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THE ARCTIC UNIVERSITY OF NORWAY

Faculty of Health Sciences

A Comparison Between Office Blood Pressure Measurements and Ambulatory Blood Pressure Measurements in the Healthy Middle-Aged General Population

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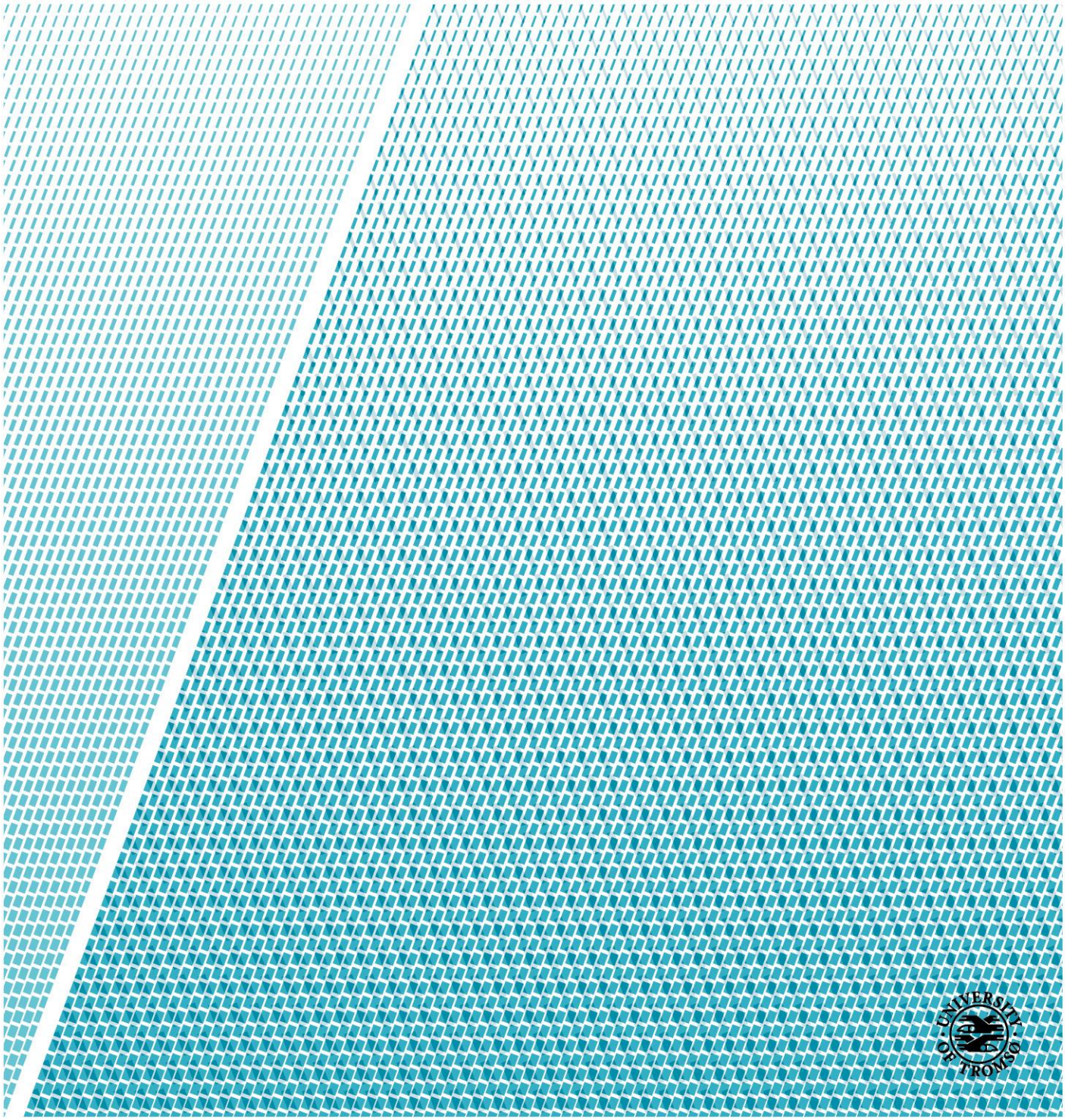
Master's thesis in medicine, MED-3950, MK-14

UiT – The Arctic University of Norway, 2019



Preface

I have worked on this master thesis from August 2018 to June 2019. I have conducted literature searches, worked with and conducted the statistical analysis in the statistical software Stata and read over 30 articles related to the topic of the thesis – all of which I am certain will be valuable experiences to future scientific work.

The aim of this master thesis is to compare and to quantify the difference between office measured blood pressure and ambulatory blood pressure measurement, in the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6). The project required no extra funding.

I have previously used data from the RENIS-T6 in my work at the integrated research program at the medical studies in Tromsø. In 2016/2017 I had a full year of research in the Metabolic and Renal Research group at the Department of Clinical Medicine. My first article, *Low-grade impairments in cognitive and kidney function in a healthy middle-aged general population: a cross-sectional study*, has been published in BMC Nephrology.

I would like to thank my supervisors and mentors Professor Dr. Med Bjørn Odvar Eriksen and Associate Professor Dr. Med Toralf Melsom for excellent help and guidance. Bjørn always knows what to do - whether I am stuck with some coding in Stata, or if I need help in interpreting results. I appreciate the discussions with Toralf, as he is very knowledgeable as well as updated on recent studies. Bjørn and Toralf also proofread my work – educating me in how to write good scientific English. I would also like to thank my family for proofreading the thesis and for valuable discussions.

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Summary

Background: Ambulatory blood pressure measurements are frequently lower compared to office measurements. Our aims were to investigate the relationship between office blood pressure measurements and ambulatory measurements, and to quantify the difference between the two methods.

Methods: This study included 1608 participants aged 50 – 62 years from the municipality of Tromsø, Norway. Office blood pressure measurements and ambulatory measurements was compared using the Bland-Altman plot, Deming regression and paired sample t-test. The Pearson correlation coefficient was also calculated.

Results: The mean (standard deviation) daytime ambulatory systolic and diastolic blood pressure were 130.2 mmHg (13.2) and 82.1 mmHg (8.7), respectively. The mean systolic and diastolic observed office blood pressure were 129.6 mmHg (17.7) and 83.4 mmHg (9.8), respectively. Office diastolic blood pressure was significantly higher than ambulatory diastolic blood pressure ($P<0.001$). In Bland-Altman plot, office systolic blood pressure was on average 0.53 mmHg lower than daytime ambulatory systolic blood pressure, and office diastolic blood pressure was on average 1.33 mmHg higher than daytime ambulatory diastolic pressure. In Deming regression, for each unit increase in ambulatory systolic blood pressure and ambulatory diastolic blood pressure, office systolic blood pressure increased with 0.68 mmHg ($P<0.01$) and office diastolic blood pressure increased with 0.85 mmHg ($P<0.01$), respectively. The Pearson R correlation between daytime ambulatory and office systolic blood pressure, and daytime ambulatory and office diastolic blood pressure was 0.73 ($P<0.01$) and 0.72 ($P<0.01$), respectively.

Conclusion: We found significantly higher observed office diastolic blood pressure compared to ambulatory diastolic blood pressure. However, the difference was small and probably not clinically significant for the individual patient. The blood pressure measurements conducted by trained study nurses are not directly comparable to measurements in the doctor's office. In future studies, measurements in the doctor's office should be compared to office blood pressure measurements conducted by trained research personnel.

Abbreviations

ABPM	Ambulatory blood pressure measurement
ACC	American College of Cardiology
AHA	American Heart Association
ADBP	Ambulatory diastolic blood pressure
ASBP	Ambulatory systolic blood pressure
CI	Confidence interval
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
ESC	European Society of Cardiology
ESH	European Society of Hypertension
HDL	High density lipoprotein
LDL	Low density lipoprotein
OBPM	Office blood pressure measurement
ODBP	Office diastolic blood pressure
OSBP	Office systolic blood pressure
RENIS-T6	Renal Iohexol Clearance Survey Tromsø 6
SBP	Systolic blood pressure
SD	Standard deviation

1 Introduction

According to the World Health Organization, 1/3 of all deaths worldwide are due to cardiovascular diseases (CVD). Hypertension is the most important risk factor for developing CVD, and it is estimated that 1.13 billion people worldwide are affected by this condition (1). Hypertension is associated with premature morbidity and mortality, and contributes enormously to increased healthcare costs. In 2015, Centers for Disease Control and Prevention in US estimated that 48 billion USD are related to hypertension costs in health care services, medications and missed days of work (2). Hypertension remains the major preventable cause of CVD and all-cause death in Europe despite that average blood pressure has decreased in all western countries from 1975 to 2015 (3-5).

