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Effectiveness of clinic blood pressure monitoring, home blood pressure telemonitoring and ambulatory blood pressure monitoring in evaluating blood pressure control in hypertensive patients with and without chronic kidney disease

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Xavier Galloo

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Promotor: Prof. dr. P. Van der Niepen
Dienst Nefrologie en Hypertensie UZ Brussel

Table of contents

Abstract

Background and aim Few direct comparative studies have been done between ambulatory blood pressure monitoring (ABPM) and home blood pressure monitoring (HBPM). In a previous study Robberechts et al. found significant discrepancy between daytime-ABP and telemedicine-guided HBP. Since there is discrepancy in the literature and there remains uncertainty regarding the reference values of the latter measuring method, we wondered if we could replicate this discrepancy in a larger and broader group of patients, including normal volunteers, patients with arterial hypertension (HT) and patients with HT, with and without chronic kidney disease (CKD).

Methods We conducted a prospective clinical trial to investigate the effectiveness of office blood pressure (BP), 24h-ABPM and telemedicine-guided HBPM (tele-HBPM) in assessing BP control. We consequently enrolled 46 subjects; untreated normotensive volunteers (33%) and treated hypertensive patients with/without CKD (67%). All subjects underwent with a 1-month interval twice one-week of BP monitoring with office BP (3 measurements at 2 consultations), 24h-ABPM (every 15' during daytime and every 30' during nighttime for 24h) and tele-HBPM (3 morning and evening measurements during 7 consecutive days).

Results Mean BP levels were 134/ 76 mmHg and 130/ 73 mmHg for office BP, 130/ 77 mmHg and 128/ 75 mmHg for daytime-ABPM, and 129/ 77 mmHg and 127/ 76 mmHg for tele-HBPM, all respectively the first and second time. No significant differences between the three techniques could be found. Blood pressure control ranged between 46% and 67%, was analogous between the different techniques and significantly improved during the second BP monitoring. Good agreement between the out-of-office techniques was found.

Conclusion No significant differences between the different techniques in mean blood pressure nor in blood pressure control could be found. Both out-of-office techniques (24h-ABPM and tele-HBPM) showed good agreement for systolic as well as diastolic BP.

Introduction

1. Epidemiology of hypertension

Hypertension (HT) is the most important risk factor for cardiovascular (CV) disease and it is a major cause of morbidity and mortality worldwide. Office blood pressure (BP) is still considered as the reference method for diagnosis of HT and follow-up. According to the European Society of Hypertension/ European Society of Cardiology (ESH/ESC) guidelines, HT is defined as office systolic blood pressure (SBP) values ≥ 140 mmHg and/or office diastolic blood pressure (DBP) values ≥ 90 mmHg, measured in a standardized way. However, office BP may be unrepresentative of the actual BP due to the white-coat and masked hypertension phenomena. Therefore out-of-office BP measurements have gained increasing interest the last few years.[1]

The prevalence of HT is still increasing. According to a review by Kearney et al. worldwide prevalence is estimated at 26%, but prevalence varies a lot between countries.[2] In a review by Pereira et al. worldwide prevalence is estimated at 37.8% and 32.1% in men and women, respectively (table 1). In Western Europe prevalence in women (29.3%) is similar to worldwide prevalence, but in men (42.4%) prevalence is even higher.[3] The ESH, reviewing prevalence in Europe, estimates prevalence around 30-45% of the general population in Europe. Moreover they conclude HT significantly increases with age. As there is an increasing prevalence of elderly in Western countries, this may in part account for the increasing HT prevalence.[1]

	World		Western Europe	
	Men	Women	Men	Women
Prevalence (%)	37.8	32.1	42.4	29.3
Awareness (%)	46.2	58.5	46.4	63.0
Treatment (%)	29.2	40.6	27.1	42.7
Control ^{I} (%)	31.9	36.8	29.7	44.5
Control ^{II} (%)	10.5	16.9	9.5	22.2

Table 1: Statistics concerning hypertension; I = control among treated hypertensive patients; II = control among treated and non-treated hypertensive patients.[3]

Hypertension is a worldwide problem and a leading cause of morbidity and mortality. Several clinical studies have shown that optimal BP control reduces the CV risk such as heart failure, myocardial infarction and stroke.[4] Interventions that decrease BP in patients with chronic kidney disease and proteinuria have shown to delay progression of kidney injury.[5]

The Framingham Heart Study is one of the most important studies on hypertension with a 38-year follow-up. They conclude that BP is a common and important contributor to the major cardiovascular diseases (CVD). At all ages risk of developing CVD increases with SBP and in elderly people the absolute vascular risk is substantially greater at any given BP.[6,7]

The ESH/ESC guidelines advise that HT diagnosis and management should be related to the total CV risk. Several methods have been developed to estimate CV risk. The Systematic COronary Risk Evaluation (SCORE) model estimates the absolute risk of dying from CVD over 10 years based on age, sex, smoking, total cholesterol and SBP. Two sets of charts are available: one for low-risk and one for high-risk countries. The ESH guidelines have stratified CV risk in different categories, based on BP, other CV risk factors, asymptomatic organ damage, diabetes, symptomatic CVD and chronic kidney disease. Patients are classified being at low, moderate, high or very high risk, which refers to the 10-year risk of CV mortality (figure 1).[1]

Other risk factors, asymptomatic organ damage or disease	Blood pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF		Low risk	Moderate risk	High risk
1–2 RF	Low risk	Moderate risk	Moderate to high risk	High risk
≥3 RF	Low to moderate risk	Moderate to high risk	High risk	High risk
OD, CKD stage 3 or diabetes	Moderate to high risk	High risk	High risk	High to very high risk
Symptomatic CVD, CKD stage ≥ 4 or diabetes with OD/RFs	Very high risk	Very high risk	Very high risk	Very high risk

BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DBP = diastolic blood pressure; HT = hypertension; OD = organ damage; RF = risk factor; SBP = systolic blood pressure.

Figure 1: Stratification of total CV risk in categories low, moderate, high and very high risk.[1]

Hypertension is not only a very important CV risk factor but it has great influence on multiple organs[1]:

(1) Heart: left ventricle hypertrophy (LVH), diastolic dysfunction, congestive heart failure (CHF), atherosclerosis of the coronary arteries, …
(2) Cerebrovascular: either ischemic or haemorrhagic cerebrovascular accident (CVA), vascular dementia
(3) Kidney: renal insufficiency
(4) Retina: hypertensive retinopathy
(5) Aorta: aneurysms
(6) Peripheral vessels: arteriosclerosis, atherosclerosis and its complications (embolism)

Although HT has become an important public concern, BP control is far from optimal. Hypertension control is rather low, varying from 5% to 58%.[2] Hypertension control is been achieved in barely 50.1% of the North American patients according to data of the National Health and Nutrition Examination Survey (NHANES).[4] According to the National Centre for Health Statistics 53.3% of North American people with HT had a good control of their BP in 2009 – 2010.[8] Pereira et al. conclude that 29.7% of the Western European men and 44.5% of the Western European women had a good BP control.[3]

In a large prospective cross-sectional survey in primary care in Belgium Van der Niepen et al. evaluated the overall BP control in threated hypertensive patients. The mean age was 63 years and 51% were men. Control of systolic and diastolic BP was achieved only in 21.5% of all patients enrolled by primary care physicians. Among the 78.5% uncontrolled patients 47.8% had uncontrolled SBP and DBP, 28.5% had isolated systolic HT (ISH) and 2.3% had isolated diastolic HT (IDH).[9]

All these data demonstrate the importance of HT and its management. Although a good BP control is able to considerably reduce the CV morbidity and mortality, HT control is rather poor.

