertensive end-organ damage, the results of our study need to be interpreted in the context of its limitations. One of the major limitations of our study is its cross-sectional nature. A prospective setting would be a better way to assess the relationship between exposure and outcome and hence to estimate the true clinical value of the different measurement methods.

In Study I, participants were instructed to fill in the questionnaire after having completed all of the BP measurements. Consequently, there was approximately a seven-day time period between the office and ambulatory monitoring and the filling in of the questionnaire. In contrast, the scoring of acceptability of different BP measuring methods was carried out almost immediately after the home measurements. In some participants, this time gap might have biased the scoring or led to careless responding. Indeed, we had to exclude ten participants from Study I because they gave identical scores for three or even all four measurement methods.

Studies II and IV shared some common limitations. First, ambulatory and home night-time BP were measured with different oscillometric monitors with the monitoring being carried out on different days approximately a week apart for feasibility reasons, thus day-to-day BP variability might confound our results. However, simultaneous recordings during the same night would probably have been poorly tolerated by most of the participants. Second, the order of conducting ambulatory and home monitoring was not randomized, i.e. ambulatory monitoring

was invariably measured prior to home monitoring. Third, we did not thoroughly assess the quality of sleep during measurement nights, although it might have affected the absolute BP values, and consequently the dipping pattern (223,231). Fourth, we used the same diagnostic threshold for home and ambulatory monitoring because the optimal definition for night-time home dipping has not yet been determined. However, as discussed above, this might not be appropriate due to the differences in measurement conditions.

Study III had some limitations. Although several studies have shown that different antihypertensive medication might differently influence peripheral and central BP, we could not adjust the results with respect to the antihypertensive medication class due to the low number of participants being treated for hypertension. Second, the noninvasive brachial BP measures used to calibrate pulse waveform were performed approximately 30 seconds before the pulse waveform recording. Thus, the effect of beat-to-beat BP variability may have confounded our results. Finally, the possible inaccuracies in brachial BP measurement used in the calibration of the estimated central pulse waveform might have adversely affected the accuracy of the central BP measures determined in our study.

7 Summary/Conclusions

The aims of this thesis were to elucidate how BP measures obtained with a timer-equipped home monitor during the night and with a stand-alone noninvasive central monitor in order to compare to current measurement methods and whether they improve the diagnostics for hypertensive end-organ damage in a Finnish population. We also studied patients' preferences between measurement methods.

All measurement methods were generally well-accepted by the participants. The most preferred measurement method was the office BP measurement whereas the least acceptable method was ambulatory monitoring. Home night-time measurement was slightly more preferred than ambulatory monitoring.

Night-time mean BP levels obtained with ambulatory and home monitoring were similar, and there was substantial agreement between the two methods in detecting night-time hypertension. Moreover, home and ambulatory BP values correlated similarly with end-organ damage, except for a slightly stronger correlation between ambulatory monitoring and PWV compared with home monitoring.

Based on these results and previous findings, home night-time monitoring is a convenient, accurate, well-accepted alternative to the relatively onerous ambulatory monitoring in detecting night-time hypertension. In a clinical setting, the adoption of home night-time BP measurement would result in a reduction in costs and the number of laborious, uncomfortable procedures. However, more data on the prospective accuracy of night-time home BP for predicting adverse cardiovascular outcomes are needed until it can be widely endorsed.

The diagnostic agreement between the two methods in diagnosing the nondipping pattern was only fair. Similarly, the reproducibility of nondipping pattern between two consecutive nights was suboptimal. The nondipping pattern on home monitoring did not seem to identify those participants with established end-organ damage. However, based on previous studies, the independent value of the nondipping pattern irrespective of the BP level seems to be relatively small.

Surprisingly, we found that office brachial SBP and pulse pressure were similarly or even more strongly correlated to end-organ damage than the corresponding noninvasive central measures. Thus, the determination of central hemodynamics with the stand-alone monitor used in our study does not seem to

improve end-organ diagnostics over conventional office BP. Based on recent publications, it is evident that noninvasive central BP values are technique and device-dependent. Although these results might not be generalized to noninvasive central BP obtained with other devices, our initial results do not support the routine use of central hemodynamics as measured with this device.

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