There has been a continuous progress in the understanding of the epidemiology, pathophysiology and risk associated with hypertension over the last 50 years, and it is accepted that lowering high blood pressure will reduce premature morbidity and mortality (3). We also acknowledge the association between physical inactivity, overweight and obesity, tobacco, alcohol use, and diet (increased salt intake) and hypertension (2).

Hypertension is primarily an asymptomatic condition best detected by opportunistic measurement of blood pressure or population screening programs (3). In 2018, the European Society of Cardiology (ESC) and European Society of Hypertension (ESH) published new guidelines for the management of arterial hypertension. The guidelines define hypertension as office measured systolic blood pressure (SBP) ≥140 mmHg and/or office measured diastolic blood pressure (DBP) ≥90 mmHg. They recommend a wider use of out-of-office ambulatory blood pressure measurements (ABPM) and/or home blood pressure measurements. This should be used as an alternative to office blood pressure measurements (OBPM) to confirm the diagnosis of hypertension as well as to detect white coat and masked hypertension, and monitor blood pressure control (3). The American College of Cardiology (ACC) and the American Heart Association (AHA) published new guidelines on management of hypertension in 2017. They previously defined hypertension as office measured SBP ≥140 mmHg and/or DBP ≥90 mmHg, but in the new guidelines, they lowered the definition of hypertension to SBP of ≥130 mmHg and/or DBP to ≥80 mmHg. The AHA/ACC argue that a lower definition of hypertension allows earlier intervention, and that the new definitions can address

complications occurring at lower blood pressure levels (6). The ESH/ESC on the other hand, found no beneficial evidence from RCTs, meta-analysis and post hoc analysis of lowering blood pressure to <130/80 mmHg, except perhaps further reductions in the risk of stroke. However, a consistent finding was that reducing SBP to <120 mmHg increase the incidence of cardiovascular events and death (3).

Blood pressure in clinical settings are measured either manually with a sphygmomanometer or with an electronic automated device. Observed OBPM refers to medical staff taking the blood pressure when in the same room as the patient. Accordingly, unobserved OBPM refers to automatic measurements unattended by medical staff (7). Out-of-office measurements refer to either ABPM or home blood pressure measurements. ABPM measures the blood pressure at intervals normally over 24 hours, thereby including measurements during normal daily activities. The home blood pressure measurement provides a record of multiple measurements taken by the patients in their own home (3).

One of the motions of conducting this study was the claim that blood pressure differs significantly between the two methods of measurement. Previous studies have investigated the relationship between OBPM and ABPM, and found that ABPM is a better predictor of hypertension-mediated organ damage and a better predictor than office blood pressure of cardiovascular morbidity and mortality (3, 8-13). On average, ABPM is lower than blood pressure taken in the office setting, partially because white coat hypertension being present (3). However, large population based studies on this issue are scarce. ABPM is often viewed as the gold-standard of measuring blood pressure (14).

In the present study, we investigated the relationship between OBPM and ABPM in a healthy middle-aged general population. Further, our aim was to quantify the difference between OBPM measurements and ABPM in this population.

2 Materials and methods

2.1 Study population

The Tromsø study is a series of population-based surveys in the municipality of Tromsø, North Norway. The current study is based on the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6, conducted from October 2007 to June 2009), which is a substudy of the sixth survey of the Tromsø Study (T6). Details on T6 has been published previously (15).

All individuals between 60-62 years and a random sample of 40 % of all individuals between 50-59 years were drawn from the population registry (n=5464) and invited to participate. In total, 3564 completed the T6 of which 739 were excluded because of self-reported myocardial infarction, angina pectoris, stroke, diabetes mellitus or renal disease. The remaining 2825 eligible subjects were invited to participate in RENIS-T6. Of the 2107 that responded positively, 48 withdrew, 12 were excluded due to allergies to either iodine, latex or contrast media and 65 were excluded for other reasons. The remaining 1982 participants were eligible for inclusion and 1632 were investigated according to predetermined power calculations. Five additional participants were excluded because of technical failures of iohexol-clearance measurements, leaving 1627 participants (826 women and 801 men) in the RENIS-T6 cohort. Another 19 had invalid ambulatory measurements, consequently, there were 1608 participants in the present study (Figure 1). RENIS-T6 has shown to be representative of the participants eligible for T6 with regard to important variables (16).

The study complied with the Declaration of Helsinki and all participants gave written consent. The Data Inspectorate of Norway and the Regional Committee of Medical and Health Research Ethics of North Norway approved T6 and RENIS-T6. All investigations in RENIS-T6 took place at the Clinical Research Unit of the University Hospital of North Norway.

2.2 Office blood pressure measurements

OBPM were performed by trained study nurses according to recommendations from the ESC/ESH (Table 1 is adapted from the ESC/ESH guidelines of how to conduct OBPM) (3). The participants were in a comfortable seated position, and the blood pressure was measured

after 2 min rest using an automated device and the appropriate cuff size (model UA 799; A&D, Tokyo, Japan) with the study nurses present. Blood pressure was measured three times, with 1 min between measurements. The average of the second and third measurement was used in the analysis (17). According to the guidelines for management of hypertension from ESC/ESH, OBPM was categorized as hypertensive if OSBP ≥140 mmHg and/or ODBP ≥90 mmHg (3) or the use of antihypertensive medication.

2.3 Ambulatory blood pressure measurements

ABPM was measured with Spacelab 90207 (Spacelab Inc, Redmond, Washington, USA) using the appropriate cuff size. The participants had their ambulatory blood pressure monitor fastened before they left the Clinical Research Unit. They were instructed to do their normal daily activities, but to keep their arm still and to avoid energetic exercise during measurement periods. The portable ambulatory blood pressure monitor was programmed to measure the blood pressure at 20 min intervals from 08:00 to 22:00 h and at 45 min intervals from 22:00 to 08:00 h (17). The registration was valid if it covered 22 h duration, if there were at least 10 readings between 10:00 and 22:00 h and five readings between midnight and 06:00 h (18).

Daytime mean systolic and diastolic ambulatory blood pressure were calculated as the weighted mean from recordings between 10:00-20:00 h (17). According to the guidelines for management of hypertension from ESC/ESH, hypertension was defined as mean daytime SBP ≥135 mmHg and/or mean daytime DBP ≥85 mmHg (3) or the use of antihypertensive medication.

Table 2 is adapted from the ESC/ESH guidelines and shows the relationship between hypertensive cut off values of OBPM, ABPM and home blood pressure measurements (3).

2.4 Other measurements

Smoking, alcohol habits and education level was collected from two self-administered questionnaires. Alcohol consumption was dichotomized into the consumption of alcohol >2-

4 times a month (yes/no). Smoking was stratified into current smokers or non-smokers, and previous smokers were categorized as non-smokers. Education level 1 indicated primary/secondary school, modern school, or technical school; level 2 indicated vocational school or 1-2 years senior high school; level 3 indicated a high school diploma; level 4 indicated college/university for less than 4 years; and level 5 indicated college/university for 4 years or more (19).

Triglycerides, fasting serum glucose, high density lipoprotein (HDL) and low density lipoprotein (LDL) levels were measured with the Modular model P800 (Roche Diagnostics, Indianapolis, IN) (19).

2.5 Statistical analysis

In Table 3 Baseline Characteristics, continuous variables are presented as the means (standard deviations (SD)) or medians (interquartile ranges) as applicable, and categorical variables are presented as numbers of observations and the percentage of the observations. Normotensive blood pressure was defined as office systolic blood pressure (OSBP) <140 mmHg and office diastolic blood pressure (ODBP) <90 mmHg without the use of antihypertensive medication. Hypertensive blood pressure was defined as OSBP ≥140 mmHg or ODBP ≥90 mmHg or the use of antihypertensive medication according to the definitions by ESH. ANOVA, median regression, logistic regression and chi square test were used as appropriate to examine differences between the normotensive and hypertensive groups in Table 3. The paired sample t-test was used to determine whether the mean difference between OBPM and ABPM was different from zero, see Table 4.