2. Definitions

Epidemiologic studies have shown that there is no specific BP level where complications start to occur. Defining hypertension is arbitrary but mandatory for practical reasons in the assessment and treatment of elevated blood pressure.[10,11]

The European Society of Hypertension and the European Society of Cardiology define hypertension as office SBP values of at least 140 mmHg and/or office DBP values of at least 90 mmHg (table 2). This classification can only be used when at least three measurements have been performed at three different occasions, since the BP is influenced by different stimuli and therefore an elevated BP on one occasion is not sufficient to define hypertension.[1]

Further subclassification in grade 1, 2 or 3 HT is based upon the elevation of the BP. Isolated systolic hypertension (ISH) is defined as SBP ≥ 140 mmHg and DBP < 90 mmHg. This classification is applicable in young, middle-aged and elderly adults. Different cut-off values, based on percentiles, are used in children and adolescents.[1,12]

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	< 120	And	< 80
Normal	120 - 129	And/or	80 - 84
High-normal	130 - 139	And/or	85 - 89
Grade 1 hypertension	140 - 159	And/or	90 - 99
Grade 2 hypertension	160- 179	And/or	100 - 109
Grade 3 hypertension	≥ 180	And/or	≥ 110
Isolated systolic hypertension	≥ 140	And	< 90

Table 2. Definition and classification of office blood pressure levels.[1]

Hypertension is resistant to treatment (*resistant hypertension*) when there is a failure to lower SBP and DBP values under140 mmHg and 90 mmHg, respectively, with a therapeutic strategy that includes appropriate lifestyle changes and a pharmacotherapy that consists of a diuretic and two other antihypertensive drugs belonging to different classes at adequate doses.[1]

The presence of very high BP associated with ischemic OD (retina, kidney, heart or brain) is called *malignant hypertension*.[1]

Hypertensive emergencies are defined as high SBP or DBP (respectively >180 mmHg or >120 mmHg) associated with impeding or progressive OD, such as major neurological changes, hypertensive encephalopathy, cerebral infarction, intracranial haemorrhage, acute LV failure, acute pulmonary oedema, aortic dissection, renal failure or eclampsia.[1]

High SBP or DBP (respectively >180 mmHg or >120 mmHg) without acute OD is defined as *hypertensive urgency*.[1]

The definitions concerning the physiology of blood pressure will not be discussed in this introduction. For more detailed information concerning this subject, the reader is referred to the appendix.

3. Causes of hypertension

Two different types of hypertension are distinguished: primary (also called essential or idiopathic) hypertension on the one hand and secondary hypertension on the other hand. Essential hypertension accounts for approximately 95% of all HT cases and only in ± 5% of all cases a specific cause can be found (= secondary hypertension). Yet searching for these conditions remains useful as treating these conditions can result in permanent healing.[10,12]

In secondary hypertension an underlying condition is causing the elevated blood pressure. So when people present with symptoms or signs indicative for a secondary cause, this should be ruled out by doing supplementary examinations. Chronic renal parenchymal disease, usually the result from diabetic nephropathy or hypertensive nephrosclerosis, is the most common cause of secondary HT. Atherosclerotic renovascular disease leads to renal arterial stenosis and is also a frequent cause of secondary HT. Other causes include: renal artery disease due to fibromuscular dysplasia, endocrine causes (such as primary hyperaldosteronism or Conn's syndrome, pheochromocytoma, Cushing's syndrome and Cushing's disease, hyper- and hypothyroidism), sleep apnea, coarctation of the aorta, medication side-effects, lifestyle (obesity, sedentary lifestyle, stress, high alcohol consumption, high sodium and low potassium and calcium intake).[10,12,13,14,15]

The diagnosis of essential HT can only be made if no cause has been found. Several pathophysiologic mechanisms have been suggested and tested, but the reason of essential HT has not yet been found. Currently essential HT is been regarded as a multifactorial disease due to the combined action of genetic, environmental and behavioural factors. At this moment the exact genes causing HT are not known. Many environmental factors can influence the blood pressure: race (higher BP in blacks than whites), age (BP rises with age), geographic patterns, gender (more in men than women) and socioeconomic status (indicator of the lifestyle). Behavioural and lifestyle factors are already summed up in the section discussing secondary HT. Especially a high salt-intake and metabolic syndrome (obesity, hyperglycemia, hyperlipidemia) are associated with arterial hypertension.[10,12,14]

4. Diagnostic evaluation

The diagnostic evaluation of HT should consist of (1) confirming the diagnosis of HT, (2) uncovering secondary causes of HT and (3) an assessment of the CV risk, organ damage and associated clinical condition of the patient. As an overview of the secondary causes of HT has already been discussed in the section handling causes of hypertension and the assessment of the CV risk and organ damage has already been pointed out in the epidemiology of HT, these topics will not be further addressed in this paper because this leads us too far from the actual study.[1]

4.1. Confirmation of hypertension

Non-invasive and (less frequently used) invasive techniques have been described to confirm the diagnosis of HT. Non-invasive techniques consist on the one hand of office (or clinic) BP measurements and on the other hand of out-of-office BP measurements. Invasive techniques consist of measuring the intra-arterial BP.

4.1.1. Non-invasive techniques

A. Office or clinic BP measurement

The use of auscultatory and automated BP measurement will be discussed. The use of wrist and finger monitors will not be discussed as they will not be used in the study and they have shown to provide inaccurate readings.[16]

Because of its simplicity and accuracy the auscultatory method remains very important in everyday medical practice. Furthermore this method is one of few techniques that has not undergone significant changes since it was introduced. Two discoveries have played an important role in BP measurement: the *Riva-Rocci sphygmomanometer* (1886-1887) and the *Korotkoff sounds* (1905). Riva-Rocci suggested measuring the BP with an arm-encircling inflatable elastic cuff, a rubber bulb to inflate the cuff and a mercury sphygmomanometer to measure the cuff pressure. Systolic BP was measured by reading the pressure at which the radial pulse was obliterated as determined by palpation. Diastolic BP could not be measured by the palpation technique. The second discovery was the 'Korotkoff sounds'; named after the Russian physician and scientist Nokolai Sergeevich Korotkoff. A cuff placed around the upper arm and inflated above SBP occludes the brachial artery. Deflating the cuff results in a pulsatile blood flow that is accompanied by sounds that can be detected by a stethoscope placed along the artery below the cuff. The sounds originate from a combination of turbulent blood flow and oscillations of the arterial wall.

The sounds are classified in five phases (figure 2):

- Phase I: Appearance of clear tapping sounds
- Phase II: Sounds become softer and longer
- Phase III: Sounds become crisper and louder
- Phase IV: Sounds become muffled and softer
- Phase V: Sounds disappear

The onset of phase I corresponds to SBP and phase V corresponds to DBP. The Korotkoff sound method is an accurate method, but tends to underestimate the SBP and overestimate the DBP compared to BP measured by invasive techniques.[16,17,18,19]

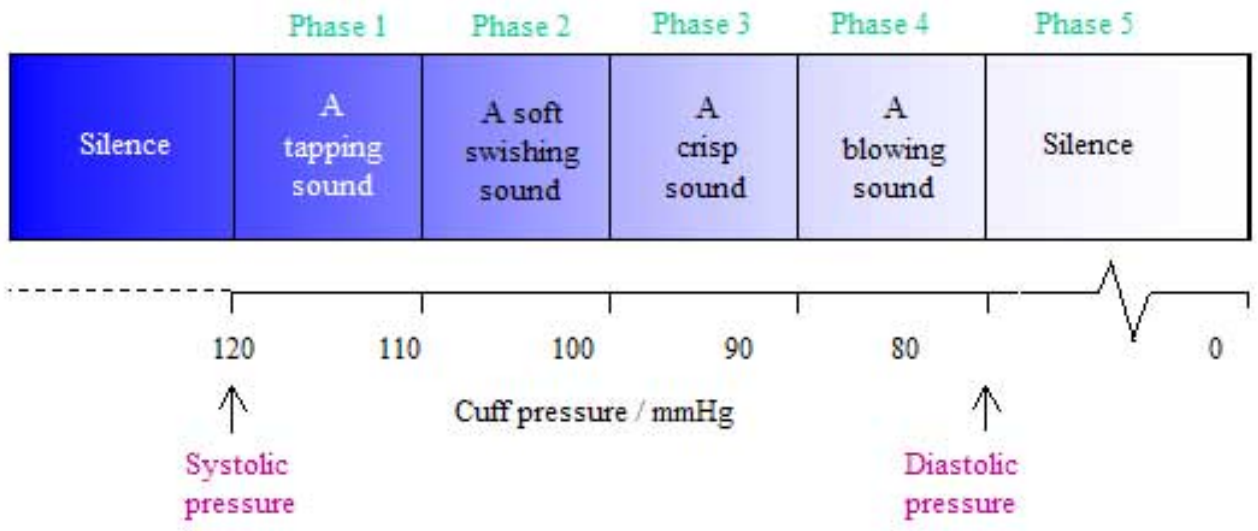


Figure 2: Five phases of the Korotkoff sounds.[20]

Additional attention should be paid in elderly patients with a wide pulse pressure as they may present an *auscultatory gap*. This phenomenon is defined as disappearance of the Korotkoff sounds between SBP and DBP and reappearance with further cuff deflation. This may be overcome by asking the patients to elevate the arm overhead for 30 seconds before inflating the cuff.[16]

Conditions: Measurements are performed by a health care provider in the doctor's office, using the ESH/ ESC guidelines[1,21]:

1) *Patient conditions*: the patient should be seated in a quiet room for 3 to 5 minutes before beginning BP measurements; his back and arm should be supported and legs should be uncrossed; he should not have smoked/taken a meal or caffeine/done physical exercise for the last 30 minutes prior to the measurements; and the patient should not talk during measurements.