The Bland-Altman plot examines the agreement between two measurements by plotting the differences between the two measurements on the Y-axis, against the mean of each on the X-axis and constructing limits of agreement (20, 21). In this thesis, we compared observed office systolic blood pressure (OSBP) to daytime ambulatory systolic blood pressure (ASBP) and observed office diastolic blood pressure (ODBP) to daytime ambulatory diastolic blood pressure (ADBP), see Figure 2 and 3, respectively. The scatterplot between OSBP versus ASBP and ODBP versus ADBP is presented in Figure 4 and 5, respectively.

Deming regression was used to estimate the relationship between OSBP and ODBP, and ASBP and ADBP. Deming regression finds the line of best fit by minimizing the sum of the distances between the measured values and the regression line, at an angle specified by the variance ratio (22). Deming regression differs from ordinary least square linear regression, because it account for errors in both the Y-axis and X-axis. The errors for both OBPM and ABPM are assumed to be independent and normally distributed and the ratio of variance is known (23). If the two methods of measuring blood pressure are the same, then X=Y, and X=1 and the intercept will be zero.

The statistical analyses were performed using Stata version 15.0 (StataCorp. 2017. *Stata Statistical Software: Release 15.* College Station, TX: StataCorp LLC).

3 Results

The baseline characteristics of the participants are presented in Table 3. In total, 923 participants had OSBP <140 mmHg and ODBP <90 mmHg without antihypertensive medication, and 685 participants had OSBP ≥140 mmHg or ODBP ≥ 90 mmHg or used antihypertensive medication. Significant differences between the normotensive and hypertensive group was observed for gender, age, height, body weight, body mass index, daily smoking, LDL, HDL, triglycerides, HbA1c, ASBP and ADBP, office pulse pressure and education (see Table 3).

The differences between daytime ABPM and OBPM and their correlation are presented in Table 4. The mean daytime ASBP and mean daytime ambulatory diastolic blood pressure (ADBP) was 130.2 mmHg (13.2) and 82.1 mmHg (8.7), respectively. The mean OSBP and ODBP was 129 mmHg (17.7) and 83.4 mmHg (9.8), respectively. The difference between the mean OSBP and ASBP was not significant (P=0.08, (95 % confidence interval (CI) -0.06 to 1.12)), whereas the difference between the mean ODBP and ADBP was highly significant (P<0.001, (95 % CI -1.67 to -0.99)).

Figure 2 shows the Bland-Altman plot for daytime ASBP and OSBP. Mean differences (the middle line) and ±2 SDs (the two outer lines) are shown. OSBP were on average 0.53 mmHg lower than daytime ASBP. Figure 3 shows Bland-Altman plot of daytime ADBP and

ODBP. Mean differences (the middle line) and ±2 SDs (the two outer lines) are shown. ODBP were on average 1.33 mmHg higher than daytime ADBP. Figure 4 and 5 shows the scatterplot with the regression line of OSBP versus ASBP and ADBP versus OSBP, respectively. The scatter plot shows especially for SBP that for higher blood pressure values, there is a greater difference between the two measurements.

The results from the Deming regression with OSBP and ODBP as the independent variable and the daytime ASBP and ADBP as the dependent variables can be found in Table 5. For each unit increase in daytime ASBP, the OSBP increased with 0.68 mmHg. For each unit increase in ADBP, there was a 0.85 mmHg increase in ODBP. The p-value was significant for regression coefficient, and the CI does not include 1. Thus, the two measurements are significantly different from each other.

4 Discussion

Our main findings from the study were that observed ODBP was statistically significant ($P<0.001$) higher than daytime ADBP in the healthy middle-aged participants recruited from the general population in Tromsø. The difference was small and probably of little clinical significance. The observed OSBP was nearly identical to the ADBP. These findings were unexpected, because on average, both daytime ASBP and ADBP are measured lower compared to observed OSBP and ODBP according to the guidelines from ESC/ESH (3). The SD for OSBP and ODBP were higher than the SD for both daytime ASBP and daytime ADBP. This could be explained by daytime ASBP and daytime ADBP are based on the average of more measurements than OSBP and ODBP. The correlation between the two measurement are moderately strong (24), but different from 1, which means that there is not a perfect linear relationship between the two measurements. However, it should be noted that the relationship between the two measurements varies with the blood pressure level, especially for SBP, such that the higher levels of blood pressure gives greater difference in the two measurements, see Figure 4 and 5.

The cross-sectional relationship between observed OBPM and ABPM has been examined previously, and several studies reported higher observed OBPM compared with

ABPM (25-30). The study by Brown et al. investigated the blood pressure in 611 patients referred to 24-hour ABPM. The daytime ABPM was on average 22/13 (SBP/DBP) mmHg lower than the referring doctors observed OBPM. In the same study, blood pressure measured by a trained study nurse in the research unit using a standard protocol was 9/10 mmHg lower than the blood pressure measured by the doctor (26, 31). Similar findings were reported in a study by Myers et al. Data on blood pressure was collected from 309 patients referred to 24-hour ABPM. The mean observed OBPM taken by the patients´ own doctor (152/87 mmHg) was significantly higher than the observed OBPM taken by the technician in the research unit (140/80 mmHg). The ABPM gave the lowest blood pressure levels in the study, by 134/77 mmHg (25, 31). Another study that compared observed OBPM to ABPM found that observed OBPM measured higher levels than ABPM (29). However, this study only included 64 patients with stage 3-4 chronic kidney disease and these results may therefore not be comparable to the results from our study which excluded all participants with chronic kidney disease. It should be noted that the study by Brown et al. and Myers et al. used a manual device to measure blood pressure in the office, whereas in our study the office blood pressure were taken with an automated device by trained study nurse (see Table 1 for blood pressure protocol) (3). However, evidence suggest that there is not a significant difference between observed OBPM done with a manual and an automated device (28). Nevertheless, it is likely that the research setting with the participants being included as study participants rather than patients at the doctor's office would impact the blood pressure less in regard of white coat hypertension. Also, in our study the blood pressure measurements were done by the same personnel and at the same time in the research setting, eliminating the intervariability between measurements conducted by different health personnel and patient intraindividual variation. Another possible factor contributing to our results could be that the participants managed to relax more, thereby accomplishing a relatively higher reduction in blood pressure during the automated observed measurements than during the daytime ABPM. Office blood pressure measurements provide an instantaneous measurement, and therefore the short-term changes in blood pressure are difficult to detect, consequently resulting in a possible inaccurate representation of the individual's blood pressure over time. Thus, our OBPM would not represent the blood pressure for the participants throughout the day.

To examine the long-term effects of hypertension, prospective studies have investigated hypertension-mediated organ damage. Hypertension-mediated organ damage refers to structural or functional changes in arteries or organs such as the heart, blood vessels, brain, eyes or kidneys as markers of pre-clinical CVD (3). A meta-analysis examined the associations between out-of-office blood pressure measurements with target organ damage. The authors found that out-of-office measurements was superior to office measurements to detect the association with preclinical damage assessed by echocardiographic of left ventricular mass index (32). Another study examined the relationship between home blood pressure measurements and risk for all-cause mortality, cardiovascular mortality and cardiovascular events. They found that home blood pressure measurements remained a significant predictor of cardiovascular mortality and cardiovascular events after adjusting for office blood pressure (33). According to the guidelines from ESC/ESH, ABPM are better predicting health outcomes than OBPM (3).

The new guidelines from ESC/ESH and AHA/ACC define hypertension measured in the office differently, i.e. ESC/ESH ≥140/90 and ACC/AHAC ≥130/80. However, they both address the importance of using out-of-office measurements when diagnosing and treating hypertension (3, 6). At the family's doctor's office, routine clinical practice often include the use of manually measured blood pressure ≥140/90 mmHg as a cut-off value for establishing the diagnosis of hypertension. This assumes that routine office blood pressure measurements is equivalent to research study blood pressure measurements, and it further implies that office readings are taken using the same guidelines as in research setting. This assumption is probably invalid (34). In 2015 the SPRINT study published in NEJM received a lot of criticism about their methods of measuring hypertension (7). They aimed to examine how maintaining SBP at a lower cut-off (<120/80 mmHg) than the currently recommended level (<140/90 mmHg) would impact the mortality, CVD and kidney disease. They reported a significant lower rate of myocardial infarction, other acute coronary syndromes, stroke, heart failure or death from cardiovascular causes in the group treated to a blood pressure <120/80 mmHg (35). However, they used a technique in measuring blood pressure that is not representative and applicable for practice outside the specific study (36-39). They measured blood pressure with patients unobserved, seated in a quiet room without talking (35). Previous studies have shown that SBP measured by this method may be 5-10 mmHg lower compared to observed OBPM

(31). Lowering SBP beneath 120 mmHg can have unknown adverse consequences, and potentially result in acute kidney failure, hypotension and syncope as this was reported in the intensive treatment group (35). Consequently, initiating drug therapy cannot be directly determined from the SPRINT study to current clinical practice (7).