2) *Cuff conditions*: the cuff should be placed at the upper arm at the heart level with it's inflatable bladder centered on the arms' anterior surface with the lower edge of the cuff approximately 2-3 cm above the bend of the elbow; cuff and bladder dimensions should be adapted to the arm circumference since a cuff that is too narrow or too short may reproduce readings that are erroneously high (i.e. obese patients); the sleeve should not be rolled up as this has a tourniquet effect above the cuff.

3) *Measurement*: at least two measurements should be taken spaced 1 to 2 minutes apart (repeated measurements improve accuracy). The cuff should be inflated 30 mmHg above the point at which the radial pulse disappears. It is recommended to deflate the cuff at a rate of 2 to 3 mmHg per second (or per pulse when the heart rate is very slow). Deflating the cuff faster results in an underestimation of the SBP and an overestimation of the DBP. At first visit BP should be measured in both arms as this may be helpful in detecting coarctation of the aorta or upper extremity arterial obstruction, and if suspicion of orthostatic hypotension[i] BP should be measured after 1 and 3 minutes in standing position.

Figure 3 illustrates how the patient and cuff should be positioned.

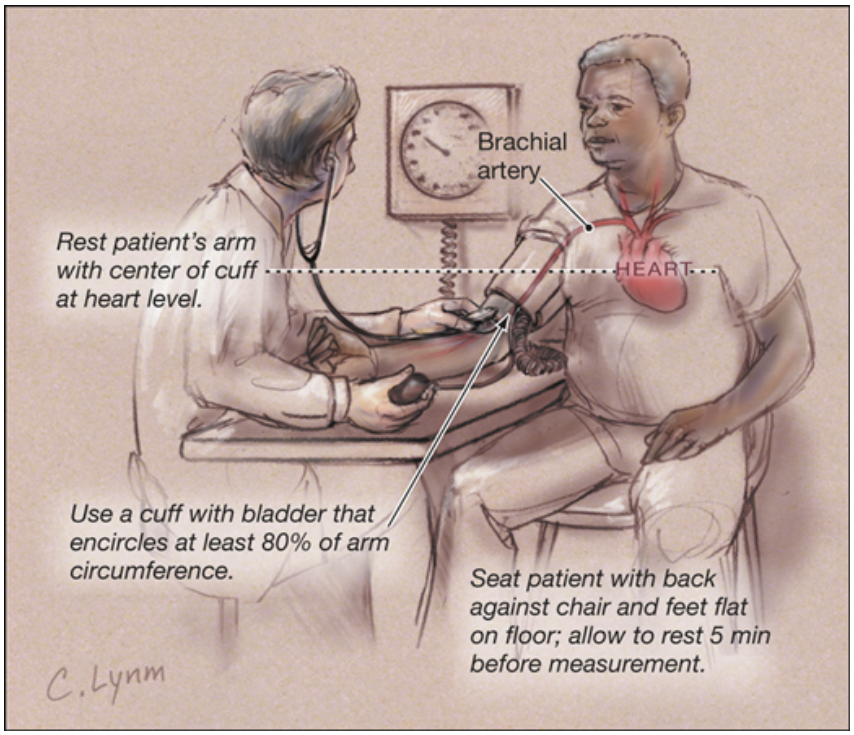


Figure 3: Illustration on the position of the patient and cuff in measuring office BP.[22]

Clinical indications: Office BP measurement is the globally accepted method for screening, diagnosis and management of hypertension.[1]

[i] *Orthostatic hypotension is defined as a reduction in SBP of ≥ 20mmHg or in DBP of ≥ 10mmHg within 3 minutes of standing.*

Advantages and disadvantages of office BP measurement compared to out-of-office BP measurement: Trained medical staff (doctors and nurses) measures office BP and thereby excluding patient errors, errors in measurement technique and miscommunication. There is also a better control on the patient's position, the cuff's position and the measuring technique than if the patient measures his BP himself. On the other hand surveys have shown that in measuring office BP clinicians rarely follow official guidelines; besides white-coat HT (WCHT) plays an important role in elevated office readings. In addition, drugs may have a greater influence on office BP (peak and trough effects) as this indicates only a given moment in time and out-of-office measurements can be performed at different time points.[16,23]

To reduce the disadvantage of the white-coat effect of traditional office BP measurement, two alternative measurement techniques were introduced. On the one hand the automated office BP measurement, and on the other hand the out-of-office BP measurement.

Automated office BP: Although the manual auscultatory method is widely used, it has raised concern about its quality and accuracy. The Conventional versus Automated Measurement of Blood pressure in the Office (CAMBO) trial investigated the effect of automated versus manual office BP measurement and showed a decrease in BP after enrollment in both groups, but which was greater in the automated group. Replacement of manual by automated measurement nearly reduces the white-coat effect and the difference between daytime ambulatory BP monitoring (ABPM) and office BP (using ABPM as a reference, automated office BP was 2.3/ 3.3 mmHg higher than daytime-ABPM and manual office BP was 6.5/ 4.3 mmHg higher than daytime-ABPM) and therefore it correlates better with CVD and organ damage. Using an automated method also excludes observer errors (i.e. rounding of values, digit preferences, …) and inter-observer variability and therefore improves reproducibility.[1,24]

B. Out-of-office BP

Out-of-office BP measurements usually consist of self-measurement. It provides measurements away from the clinic and excludes the white-coat effect; it therefore provides a better representation of the actual BP than office BP. There are two types of out-of-office BP measurement: (1) 24h ambulatory blood pressure monitoring (ABPM) and (2) home blood pressure monitoring (HBPM).

Out-of-office measurements are usually lower than office measurements; so different cut-off values are used to define HT in ABPM and HBPM (table 3).[1]

Category	SBP (mmHg)		DBP (mmHg)
Office BP	≥ 140	And/or	≥ 90
Ambulatory BP			
Daytime (or awake)	≥ 135	And/or	≥ 85
Nighttime (or asleep)	≥ 120	And/or	≥ 70
24-h (or mean)	≥ 130	And/or	≥ 80
Home BP	≥ 135	And/or	≥ 85

Table 3. Definition of HT in office BP, ABPM and HBPM.[1]

We looked into the studies on which ESH/ESC based their recommendations to define BP control measured by ABPM and HBPM. Blood pressure control in daytime-ABPM has been defined as BP < 135/ 85 mmHg based on the International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome (IDACO). This study comprised 5682 participants who were followed for 9.7 years and whose 10-year CV risk with daytime-BP values of 135/ 85 mmHg corresponded to the 10-year CV risk with office BP values of 140/ 90 mmHg. Recommendations on HBPM are based on meta-analyses, observational studies and clinical trials. The thresholds were defined through analysis of relative distributions of HBPM and office BP and evaluating the corresponding BP levels. They concluded that 135/ 85 mmHg corresponded to office BP values of 140/ 90 mmHg.[25,26,27]

We also looked into the thresholds for tele-HBPM, but we only found studies on the thresholds in manual-HBPM and storage-HBPM (definitions see B.2. Home BP monitoring – telemedicine). We assume that thresholds for tele-HBPM were extrapolated from these for manual-HBPM and storage-HBPM.

Out-of-office BP measurements are complementary to office BP measurements. For the initial assessment HBPM may be more suitable in primary care whereas ABPM in specialist care. ABPM is considered to be slightly superior to HBPM since it provides additional information on nighttime BP values and it is therefore considered as the reference for out-of-office BP. Thus, according to the ESH/ESC guidelines, abnormal values on HBPM should be confirmed by ABPM.

B.1. Ambulatory BP monitoring

Conditions: Blood pressure is measured while the patient is wearing a portable BP measuring device, usually on the non-dominant arm, for a 24h period. During daytime measurements are performed with an interval of 15 minutes and overnight every 30 minutes. The patient should be instructed to perform normal, routine day-to-day activities but at the time of cuff inflation he should stop moving or talking and keep the arm still. At least 70% of the BP values should be satisfactory; otherwise the ABPM should be repeated. Average 24h-, daytime– and nighttime-BP are calculated as well as the dipping status, and are used in the further management of HT.

Dipping: An important parameter is the night-to-day BP ratio. Normally BP decreases during the night, defined as 'dipping'. 'Dippers' are defined as people whose BP decreases during the night with > 10% compared to daytime values (night-to-day BP ratio <0.9). Further sub classification is based upon the amount of dipping: absence of dipping (nocturnal BP increase; night-to-day BP ratio > 1.0); mild dipping (0.9 < night-to-day BP ratio ≤ 1.0); dipping (0.8 < night-to-day BP ratio ≤ 0.9); extreme dipping (night-to-day BP ratio ≤ 0.8). The dipping pattern is important as several studies have shown that the incidence of CV events is higher in people with smaller or no drop in nighttime-BP. Several reasons for non-dipping are suggested: sleep disturbance, obstructive sleep apnea, obesity, high salt-intake, orthostatic hypotension, autonomic dysfunction, chronic kidney disease, diabetes neuropathy and old age.[1]

Advantages and disadvantages of ABPM compared to office BP: Ambulatory BP monitoring provides multiple measurements (even night BP readings) away from the potentially stressful clinic and therefore it has an important prognostic significance. According to several studies it has a stronger correlation with left ventricular hypertrophy (LVH), increased carotid intima-media thickness (IMT) and several other markers of organ damage (OD) than office BP. Ambulatory BP monitoring is superior to office BP in predicting the risk of CV events, even after adjustment for classic risk factors. An additional advantage is the possibility to uncover WCHT and masked HT. There are also several disadvantages: ABPM is a rather unpleasant method for the patient as he is branched during 24 hours and there is a higher cost compared to office BP.[1,23,28,29]

B.2. Home BP monitoring

Conditions: Home BP monitoring generally consists of daily self-measurements, preferably during 7 consecutive days, in the morning as well as in the evening. Semi-automated (manual cuff inflation) or automated electronic devices at the level of the upper arm are preferred for HBPM. Finger cuff - and wrist cuff devices are not recommended, as they are less accurate and more susceptible to inaccuracies due to measurement techniques. Home BP monitoring should be performed under the same conditions as office BP measurements (described above). Home BP is the average of these readings, with exclusion of the first monitoring day. These values are communicated to a health care provider or clinic either in person (the patient keeps a logbook with the BP values or the device stores the BP values) or either by a more recent technology where BP values are transmitted via telephone or an e-Health-related technology, which is called telemonitoring.[1]

Advantages and disadvantages of HBPM compared to office BP: Home BP monitoring shares several advantages with ABPM (readings away from the clinic and so revealing white-coat HT and masked HT; HBPM has shown similar correlations with ABPM for OD and CV-risk prediction and is superior to office BP). Home BP monitoring is well accepted by patients and has shown good reproducibility and prognostic value at a relatively low cost (although it still is more expensive than office BP) and therefore is suitable for HT follow-up. Yet some studies conclude follow-up by HBPM is indeed possible at a relatively low cost, but the cost of purchase is considerably high. Patients' participation in HBPM is greater than in office BP or ABPM and therefore it might increase the patients' awareness of their HT and improve compliance to medication treatment. On the other hand there are several limitations: need of patient education, more measurement errors, questionable reliability of BP values reported by the patient and the greater participation of the patient may result in an induction of anxiety and a risk of treatment adaptation made by the patient without doctor's guidance.[21,29]

Telemedicine: As described above the results obtained by HBPM are often incomplete and imprecise owing to BP values reported by patients in handwritten logbooks being regularly inaccurate, illegible or unreliable. Comparing HBPM with manual logbook entries (conventional-HBPM) with office BP studies revealed significant lower SBP and DBP at 6 months follow-up, but these changes were no longer significant at 12 months follow-up.[30] A comparison of conventional-HBPM and HBPM with automatically stored readings (storage-HBPM) revealed 2-35% under-reporting of readings (due to omission), 7-9% over-reporting (due to addition of never measured values) and precise values in 68-76% of the cases in the manual logbook entries.[31] Even the automatic storage of BP values has its disadvantages: downloading the values by the doctor takes time and this may result in less time spent on the patient's consultation and the patient has to bring the device, which is often forgotten. To overcome these disadvantages the use of telemonitoring has been introduced. Telemonitoring consists of an automatic data transmission from the point of care to the doctor's office; so BP values obtained by HBPM are transferred to a computer through a telephone line, a modem or an internet connection. Home BP monitoring with telemonitoring (tele-HBPM) has the same advantages of manual registration of the BP values, but there is no possibility of false reporting by the patient. According to a study comparing the conventional-HBPM and tele-HBPM there was a considerable increase in patient's compliance (49% vs 94%, respectively).[31] Moreover different studies have shown there is a greater increase in BP control by tele-HBPM than by conventional-HBPM. Working patients often have difficulties going to the doctor, as they have to take time off from work for visits. Tele-HBPM may provide a solution for these patients to reduce the face-to-face contacts. On the other hand there are some disadvantages: the telemonitoring-system is costly compared to office BP measurements, there is need of user training and there is an internet connection required (but nowadays the latter is

usually not a problem).[32] There has been conflicting information about the number of medications that have to be taken to control HT using tele-HBPM as follow-up. Some studies conclude there is a decrease, while others conclude there is an increase by using tele-HBPM. We must stipulate that there is significant heterogeneity between studies that have been reviewed in the meta-analyses and therefore it is difficult to compare all studies to one another. By consequence of the heterogeneity and often a small sample size or a short follow-up period researchers have been unable to confirm if tele-HBPM is associated with a higher cost (even though small studies have shown tele-HBPM is more costly compared with conventional-HBPM), if it has an impact on 'hard' end-points as mortality or CV-events (e.g. stroke) and which variables (age, sex, race, education, social status, …) have an influence on HBPM.[33] Although there has not yet been evidence for better results on long-term mortality or morbidity, tele-HBPM has a significant better BP control and compliance than conventional-HBPM.[31,34,35,36,37,38,39]

B.3. Clinical indications for out-of-office BP measurement

Out-of-office BP measurement should be performed when suspicion of WCHT or masked HT. It can unveil a white-coat effect in hypertensive patients. It should be performed when there is considerable variability of the office BP or when there is autonomic/postural/post-prandial/siesta- or drug-induced hypotension. It can identify true or false resistant hypertension. It provides additional information in pregnant women with elevated office BP or suspected pre-eclampsia.

Marked discordance between office BP and HBPM, an assessment of the dipping status, suspicion of nocturnal hypertension and an assessment of BP variability are specific indications for ABPM.[1]

C. Hypertension pitfalls

An alerting response, anxiety and/or conditional response to an unusual situation are some reasons accountable for a higher office BP than out-of-office BP. The difference between office BP and out-of-office BP is referred to as the white-coat effect. An elevated BP at the consultation that is sustained during out-of-office measurements is defined as 'sustained HT', whereas normal BP at office BP measurements and out-of-office BP measurements is defined as 'consistent normotension'. There are patients where either the office BP or the out-of-office is elevated and the other one is normal. Elevated office BP with normal out-of-office BP is defined as white-coat hypertension (WCHT); synonyms are 'isolated office or clinic HT'. The contrary, normal office BP with elevated out-of-office BP, is defined as masked HT (MHT); of which 'isolated ambulatory HT' is a synonym. Table 4 provides an overview of this classification.