In light of the results of previous studies, our study suggests that blood pressure measured by trained personnel at research units give lower blood pressure readings than blood pressure measured in the doctor's office, even though both measurements are observed. Consequently, the blood pressure measurements done in our study by trained study nurses cannot be compared to blood pressure measurements done in the doctor's office, because the research setting is not representative for blood pressure taken at the doctor's office. It seems that blood pressure measured in the research setting is "closer" to daytime ABPM than OBPM done in the doctor's office.

Our study has several strengths and limitations. The most important strength is the use of accurate methods of measuring blood pressure in a representative cohort of the healthy general population. Further, after conducting literature searches, it is clear that RENIS-T6 is one of the larger cohorts were there are ambulatory blood pressure measurement of >1600 participants. Consequently, the large study population is an important strength because this provides statistical power to report associations with narrow confidence intervals. Important limitations are the narrow age range and the inclusion of only Caucasians. This limits the possibility to study the relationships between ethnicity and the generalizability of the results.

5 Conclusion

We found that observed ODBP conducted by the study nurse measured significantly higher blood pressure than ADBP in our healthy study population aged 50-62 years who were representative of the general population. However, the difference was small and probably not clinically significant for the individual patient. There was no significant difference between observed OSBP and ASBP. The blood pressure measurements conducted in our study by trained study nurses cannot be directly compared to blood pressure measurement done in the doctor's office. In future studies, observed OBPM in the doctor's office should be

compared to observed OBPM conducted in research units by trained study staff. Further, it would be interesting to compare OBPM conducted by doctors and nurses in a clinical setting with regard to cardiovascular outcomes in order to guide future clinical practice.

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7 Tables and figures

Table 1. Guidelines of how to conduct office blood pressure measurement. Adapted from the ESC/ESH guidelines from 2018 (3).

Preparation of measurements
Patients should be seated comfortably in a quit rom for 5 min before beginning OBPM
Use a standard bladder cuff (12–13 cm wide and 35 cm long) for most patients, but have larger and smaller cuffs available for larger and thinner arms
Measure blood pressure in both arms at the first visit to detect possible between-arm differences. Use the arm with the higher value as the reference
Execution of measurements
Three blood pressure measurements should be recorded, 1–2 min apart, and additional measurements only if the first two readings differ by >10 mmHg. Blood pressure is recorded as the average of the last two blood pressure readings*
The cuff should be positioned at the level of the heart, with the back and arm supported to avoid muscle contraction and isometric exercise-dependent increases in blood pressure
Record heart rate and use pulse palpation to exclude arrhythmia
When using auscultatory methods, use sudden reduction/disappearance sounds to identify SBP and DBP, respectively
Orthostatic hypotension
Measure blood pressure 1 min and 3 min after standing from a seated position in all patients at the first measurement to exclude orthostatic hypotension. Lying and standing blood pressure measurements should also be considered in subsequent visits in older people, people with diabetes, and people with other conditions in which orthostatic hypotension may frequently occur

*Additional measurements should be performed in patients with unstable blood pressure values due to arrhythmias, such as in patents with atrial fibrillation. Manual auscultatory methods should be used in atrial fibrillation because most automated devices have not been validated for blood pressure measurement in patients with atrial fibrillation. Abbreviations: OBPM; office blood pressure measurements, SBP; systolic blood pressure, DBP; diastolic blood pressure

Table 2. Definitions of hypertension according to office, ambulatory and home blood pressure measurements. Adapted from the ESC/ESH guidelines from 2018 (3).

	Definitions of hypertension		
	SBP (mmHg)		**DBP (mmHg)**
OBPM	≥140	and/or	≥90
Daytime mean ABPM	≥135	and/or	≥85
Home blood pressure measurements	≥135	and/or	≥85

Abbreviations: OBPM, office blood pressure measurements; ABPM, ambulatory blood pressure measurements; SBP, systolic blood pressure; DBP, diastolic blood pressure

Table 3. Baseline characteristics of the RENIS-T6 participants according to office normotensive and hypertensive group, i.e. systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg and systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or the use of antihypertensive medication, n=1608

	Baseline characteristics			
	All participants	**Normotensive** <140 mmHg OSBP and <90 mmHg ODBP and no use of antihypertensive medication	**Hypertensive** ≥140 mmHg OSBP or ≥90 mmHg ODBP or the use of antihypertensive medication	**P-value for difference**
N (%)	1608 (100)	923 (100)	685 (100)	
Female, n (%)	818 (50.9)	536 (58.1)	282 (41.2)	P<0.001
Age, years	58.1 ± 3.8	57.5 ± 3.9	58.8 ± 3.6	P<0.001
Height, cm	170.6 ± 8.7	170.0 ± 8.6	171.5 ± 8.8	P<0.001
Body weight, kg	79.7 ± 14.4	76.3 ± 13.6	84.2 ± 14.3	P<0.001
Body mass index, kg/m^2	27.3 ± 4.0	26.3 ± 3.8	28.6 ± 4.0	P<0.001
Daily smoking, n (%)	342 (21.3)	237 (25.7)	105 (15.3)	P<0.001
Use of alcohol >2-4 times a month, n (%)	438 (27.2)	253 (27.4)	185 (27.0)	P=0.85
LDL cholesterol, mmol/l	3.67 ± 0.86	3.61 ± 0.84	3.73 ± 0.87	P<0.01
HDL cholesterol, mmol/l	1.53 ± 0.42	1.58 ± 0.43	1.46 ± 0.39	P<0.001
Triglycerides, mmol/l	1.2 (0.8 to 1.5)	1.1 (0.7 to 1.3)	1.2 (0.9 to 1.6)	P<0.001
HbA1c %	5.56 ± 0.36	5.54 ± 0.36	5.58 ± 0.36	P<0.05
ASBP, mmHg	130.2 ± 13.2	124.5 ± 10.4	137.8 ± 12.8	P<0.001
ADBP, mmHg	82.1 ± 8.7	78.6 ± 7.1	86.8 ± 8.4	P<0.001
Office pulse pressure, mmHg	66.7 ± 9.8	65.1 ± 9.0	68.9 ± 10.5	P<0.001
Antihypertensive medication, n (%)	468 (29.1)		468 (68.3)	
Diuretics	-	-	146 (21.3)	-
Beta blockers	-	-	72 (10.5)	-
Calcium blockers	-	-	81 (11.8)	-
Angiotensin-converting enzyme inhibitor	-	-	29 (4.2)	-
Angiotensin II blockers	-	-	138 (20.1)	-

Other	-	-	2 (0.3)	-
Education, n (%)				P<0.001
Level 1	404 (25.1)	193 (20.9)	211 (30.8)	
Level 2	487 (30.3)	302 (32.7)	185 (27.0)	
Level 3	115 (7.2)	70 (7.6)	45 (6.6)	
Level 4	301 (18.7)	178 (19.3)	123 (18.0)	
Level 5	294 (18.3)	176 (19.1)	118 (17.2)	

Values are presented as n (%), means ± SD, or medians (interquartile ranges). Abbreviations: OSBP, office systolic blood pressure; ODBP, office diastolic blood pressure; HDL, high density lipoproteins cholesterol; LDL, low density lipoproteins cholesterol; ASBP, ambulatory systolic blood pressure; ADBP, ambulatory diastolic blood pressure
Education level 1 indicated primary/secondary school, modern school, or technical school; level 2 indicated vocational school or 1-2 years senior high school; level 3 indicated a high school diploma; level 4 indicated college/university for less than 4 years; and level 5 indicated college/university for 4 years or more

Table 4. Ambulatory blood pressure measurements, office blood pressure measurements, their correlations and the significance level

	Mean ABPM	Mean OBPM	Difference between mean ABPM and OBPM (95 % CI)	Pearson R between ABMP and OBP	Paired sample t-test P-value for difference
SBP	130.2 ± 13.2	129.6 ± 17.7	0.6 (-0.06 to 1.12)	0.73 (P<0.01)	P=0.08
DBP	82.1 ± 8.7	83.4 ± 9.8	-1.3(-1.67 to -0.99)	0.72 (P<0.01)	P<0.001

Values are presented as means ± SD. Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; AMPM, ambulatory blood pressure measurement; OBPM, office blood pressure measurement; Pearson R, Pearson R correlation coefficient; SD, standard deviation.