	Normal office BP	Office HT
Normal out-of-office BP	Consistent normotension	White-coat hypertension
Out-of-office HT	Masked hypertension	Sustained hypertension

Table 4: Classification of the blood pressure according to office BP and out-of-office BP values.

Rarely elderly patients may present with resistant hypertension but actually it represents a falsely elevated cuff BP due to severely sclerotic and/or calcified arteries (i.e. *pseudohypertension*). Elderly people with concomitant history of renal insufficiency, peripheral arterial disease or diabetes mellitus are more likely to present with pseudohypertension. Pseudohypertension is an important clinical feature as it may lead to overmedication and adverse events. The clinician may suspect this condition when the radial pulse is still palpable despite the occlusion of the brachial artery by the cuff (Osler maneuver), but this test is a poor clinical predictor of pseudohypertension. The 'gold standard' for pseudohypertension is the invasive measurement of BP. Non-invasive Doppler BP measurement has been proposed as a screening test for pseudohypertension.[13,40]

4.1.2. Invasive techniques

Invasive techniques consist of measuring the BP in the arteries. Of course this requires arterial puncture, which has a higher risk of complications than non-invasive BP measurement. Measuring the BP with invasive techniques results in accurate beat-to-beat information and are considered as more accurate than non-invasive techniques. Invasive measurement is advised when (1) rapid changes of the BP are expected (e.g. CV instability, pharmacological effects), (2) non-invasive measurement is not possible or likely to be inaccurate (e.g. obesity, cardiac arrhythmias), (3) long-term measurement in sick patients is required (e.g. intensive care).[41]

4.1.3. Conclusion

Office BP measurement still remains the 'gold standard' for screening, diagnosis and management of hypertension, but out-of-office BP measurements are an important added value to conventional office BP measurements. Home BP monitoring supported by telemonitoring is an effective method to decrease BP in patients with uncontrolled HT. Home BP monitoring is more suitable in primary care and ABPM is more suitable in specialist care, but availability, facility, cost of use and patient preference will determine if either ABPM or HBPM will be chosen. Since ABPM is currently considered the reference for out-of-office BP, it is advisable that abnormalities on HBPM are confirmed with ABPM.[1,38]

5. Hypertension and chronic kidney disease

Hypertension is, along with diabetes, the most common cause of initiating and promoting a progressive loss of kidney function. Good control of the BP has shown to delay the progression of kidney injury. On the other hand is a reduced kidney function a major risk for developing HT. Chronic kidney disease (CKD) is subdivided in 5 stages based upon the estimated Glomerular Filtration Rate (eGFR) (table 5).[42]

Stage	Description	eGFR (mL/min/1,73m²)
1	Kidney damage with normal or elevated eGFR	≥ 90
2	Kidney damage with mild decreased eGFR	60 – 89
3	Moderate decreased eGFR	30 – 59
4	Severe decreased eGFR	15 – 29
5	End Stage Renal Disease (ESRD) = Kidney Failure	< 15 or dialysis

Table 5: Classification of CKD.[43]

The prevalence of CKD in adults is estimated at 10%. Overall prevalence of HT in patients with CKD is estimated around 70–80% (in some studies even up to 86%) and gradually increases with advancing CKD stages. Prevalence of HT in patients on dialysis decreases from over 95% to 50-60%, probably due to better volume control. Although there is high prevalence of HT in patients with CKD, HT control is low, with an overall HT control estimated at 34%. Awareness and treatment of HT increases with advancing stages of CKD. The latter translates into increasing HT control from stage 1 CKD to stage 4 and 5 CKD.[44]

An early diagnosis and treatment of HT is very important in patients with CKD as HT plays an important role in the progression to ESRD and these people have a higher CV morbidity, CV mortality and stroke risk. Management of HT in patients with CKD is considerably difficult, especially in patients on dialysis, as these patients may present with great volume shifts. Decisions concerning diagnosis and treatment are mostly based on office BP. In patients with CKD, and especially on dialysis, office BP values often seem to be inaccurate. By consequence ABPM and HBPM are both very important in the diagnosis and treatment of HT in patients with CKD.[45]

Advantages of ABPM have already been summed up previously in this paper. These advantages are even more distinct in patients with CKD as these patients (already from a mild decrease in kidney function) are at greater CV risk compared to patients with normal kidney function. Good BP control is needed to prevent the progression of kidney injury. According to Palatini office BP fails to provide a thorough picture of the BP in patients with CKD.[46] Andersen et al. compared office BP to ABPM (with ABPM regarded as the reference method) and found that 28% of the patients presented with lower

office BP and 30% presented with higher office BP.[47] Minutolo et al. revealed a 14,2 mmHg overestimation of the daytime BP by office BP measurements.[48] In patients on dialysis correlation between office BP during dialysis and ABPM during the interdialytic period was even lower.

Moreover the diagnosis of WCHT and MHT is warranted, as an early initiation of treatment is very important in patients with CKD to prevent further progression of the kidney injury. Furthermore ABPM has also shown to have a higher correlation with end-organ-damage than office BP. Loss of diurnal rhythm in BP has been described in more than 80% in patients with ESRD (compared to 10-20% in patients aged over 70 without CKD).

Patients with CKD are at high risk of developing HT. Ambulatory BP monitoring allows the health care provider to obtain a better view on the hypertensive status of the patient than office BP, as ABPM provides information on WCHT, MHT, diurnal BP rhythm, …[46]

Advantages of HBPM have also been summed up previously in this paper. These advantages are more distinct in patients with CKD than in patients with normal kidney function. Office BP has shown to vary considerably but HBPM has shown to have a better reproducibility and therefore being more reliable, because HBPM is based upon a larger amount of readings and it excludes the white-coat effect. Furthermore HBPM also plays an important role in uncovering WCHT and MHT. Different studies have shown that HBPM is correlated better than office BP with OD in patients with early stages of CKD (proteinuria, eGFR and mortality) and in patients on dialysis (LVH, aortic stiffness, mortality). In patients on dialysis extra attention should be paid to frequency and timing of the readings, since BP increases with 4 mmHg every 10 hours elapsed after dialysis. Therefore researchers suggest measuring BP after waking up and just before going to sleep during four consecutive days after a midweek dialysis session.[45]

6. Barriers to optimal hypertension control

There is overwhelming evidence that HT is a major CV risk factor, but despite this knowledge studies have shown that there are a lot of people who are unaware of their hypertension, who are aware but do not undergo BP-lowering treatment or who fail to achieve BP targets. Taken into account that in clinical studies patients are more motivated and stimulated to achieve BP control, HT treatment and control is probably worse in real-life practice than is clinical studies. For example in the study by Van der Niepen et al. overall BP control was only 21% in a large cohort study.[1,9,49]

Different barriers to optimal hypertension control have been defined and can be categorized in three major domains: patient-related -, physician-related - and medical environment/health care system related barriers.

Patient-related barriers are the most common and most important reasons for a poor HT control. These barriers include poor medication adherence, patients' beliefs about HT and its treatment, depression, cognitive dysfunction, low health literacy, comorbidity, coping, patient motivation, etc. The principal reason is poor medication adherence. Poor medication adherence is ranged between 43% and 88%. In a study by Gale et al. patients and general practitioners (GP) expressed concerns about medication and preferred to keep medication to a minimum. Patients' belief about HT and its treatment plays an important role in their compliance to their BP-lowering treatment. Nevertheless in the study by Gale et al. patients explained that they would do whatever the doctor recommended, irrespective of their own attitudes to medication.[50] Reviewing the association between dose regimens and medication compliance showed that compliance is inversely related to the number of doses per day. The latter study, as well as the ESH/ESC guidelines, promote the use of a combination of two or three antihypertensive drugs at fixed doses in a single tablet as it reduces the amount of pills to be taken and therefore improves medication adherence.[49,51]

The most important physician-related barrier is clinical inertia. This is a failure of the physician to initiate or intensify drug therapy due to 3 main reasons: 1) overestimation of the administered care; 2) lack of training; 3) the use of soft reasons to avoid treatment intensification by a 'wait and see-policy'. Other reasons may be the financial pressures, concern about cost and medication side effect, lack of familiarity with treatment guidelines, and reflection of the patients' poor enthusiasm for the BP-lowering treatment. The study by Gale et al. showed that recommendations and guidelines were often perceived by the GP's as unrealistic when applied in the clinical practice.[49,50]

Medical environment and the health care system associated barriers are probably the least salient. They include lack of access to care, cost of medication, low socioeconomic status, etc.[1,49]

In the 2010 review of the Cochrane Collaboration few of the strategies to improve BP control were associated with a clinically significant improvement in BP control. They conclude that "practices and clinics need to have an organized system of regular follow-up and review of their hypertensive patients and antihypertensive drug therapy should be implemented by means of a vigorous stepped care approach when patients do not reach target blood pressure levels". Moreover they also conclude that "self-monitoring and appointment reminders may be useful adjuncts to improve BP control, but they require further evaluation".[52]

The 2013 ESH/ESC guidelines suggest several methods to improve BP control. As mentioned above pills containing a combination of two or three antihypertensive drugs in a single tablet may reduce the amount of pills to be taken daily and so improving medication adherence. Information about BP and its possible consequences has to be given to the patient, either in an individual meeting or in-group sessions. The patient should self-monitor his BP and there should be room for self-management either with simple patient-guided-systems or supervised by a health care provider (doctor, pharmacist[53], nurse). On health care level intensification of care is needed by good BP monitoring, telemedicine, involving pharmacists in the drug therapy, etc.[1,4,51,54]

7. ABPM versus HBPM

Most studies compare office BP with either ABPM or either HBPM and look at their correlation with OD. Few studies have been done to directly compare ABPM and HBPM and **look if there is a difference between these two methods**.[55] In a previous study by our department the effect of different dialysate sodium concentrations in patients with intradialytic hypertension was investigated.[56] Patients had to perform a telemonitoring based HBPM during 7 consecutive days with 2 morning and 2 evening measurements followed by a 24h-ABPM with measurements during the day at a 15-minute interval and during the night at a 30-minute interval. In total 11 patients with ESRD on hemodialysis were enrolled in a prospective randomized cross-over study. Significant discrepancy between daytime BP values obtained with ABPM and tele-HBPM was seen in nearly every patient. At wash-out mean-daytime-ABPM was 133.8 ± 17.8/ 71.1 ± 10.9 mmHg and mean-HBPM was 144.3 ± 17.1/ 76.4 ± 13.7 mmHg (p-values for mean-systolic BP and mean-diastolic BP were respectively 0.0323 and 0.0452).

Since the ESH uses the same cut-off values for daytime-ABPM and HBPM, we wondered if the discrepancy we have observed in the dialysis study, could be replicated in a larger and broader group of patients, including normal volunteers, patients with and without arterial hypertension and patients with and without CKD. Reviewing the literature, we concluded that there are very few comparative studies between ABPM en HBPM. These studies are summarized in the following paragraphs.

Gaborieau et al. performed a study to investigate the correlation of ABPM and HBPM with target organ damage.[57] Office BP, ABPM and storage-HBPM were measured in 302 of the initially 325 included treated (70%) or untreated hypertensive patients. The HBPM was performed by storage-HBPM during 4 consecutive days (with exclusion of the first day) with 3 measurements in the morning and 3 in the evening. The 24h-ABPM was measured by readings every 20 minutes during the day and every hour during the night. Mean-HBPM (135 ± 18/ 77 ± 9 mmHg) was significant ($p<0.001$) higher for SBP than mean-daytime-ABPM (130 ± 14/ 78 ± 9 mmHg). They concluded a significant 5 mmHg systolic BP difference between mean-daytime-ABPM and mean-HBPM. A value of 135 mmHg mean-daytime-ABPM corresponded to 140 mmHg mean-HBPM. To their knowledge this was the first report in the literature where such a discrepancy has been reported and they recommend further investigation because it may have important consequences in the definition of target values for HT.

Martinez et al. investigated if HBPM could be considered as an alternative to ABPM and if HBPM was correlated with target organ damage.[58] In all 225 included treated hypertensive patients with persistent high BP values at the clinic, office BP, 24h-ABPM and HBPM were measured. Home BP was

measured trice three times a day by storage-HBPM. They did not exclude the first day as average BP over the second and third day were similar to average BP during the whole monitoring. The ABPM was measured during 24hours but intervals were not specified in the article. Mean-daytime-ABPM was 139 ± 15/ 82 ± 9 mmHg and mean-HBPM was 144 ± 18/ 84 ± 9 mmHg. Conflicting information about significance is provided in the article. The text mentions a significant difference ($p<0.01$) of systolic-HBPM from the remaining systolic BP values, while diastolic-HBPM was similar to diastolic-daytime-ABPM. In the table a significant difference ($p<0.01$) for systolic- and diastolic-HBPM from the remaining BP values is mentioned.

In a study by Bayo et al. similar differences were observed. They examined the role of HBPM in the diagnosis of white-coat HT in four primary health care centers.[59] All 157 included untreated patients with mild-moderate hypertension underwent storage-HBPM for 3 consecutive days (3 readings in the morning and 3 in the evening), followed by 24h-ABPM (readings during the day at a 20-minute interval and during the night at a 30-minute interval). Although the difference was not statistically significant, mean-HBPM was higher than mean-daytime-ABPM, 137.4 ± 14.3/ 82.1 ± 8.3 mmHg and 134.8 ± 11.3/ 81.3 ± 9.5 mmHg, respectively.

In the SAMPLE study, by Mancia et al., they investigated if the effect of a reduction in left ventricle mass, induced by an antihypertensive treatment in 184 treated essential hypertensive patients, is better predicted by office BP or ABPM.[60] Because few studies have looked into the predictive value of conventional-HBPM on OD, they also measured home BP on several occasions and compared these values with office BP and ABPM. The average of 1 morning- and 1 evening measurement, during the 24-hour period in which ABPM was performed, was calculated and accounted for the home BP. Home BP monitoring was performed by conventional-HBPM on the dominant arm. The ABPM was performed over 24 hours on the non-dominant arm with readings taken at a 15-minute interval during the day and a 20-minute interval during the night on a routine working day. At each point of the study (with a 12 month follow-up period) mean-HBPM was consistently higher than mean-daytime-ABPM. At entry mean-HBPM values were 160 ± 14/ 102 ± 7 mmHg and mean-daytime-ABPM values were 153 ± 16/ 98 ± 12 mmHg. After 12 months follow-up mean-HBPM values were still higher than mean-daytime-ABPM values (137 ± 12/ 86 ± 8 mmHg and 134 ± 12/ 86 ± 10 mmHg, respectively). As the difference between HBPM and ABPM wasn't part of the primary objectives of this study, inter-method differences were not evaluated and only difference between office BP and mean-24h-ABPM was evaluated. Significance between mean-daytime-ABPM and mean-HBPM was not calculated.

Den Hond et al. performed a randomized controlled trial (part of the THOP trial) and investigated if HBPM could be an alternative to ABPM in the diagnosis of WCHT.[61] They included 257 untreated hypertensive patients of whom 247 underwent office BP, 24h-ABPM and conventional-HBPM. Home BP's were measured 3 times in the morning and evening during 1 week. The 24h-ABPM was measured with a 15-minute interval during the day and a 30-minute interval during the night. Their values did not follow the differences found in the studies mentioned above: on the contrary mean-daytime-ABPM was somewhat higher (148.1 ± 14.2/ 95.0 ± 9.3 mmHg) than mean-HBPM (143.1 ± 16.1/ 91.5 ± 9.0 mmHg), but significance between these two methods was not calculated. Different results for mean-HBPM were mentioned in the table and figure in this article. We used the values mentioned in the table as these values are used in the further discussion in the article.