Table 5. Results of the Deming regression with the office systolic and diastolic as the independent variables and the daytime ambulatory systolic and diastolic blood pressure as the dependent variables.

	OSBP	**ODBP**
	β coefficient	β coefficient
	P (95% CI)	P (95 % CI)
	Intercept (95 % CI)	Intercept (95 %)
Mean daytime ASBP	0.67	-
	P<0.01 (0.64 to 0.71)	-
	42.8 (38.5 to 47.1)	-
Mean daytime ADBP	-	0.85
	-	P<0.01 (0.81 to 0.89)
	-	11.4 (8.0 to 14.8)

Abbreviations: ASBP, ambulatory systolic blood pressure; ADBP, ambulatory diastolic blood pressure; OSBP, office systolic blood pressure; ODBP, office diastolic blood pressure

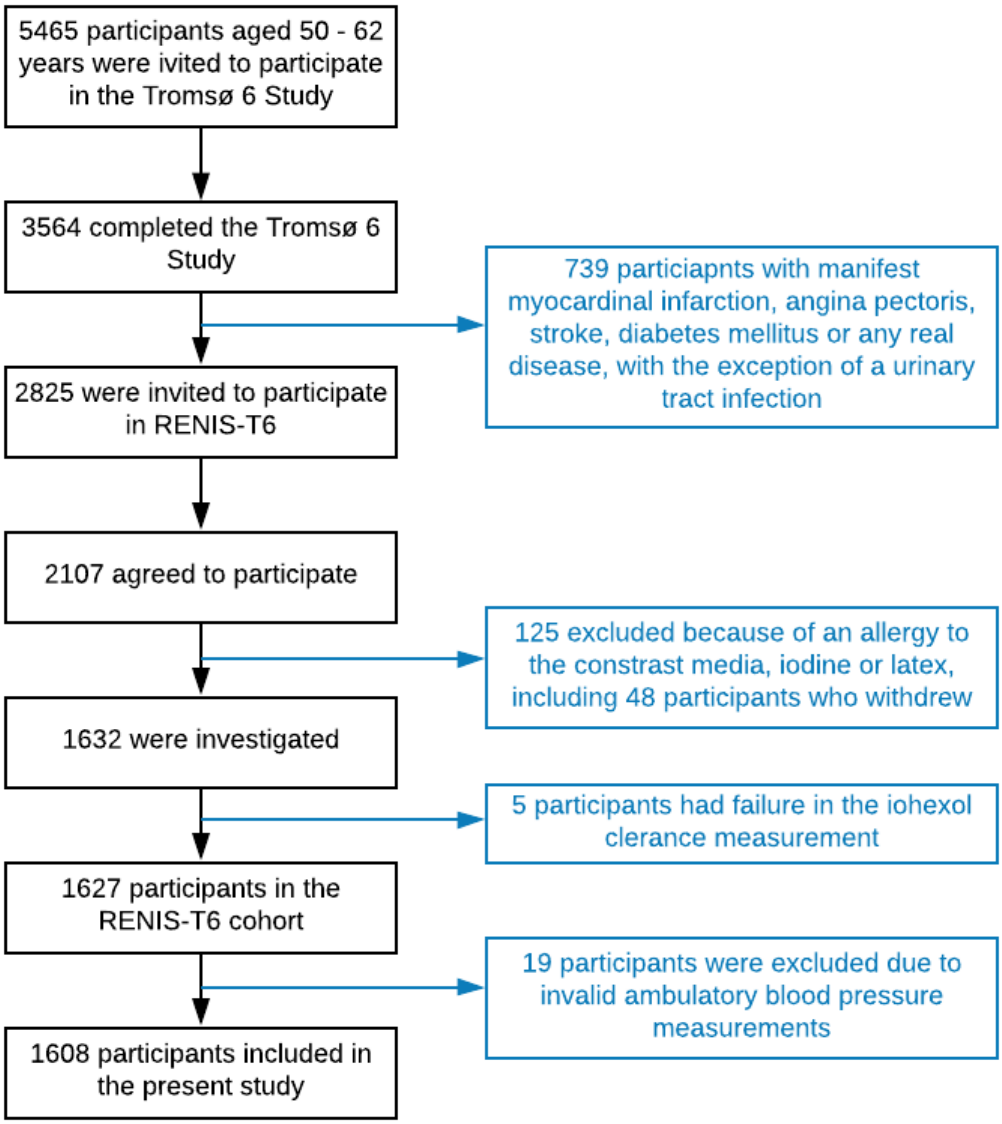

Figure 1. Inclusion of participants in the present study from the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6). Refer to the text for details.

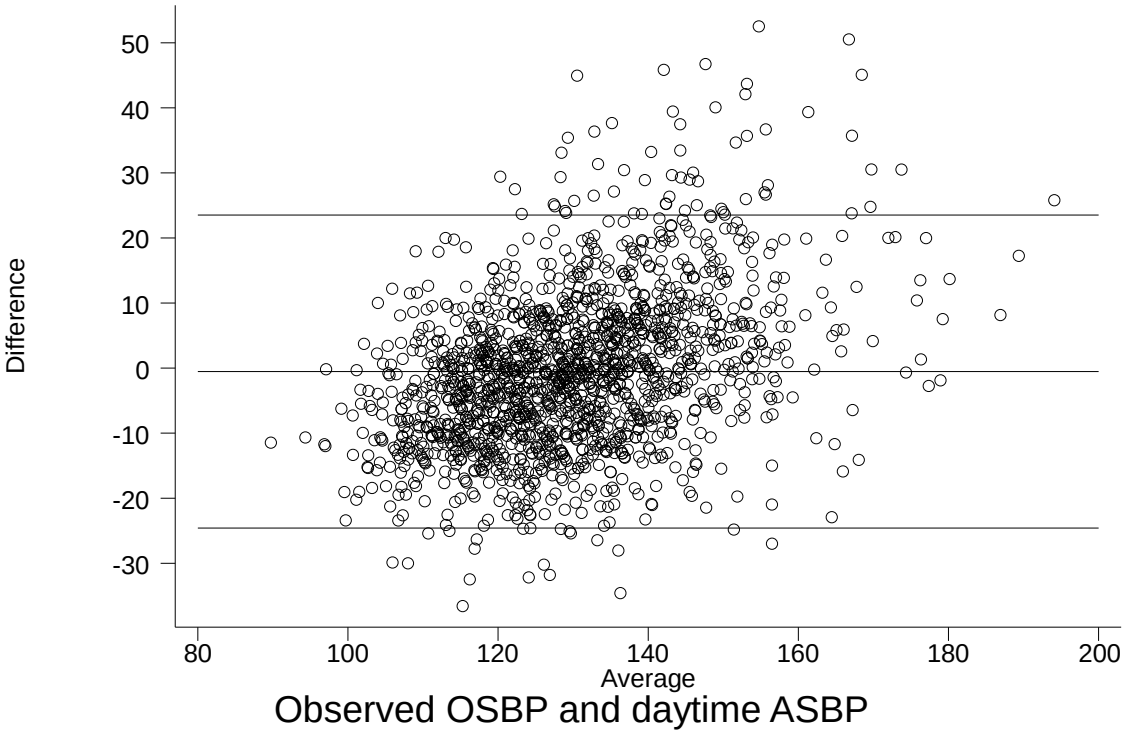

Figure 2. Bland-Altman plot of daytime ambulatory systolic blood pressure (ASBP) and office systolic blood pressure (OSBP). Mean differences (the middle line) and ±2 SDs (two outer lines) are shown.