Hara et al. investigated the correlation of silent cerebrovascular disease with office BP, 24h-ABPM and HBPM in 1007 subjects in a general population of Japan.[62] Home BP monitoring was measured by recording readings in a logbook kept by the patient (conventional-HBPM) with 1 measurement in the morning and 1 in the evening during 4 weeks. Measurements for ABPM were taken at a 30-minute interval during 24 hours. In order to compare BP values of this study with the values of other studies we will only use the measurements of the patients not suffering silent cerebrovascular disease (n=501). The results showed same differences as found in the study by Mancia et al.: mean-daytime-ABPM (129 ± 13/ 76 ± 8 mmHg) was higher than mean-HBPM (122 ± 14/ 73 ± 9 mmHg), but significance between these two methods was not calculated.

Stergiou performed two studies with a direct comparison between 24h-ABPM and HBPM. In the first study he investigated the diagnostic value of ABPM and HBPM as alternatives to office BP for the diagnosis of HT.[63] The way of reporting HBPM (conventional, storage or telemonitoring) wasn't described in the article. Home BP's were taken twice in the morning and twice in the evening on 3 workdays per week for 2 weeks. ABPM was measured twice on a routine workday with measurements at 20-minutes interval for 24hours. In total 133 untreated patients with average diastolic office BP of 90-115 mmHg on the initial clinic visit were enrolled in the study. Although findings showed no significant difference, there was a slightly higher mean-daytime-ABPM than mean-HBPM (mean difference 0.6 ± 11.8/ 1.8 ± 6.7 mmHg). Mean-daytime-ABPM was 139.3 ± 12.8/ 91.1 ± 9.9 mmHg and mean-HBPM was 138.7 ± 15.6/ 89.3 ± 8.6 mmHg. In the second study they investigated if HBPM is as reliable as ABPM in predicting target organ damage in patients with HT.[64] Methods were similar to the first study. Both conventional- and storage-HBPM were used to report the home BP. Sixty-eight untreated hypertensive patients were enrolled in the study. Mean-daytime-ABPM (146.2 ± 14.0/ 96.0 ± 9.8 mmHg) was higher than mean-HBPM (142.2 ± 14.4/ 92.3 ± 9.0 mmHg) for systolic as well as diastolic BP. Differences in SBP and DBP between mean-daytime-ABPM and mean-HBPM were significant (respectively $p<0.01$ and $p<0.001$).

In a prospective cross-sectional study by Mansoor et al. the relationship between office BP, 24h-ABPM and HBPM was examined in 48 patients with stage 1 HT and they had to be free of antihypertensive drugs for a minimum of 4 weeks.[65] Telemonitoring based HBPM was used to measure home BP, and was performed during 7 consecutive days with 3 morning and 3 evening measurements. The interval at which ABPM was measured wasn't described in the article. In general they used the left arm for tele-HBPM and ABPM. Mean-daytime-ABPM was significantly higher than tele-HBPM (139 ± 12/ 88 ± 8 mmHg and 132 ± 11/ 80 ± 8 mmHg, respectively), $p<0.001$ for both SBP and DBP.

Shimbo et al. compared office BP to ABPM and HBPM in prediction of CV end-organ damage in normotensive and hypertensive stage 1 patients (who were willing to come of antihypertensive drugs for 2 weeks prior to the study, and remain off for the duration of the study).[66] The ABPM measurements were performed over 36 hours and for about ¾ of the measurements were taken every 30 minutes and the remaining measurements were either taken at a 15-minute interval (between 6AM and 10PM) or at a 30-minute interval (between 10PM and 6AM). To compare results with other studies only the first 24 hours were used for analysis. Storage-HBPM was used with 3 measurements in the morning and 3 in the evening, 4 days a week over 10 weeks with an additional 6 readings on two occasions. Mean-daytime-ABPM (134 ± 14/ 82 ± 10 mmHg) was higher than mean-HBPM (130 ± 16/ 79 ± 10 mmHg). There was significance for SBP as well as DBP ($p< 0.001$) between ABPM and HBPM values.

Jula et al. compared multiple clinic measurements with HBPM and 24h-ABPM in the evaluation of untreated HT.[67] A total of 233 untreated moderately to severely hypertensive patients were enrolled in the study. They had to perform a 24h-ABPM (measurements every 15 minutes during the day and every 30 minutes during the night) and a HBPM during 7 days with 2 measurements in the morning and evening). The way of reporting HBPM (conventional, storage or telemonitoring) wasn't described in the article. Mean-daytime-ABPM (149.6 ± 13.8/ 92.8 ± 7.8 mmHg) was higher than mean-HBPM (138.9 ± 13,1/ 92.9 ± 8,6 mmHg) with significance in overall difference between office BP, HBPM and ABPM ($p<0.001$).

The data of all these studies are summarized in table 7.

	n	Type of patient			Mean-daytime-ABPM (mmHg)		Mean-HBPM (mmHg)		Type of HBPM recording
		NT / HT	Treated/untreated	CKD	Systolic	Diastolic	Systolic	Diastolic	
Robberechts et al.[56] *	11	HT	Treated	ESRD	133.8 ± 17,8	71.1 ± 10.9	144.3 ± 17.1	76.4 ± 13.7	**Telemedicine**
Gaborieau et al.[57] *	302	HT	Untreated	NS	130 ± 18	78 ± 9	135.5 ± 14	77 ± 9	Storage
Martinez et al.[58] Δ	225	HT	Treated	NS	139 ± 15	82 ± 9	144 ± 18	84 ± 9	Storage
Bayo et al.[59] §	190	HT	Untreated	NS	134.8 ± 11.3	81.3 ± 9.5	137.4 ± 14.3	82.1 ± 8.3	Storage
Mancia et al.[60]	184	HT	Treated	NS	153 ± 16	98 ± 12	160 ± 14	102 ± 7	Conventional
Den Hond et al. [61]	247	HT	Untreated	NS	148.1 ± 14.2	95.0 ± 9.3	143.1 ± 16.1[a]	91.5 ± 9.0[a]	Storage
Hara et al.[62]	501	NT + HT	NS	NS	129 ± 13	76 ± 8	122 ± 14	73 ± 9	Conventional
Stergiou et al. (1) [63] §	133	HT	Untreated	NS	139.3 ± 12.8	91.1 ± 9.9	138.7 ± 15.6	89.3 ± 8.6	NS
Stergiou et al. (2) [64] *	68	HT	Untreated	NS	146.2 ± 14.0	96.0 ± 9.8	142.2 ± 14.4	92.3 ± 9.0	Conventional + storage
Mansoor et al. [65] *	48	HT	Untreated	NS	139 ± 12	88 ± 8	132 ± 11	80 ± 8	**Telemedicine**
Shimbo et al. [66] *	163	NT + HT	Untreated	NS	134 ± 21	82 ± 10	130 ± 16	79 ± 10	Storage
Jula et al. [67] *	233	HT	Untreated	NS	149.6 ± 13.8	92.8 ± 7.8	138.9 ± 13.1	92.9 ± 8.6	NS

Table 7. Comparison of the values in the studies where ABPM was compared to HBPM (BP-values expressed in mmHg).

Abreviations: n: number of patients included in the study, NT: normotensive, HT: hypertensive, CKD: chronic kidney disease, ESRD: end-stage-renal-disease, NS: not specified.

[a] Mean-HBPM-values in a graph (142.4/ 91.0 mmHg) differ from the readings in the table (143.1 ± 16.1/ 91.5 ± 9.0 mmHg).

* In these studies significance between ABPM and HBPM was calculated. Robberechts et al., Gaborieau et al., Stergiou et al. (2), Mansoor et al., Shimbo et al. and Jula et al. revealed significant differences.

§ In these studies significance between ABPM and HBPM was calculated. Bayo et al. and Stergiou et al. (1) showed non-significant differences.

Δ In the study by Martinez et al. conflicting significance was mentioned in the table and text.

Although the number of studies debating this subject is rather small, we found a few studies directly comparing HBPM to ABPM. Most comparisons are obtained from studies where the difference between ABPM and HBPM is not part of the primary objectives and it is just a coincidental finding and therefore it is not further discussed in most articles. Only two previous studies used a telemonitoring system for HBPM and only two studies specified which arm was used for ABPM and HBPM. We conclude there is a discrepancy in the literature and there remains uncertainty regarding the reference values for these measuring methods. As there are few direct comparisons between these two methods as a primary objective we would like to broaden the population investigated by Robberechts et al. and investigate if the trend they found persists in normotensive patients and in patients with HT with or without CKD.