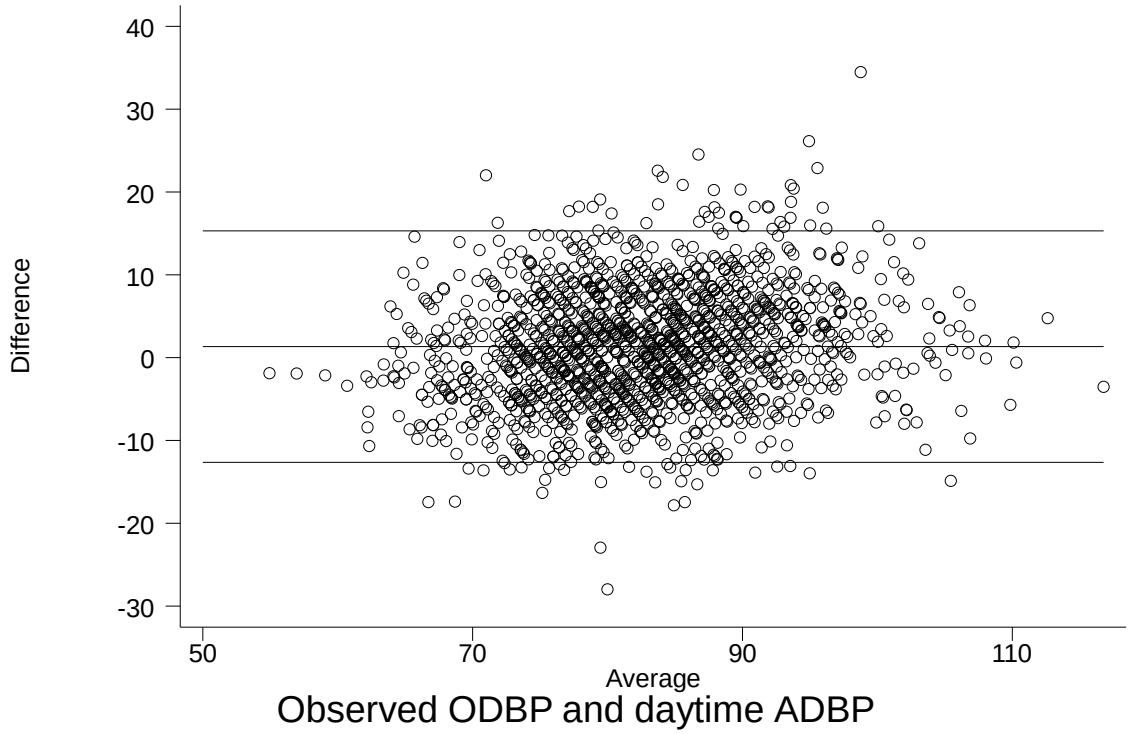

Figure 3. Bland-Altman plot of daytime ambulatory diastolic blood pressure (ADBP) and office diastolic blood pressure (ODBP). Mean differences (the middle line) and ±2 SDs (the two outer lines) are shown.

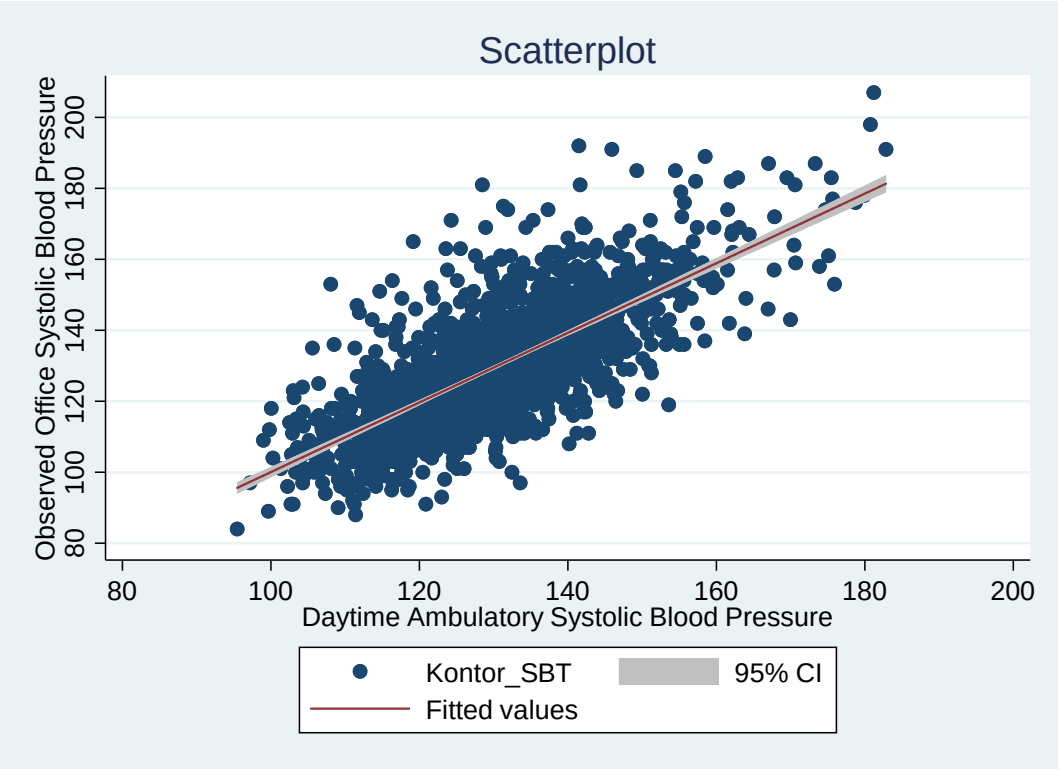

Figure 4. Scatterplot, office systolic blood pressure (Y-axis) plotted against ambulatory systolic blood pressure (X-axis) with the regression line (red line) and the corresponding 95 % confidence interval.

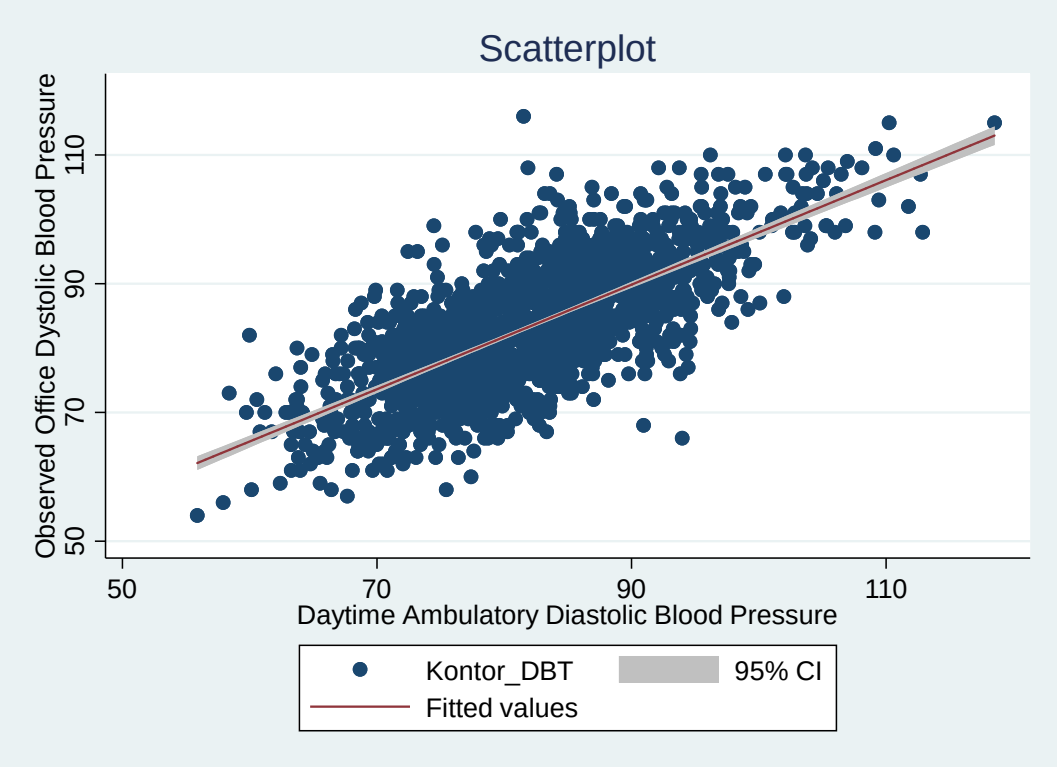

Figure 5. Scatterplot, office diastolic blood pressure (Y-axis) plotted against ambulatory diastolic blood pressure (X-axis) with the regression line (red line) and the corresponding 95 % confidence interval.

Grade tables

Reference: J.R Banegas, L. M. Ruilope, A. de la Sierra et al. Relationship between Clinic and Ambulatory Blood-Pressure Measurements and Mortality. *The New England Journal of Medicine, 2018.*

GRADE	
Quality of evidence	High
Recommendations	Strong

Aim	Material and Methods	Results	Discussion/Comments
To examine the associations of OBPM and ABPM with all-cause and cardiovascular mortality in a large cohort of patient in primary care. **Conclusion** ABPM were a stronger predictor of all-cause and cardiovascular mortality than OBPM. White Coat hypertension was not benign, and masked hypertension was associated with a greater risk of death than sustained hypertension. **Country** Spain **Year Data Collection** 2004-2014	**Study design:** Cohort. **Data foundation and material:** Spanish Blood Pressure registry, 63910 adults from the primary care**.** **Exclusion criteria:** Incomplete information on demographic and/or clinical characteristics. **Information collection:** From interviews and physical examinations during the visits and from clinical records. OBPM was conducted in accordance to guidelines. ABPM was performed with automated oscillometric devices. **Exposure:** ABPM, OBPM, hypertension phenotypes (sustained HT, white coat HT, masked HT, normotension). **Outcome:** Total and cardiovascular mortality. **Validation of exposure and outcome:** The date and cause of death were ascertained from a computerized search of the vital registry of the Spanish National Institute of Statistics. The cause of death was determined from the death certificate by a pathologist and was coded according to the international guidelines. **Statistical methods:** Cox regression models, adjusted for clinic and 24-h ABPM and confounders, HR were calculated per 1-SD in BP, untreated normotension-group was reference.	**Main results:** During median follow-up time of 4.7 years, 3808 patients died from any cause, and 1295 died from CVD. Mean OBPM was 148/87 mmHg, mean ABPM was 129/77 mmHg. 24-h SBP was more strongly associated with all-cause mortality (HR, 1.58 per 1-SD increase in pressure; 95 % CI, 1.56 to 1.60, after adjustment for clinic blood pressure) than the clinic SBP, adjusted for age, sex, obesity, DM, CVD, antihypertensive treatment. Masked hypertension was more strongly associated with all-cause mortality (HR, 2.83; 95 % CI, 2.12 to 3.79) than sustained hypertension (HR, 1.80; 95 % CI, 1.41 to 2.31) or white-coat hypertension (HR, 1.79; 95 % CI, 1.38 to 2.32). OBPM and ABPM were moderately concordant with an ICC of 0.57 for SBP (P<0.001) and 0.70 for DBP (P<0.001). OBPM and ABPM adjusted for CV RF were significantly associated with all-cause and CV mortality. However, after additional adjustment for ASBP, OSBP lost much of its predictive power (HR for all-cause mortality 1.54 before adjustment and 1.02 after adjustment). HR for ASBP did not change much after adjustment for OBPM (HR from all-cause mortality 1.58 before adjustment and 1.58 after adjustment).	**Was the groups recruited from the same population?** Yes. **Was the groups comparable?** Yes. **Was the exposure and outcome measured equal in the two groups?** Yes. ABPM and OBPM was conducted according to standardized procedure in all patients. **Was the study prospective?** Yes. **How long was the follow-up time?** Patients was enrolled from 2004-2014, median follow-up time was 4.7 years. **Is confounding attributed for?** Yes, factors known to affect exposure and outcome was adjusted for. **Can the results be used in clinical practice?** Yes. **Strengths**: Large study population, big age-range, prospective design, thorough validation of exposure and outcomes. **Limitations**: Selection bias, the study only included a white population, so the results may not apply to people of other races.

Reference: The SPRINT Research Group (J.T Wright, J. Williamson, P. K Whelton, et al). A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *Published in The New England Journal of Medicine, 2018.*	**GRADE**	
	Quality of evidence	Moderate
	Recommendations	None

Aim	**Material and Methods**	**Results**	**Discussion/Comments**
To investigate the benefit of treatment of SBP <120 mmHg compared to SBP >140 mmHg **Conclusion** High risk patients for CV events but without DM had lower rates of fatal and nonfatal major CV event and death from any cause if lowering SBP <120 mmHg compared to SBP<140 mmHg **Country** USA **Year Data Collection** 2010-2013	**Study design:** RCT. **Recruitment:** 102 clinical sites in USA. **Inclusion:** ≥50 years, SBP 130-180 mmHg, increased risk of CV events (clinical or subclinical CVD, CKD eGFR 20-<60 ml/min/1.73m^2, 10 years risk of CVD of ≥15%, ≥75 years. **Exclusion:** Prior stroke, polycystic kidney disease, DM. **Data material:** 9361 persons. **Exposure:** SBP<120 mmHg vs SBP <140 mmHg and increased risk for CV events. **Outcome:** MI, other acute coronary syndromes, stroke, heart failure, death from CV events. **Statistical methods:** Primary analysis compared the time to the first occurrence of a primary outcome event between the two study groups. Cox proportional- HR regression with two sided test p<0.05. Interactions between treatment effect and prespecified subgroups were assesses with a likelihood-ratio test for the interaction with Homel-adjusted P values. The Fine-Gray model for the competing risk of death was used as a sensitivity analysis.	**Main results:** At 1 year, the mean SBP was 121.4 mmHg in the intensive treatment group (ITG) and 136.2 mmHg in the standard treatment group (STG). The mean number of BP medication was 2.8 and 1.8 in the ITG and STG, respectively. The relative distribution of antihypertensive medication classes used was similar in the two groups, though the use of each class was greater in the ITG. Outcome event was confirmed in 562 participants, 243 (1.65%/year) in the ITG and 319 (2.19%/year) in the STG (HR intensive treatment, 0.75; 95% CI, 0.64 to 0.89; P<0.001). 365 deaths occurred, 155 in the ITG and 210 in the STG (HR 0.73; 95% CI 0.6 to 0.9; P=0.003). RR of death from CV events was 43 % lower in the ITG vs STG (P<0.005). Serious adverse event (hypotension, syncope, electrolyte abnormalities, acute kidney injury and acute renal failure) occurred in 1793 participants in the ITG (38.8%) and in 1736 participants in the STG (37.1%). A total of 220 participants in the ITG (4.7%) and 118 participants in the STG (2.5%) had serious adverse events that were classified as possibly or definitely related to the intervention (hazard ratio, 1.88; P<0.001. **Intervention:** Was stopped early after a median follow-up time of 3.26 years owing to a significant lower rate of the primary composite outcome in the ITG than in the STG.	**Aim:** To examine the appropriate targets for SBP to reduce CV morbidity **Randomization:** SBP target<140 mmHg STG or <120 mmHg ITG. Randomization was stratified according to clinical site. **Sufficient blinding:** Participants and study personnel were aware of the study- group assignments, but outcome adjucators were not. **Can the results be used in clinical practice?** No, they used a technique in measuring blood pressure that is not representative an applicable for practice outside the specific study. They measured BP unobserved, seated in a quiet room. Previous studies have shown that SBP measured by this method may be 5-10 mmHG lower compared to observed. **Was all the outcomes accounted for?** Yes. **Strengths:** Large sample size, diverse population, success in separation of the two groups. **Limitations:** Blood pressure measurement**,** not generalizability for people <50 years and to persons with DM.

Referance: J. Filipovsky, J. Seidleroá, Z. Kratochvil, et al. Automated compared to manual office blood pressure and to home blood pressure in hypertensive patients. *Published in Blood Pressure, 2016.*	**GRADE**	
	Quality of evidence	Moderate
	Recommendations	None

Aim	Material and Methods	Results	Discussion/Comments
To investigate the associations between automated BP, manual OBPM and home BPM in stable treated HT patients. **Conclusion** Automated BP was lower than home BP and no more closely related to home BP than to office BP. It did not show better repeatability than office BP. **Country** Unknown. **Year Data Collection** Unknown.	**Study design:** Cross-sectional. **Data foundation and material:** 353 patients in the Hypertensive Centre **Exclusion criteria:** Unstable treated hypertensive patients **Information collection:** Stable outpatients treated for hypertension were measured automatically, seated alone in a quiet room, six times after a 5 min rest with the BpTRU device, and immediately afterwards using the ausculatory method. Home BP was measured in a subgroup during 7 days preceding the visits. **Validation of exposure:** Blood pressure measurements were according to guidelines and conducted and administrated by three participating physicians. **Statistical methods:** Pearson and intraclass correlation coefficients and multiple regression analysis. Bland-Altman plots to compare automated BP with manual OBP and home BP, and home BP with manual OBP.	**Main results:** The automated, office and home BP values were 131.2 ± 21.8/77.8 ± 12.1 mmHg, 146.9 ± 20.8/85.8 ± 12.4 mmHg and 137.7 ± 17.7/79.4 ± 8.2 mmHg, respectively. Limits of agreement between office and automated BP (2 SDs in Bland–Altman plots) were +42.6 to –12.6/+22.6 to –6.6 mmHg for systolic/diastolic BP; for home and automated BP they were +45.8 to –25.8/+20.8 to –12.6 mmHg. For patients with two visits, intraclass correlation coefficients of BP values measured during the first and second visits were 0.66/0.72 for systolic/diastolic automated BP and 0.68/0.74 for systolic/diastolic office BP. Automated BP was lower than home BP and no more closely related to home BP than to office BP. It did not show better repeatability than office BP. Whether automated BP and the “white-coat effect”, calculated as the office BP–automated BP difference, have clinical and prognostic importance deserves further studies.	**Was the aim sufficient defined and answered?** Yes. **Was the exposure and outcome measured equal in the population?** Yes, the associations between automated BP and manual OBP in stable treated hypertensive patients were measured the same way during repeated visits. In a subgroup of patients home BP was also investigated with the association to OBP and manual automated BP. **Was the study prospective?** No, cross-sectional. **Can the results be used in clinical practice?** Yes. However, only to the same population that was investigated – i.e. hypertensive patients **Authors discussion:** Automated BP in hypertensive patients was significantly lower than both OBP and home BP, and there was a large individual difference between office and automated BP. The limit of office hypertension 140/90 mmHg corresponded with automated BP 125/82. **Strengths**: Special attention was paid to high-quality BP measurements, taken by three physicians, all of whom had more than 10 years’ clinical experience in internal medicine/cardiology **Limitations**: Higher office BP due to white-coat HT, not information on year and where the study was conducted, not information on the different types of antihypertensive medication.

Reference: V. Gaborieau, N. Delarche , P. Gosse, Ambulatory blood pressure monitoring versus self-measurement of blood pressure at home: correlation with target organ damage. *Published in Journal of Hypertension, 2008.*	**GRADE**	
	Quality of evidence	High
	Recommendations	Strong

Aim	Material and Methods	Results	Discussion/Comments
To compare ABPM and HBPM with reference to target organ damage (TOD) **Conclusion** HBPM was at least as well correlated with TOD as ABPM. Home- ambulatory correlation and their correlation with organ damage argue in favor of different cut-offs, 5 mmHg higher for systolic HBPM **Country** France **Year Data Collection** May 2005 to April 2006	**Study design:** Cross-sectional. **Data foundation and material:** Population of hypertensive patients referred to the cardiology department in Pau General Hospital, 302 patients **Exclusion criteria:** Recent history of CV events (<1month), cognitive or physical inability to use a device for HBPM, arm circumference >32 cm, pregnant women, moderate to severe mitral or aortic valve disorders, LVH, pacemakers, defibrillators, arrhythmias, difference in BP between arms >20 mmHg, and patients with modified antihypertensive treatments <3months. **Exposure:** ABPM, HBPM, OBPM. **Outcome:** LVH, IMT, LVMI, PP, RWT, Cornell. **Validation of exposure and outcome:** The mean of six measurements was taken as the OBPM, HBPM was determined over 4 days using a semiautomatic device, ABPM with Spacelab 90207 measured BP every 20 min by day and every hour at night. **Statistical methods:** Relationship between the different organ damage were analyzed by linear regression, and the correlation coefficient was calculated. ANOVA was used to identify difference between group (normo- and hypertensive ABPM, HBPM and OBPM)	**Main results:** Mean OBPMs were 142/82 mmHg, mean HBPM were 135/77 mmHg and ABPM were 128/76 mmHg (day 130/78 mmHg; night 118.5/67 mmHg). With a 135 mmHg cut-off, home and daytime blood pressure diverged in 20% of patients. ABMP and HBPM were correlated with organ damage more closely than was OBPM with a trend to better correlations with HBPM. Using regression analysis, a 140 mmHg systolic HBPM corresponded to a 135 mmHg daytime SBP; a 133 mmHg daytime ABPM and a 140 mmHg HBPM corresponded to the same organ damage cut-offs (Left ventricular mass index 50 g/m. Cornell.QRS 2440 mm/ms, carotid intima media thickness 0.9 mm). Home–ambulatory differences were significantly associated with age and antihypertensive treatment.	**Was the aim sufficient defined and answered?** Yes. **Was the exposure and outcome measured equal in the population?** Yes. ABPM, HBPM and OBPM was conducted according to standardized procedure in all patients as well as the different outcome for assessing TOD **Was the study prospective?** No, cross-sectional. **Is confounding attributed for?** Yes, factors known to affect exposure and outcome was adjusted for. **Can the results be used in clinical practice?** Yes. However, only to the same population that was investigated – i.e. hypertensive patients **Authors discussion:** The findings indicate that it might not be advisable to use the same cut-off values for daytime ABPM and HBPM in treated hypertensive patients. **Strengths**: Thorough validation of exclusion criteria, several methods of measuring TOD **Limitations**: ABPM was limited to three measurements per hour during the day and measurements every hour at night, limited number of patients, selected- high risk population, being recruited from specialized cardiologic examinations. Cross-sectional interference limits any causal explanations.

Reference: M. Kikuya, T. W Hansen, L. Thijs, et al. Diagnostic Treshold for Ambulatory Blood Pressure Monitoring Based on 10-Year Cardiovascular Risk. *Published in Circulation, 2007.*	**GRADE**	
	Quality of evidence	High
	Recommendations	Strong

Aim	**Material and Methods**	**Results**	**Discussion/Comments**
To determine diagnostic threshold for ABPM in terms of cardiovascular outcomes **Conclusion** Population-based outcome-driven threshold for optimal and normal ABPM are lower than those currently proposed by hypertension guidelines **Country** Enrolled population studies from Denmark, Belgium, Japan and Sweden **Year Data Collection** Unknown.	**Study design:** Cohort. **Data foundation and material:** 5682 residents from Copenhagen, Noorderkempen, Ohasama and Uppsala. **Eligible studies:** Random population with longitudinal follow-up of fatal and non-fatal CV outcomes. **Exclusion:** not measured OBPM, nighttime, daytime or the average of daytime and nighttime of fewer than 10 or 5 readings, respectively. **Information collection:** questionnaire to obtain detailed information of each subject's medical history, intake om medications, smoking and drinking habits **Exposure:** ABPM. **Outcome:** Vital status and incidence of fatal and non-fatal diseases from the appropriate sourced in each country. Coronary events encompassed death due to ischemic heart disease, sudden death, non-fatal myocardial infarction, surgical and percutaneous coronary revascularization. Cardiac events comprised coronary end points and fatal and nonfatal heart failure. **Statistical methods:** ANOVA to test for large-sample mean difference, Cox regression and the proportional HR.	**Main results:** In multivariate analyses, we determined ABP thresholds, which yielded 10-year cardiovascular risks similar to those associated with optimal (120/80 mm Hg), normal (130/85 mm Hg), and high (140/90 mm Hg) blood pressure on office measurement. Over 9.7 years (median), 814 cardiovascular end points occurred, including 377 strokes and 435 cardiac events. Systolic/diastolic thresholds for optimal ABP were 116.8/74.2 mm Hg for 24 hours, 121.6/78.9 mm Hg for daytime, and 100.9/65.3 mm Hg for nighttime. Corresponding thresholds for normal ABP were 123.9/76.8, 129.9/82.6, and 110.2/68.1 mm Hg, respectively, and those for ambulatory hypertension were 131.0/79.4, 138.2/86.4, and 119.5/70.8 mm Hg. After rounding, approximate thresholds for optimal ABP amounted to 115/75 mm Hg for 24 hours, 120/80 mm Hg for daytime, and 100/65 mm Hg for nighttime. Rounded thresholds for normal ABP were 125/75, 130/85, and 110/70 mm Hg, respectively, and those for ambulatory hypertension were 130/80, 140/85, and 120/70 mm Hg.	**Was the groups recruited from the same population?** Yes (random population in each study). **Was the exposure and outcome measured equal in the studies?** ABPM were set at intervals at either 20 min or 30 min, or 15 min to 30 min or from 20 min to 45 min during daytime and nighttime. **Was the study prospective?** Yes. **How long was the follow-up time?** 9.7 years mean follow-up time. **Is confounding attributed for?** Yes, factors known to affect exposure and outcome was adjusted for. **Can the results be used in clinical practice?** Yes. **Strengths**: large study population from the included cohorts (Europe and Japan), thoroughly validated exposure and outcome **Limitations**: The analysis rested only on 4-population-based cohort and might therefore not be representative for non-European and non-Japanese subjects. Inclusion of older adults. Anthropometric characteristics differed between cohorts. ABPM was not standardized in terms of device type and intervals between readings.