Methods

1. Study objectives

The following primary objective was explored:

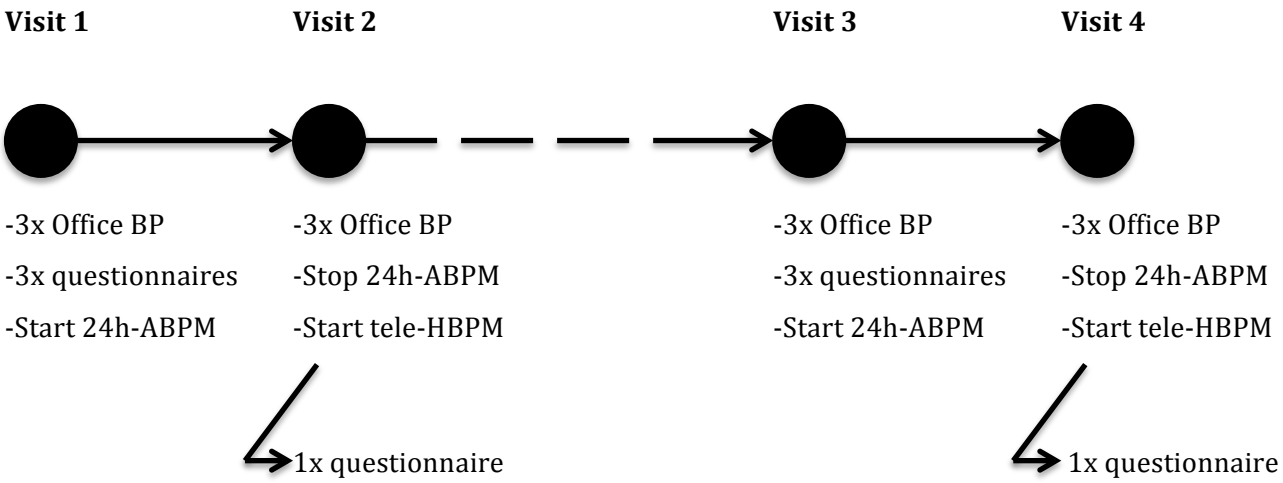
To evaluate the effectiveness of office blood pressure measurement, home blood pressure telemonitoring and 24h ambulatory blood pressure monitoring in assessing blood pressure control (defined as office BP <140/<90 mm Hg and for home/ ambulatory daytime BP as <135/<85 mm Hg).

As secondary objectives, following elements were explored:

a) To evaluate the satisfaction with the different types of blood pressure measurement.
b) To evaluate the effect of intensive blood pressure monitoring on medication adherence.
c) To evaluate the effect of intensive blood pressure monitoring on blood pressure control.
d) To evaluate the effect of intensive blood pressure monitoring on the general wellbeing of the patient.
e) To evaluate the percentage of patients with a higher blood pressure at night than during daytime.
f) To evaluate the reproducibility of BP of the different BP measurement techniques.

2. Study design

The study consists of 2 periods of 1 week of BP monitoring.



The study was conducted according to the Belgian law and the Declaration of Helsinki and ICH-GCP. Ethics committee of the Universitair Ziekenhuis Brussel approval and written patient informed consent were obtained.

The primary investigator or subinvestigator provided the patient with information. An informed consent was signed by both sides when the patient was recruited on the consultation or on the first visit (*visit 1 – day 1*). At the first visit baseline characteristics were collected (age, sex, race, weight, length, number and type of antihypertensive medication). Office BP was measured 3 times at the non-dominant arm with an automated BP monitor according to the ESH-guidelines. The patients were asked to fill in 3 questionnaires: (1) EQ-5D-3L questionnaire on the overall wellbeing, (2) Hospital Anxiety and Depression Scale (HADS) questionnaire on anxiety and depression, and (3) Morisky questionnaire on medication adherence. Afterwards the monitor for 24h-ABPM was attached on the non-dominant arm according to ESH-guidelines.

At the second visit (*visit 2 – day 2*) again office BP was measured 3 times at the non-dominant arm with an automated BP monitor according to the ESH-guidelines and tele-HBPM was started. Patients were instructed to measure their BP's at home during 7 consecutive days, 3 times in the morning and 3 times in the evening, before eating and before taking medication, and at the same arm as office BP and 24h-ABPM according to the ESH-guidelines.

When the patient returned the HBPM-device (*day 9*) she/ he was asked to fill in a questionnaire on the satisfaction concerning the type of BP measurement.

One month later the same examinations were repeated:

At the third visit (*visit 3 – after 4 weeks*) office BP was measured 3 times at the non-dominant arm with an automated BP monitor according to the ESH-guidelines. The patients were asked to fill in 3 questionnaires: (1) EQ-5D-3L questionnaire on the overall wellbeing, (2) Hospital Anxiety and Depression Scale (HADS) questionnaire on anxiety and depression, and (3) Morisky questionnaire on medication adherence. Afterwards the monitor for 24h-ABPM was attached on the non-dominant arm according to ESH-guidelines.

At the fourth visit (*visit 4 – V3+1 day*) office BP was measured 3 times at the non-dominant arm with an automated BP monitor according to the ESH-guidelines and tele-HBPM was started. Patients were instructed to measure their BP's at home during 7 consecutive days, 3 times in the morning and 3 times in the evening, before eating and before taking medication, and at the same arm as office BP and 24h-ABPM according to the ESH-guidelines.

When the patient returned the HBPM-device (*V3 + 8 days*) he was asked to fill in a questionnaire on the satisfaction concerning the type of BP measurement.

3. Population – Inclusion and exclusion criteria

Normotensive volunteers and hypertensive patients (either with or without CKD) were recruited during the Nephrology & Hypertension outpatient clinic of the Universitair Ziekenhuis Brussel.

To be eligible participants had to be at least 18 years old and had to sign the appropriate written informed consent before any study-specific procedure was performed. In addition hypertensive patients had to be on a stable antihypertensive drug treatment to be eligible for the study.

Criteria for exclusion were recent cardiovascular or cerebral event, severe HT (BP>180/ 110 mmHg), atrial fibrillation, acute kidney failure, debilitating illness (liver failure, instable patients, active bleeding, active infection, active neoplasm, …), pregnancy, impossibility to measure BP in a standardized way and any kind of disorder that compromises the ability of the subject to provide written informed consent and/or to comply with study procedures. When patients participated simultaneous in another clinical study, except observational trials, they were also excluded from the study.

Participants may withdraw from the study at any time without any influence on further treatment. Participants were also withdrawn if their mean BP exceeded 180/ 110 mmHg.

The sample size for the study is calculated based on the primary efficacy endpoint, which is detecting a difference of < 5 mm Hg between tele-HBPM and 24h-ABPM and of < 10 mmHg between office and home BP telemonitoring. A total of at least 35 and 73 patients are needed to detect a difference of 10 and 5 mmHg, respectively. The probability is 80% that the study will detect a difference at a two-sided 0.05 significance level, if the true difference between BP methods is 5 and 10 mm Hg. This is based on the assumption that the standard deviation of the difference in the response variables is 15. To account for incomplete data collection and 20% dropouts, the overall sample of the study has to include 42 or 88 patients for a BP difference of 10 and 5 mmHg, respectively.

4. Study procedures

4.1. Office blood pressure:

Office BP was measured with an automated oscillometric BP device (Omron HEM-705CP digital BP monitor (Omron Corp., Tokyo, Japan)), measuring brachial artery pressure and successfully passed validation according to the protocol of the British Hypertension Society[68], with an appropriate cuff

around the upper arm. Blood pressure readings were obtained after the patient had rested for 5 minutes in the sitting position and were measured at both arms (unless contraindication: arterio-venous fistula, ipsilateral mammectomy). Blood pressure was taken trice with 1-minute interval. For the analysis the BP values obtained at the non-dominant arm were used, as this was also the arm used for 24h-ABPM and for tele-HBPM.

The first of three measurements was always excluded in the statistical analysis and mean-office BP was calculated on the second and third measurement.

Office BP in patients on dialysis (stage 5 CKD) was calculated differently. Office BP was taken once before dialysis, every 30 minutes during dialysis and once after dialysis. The average of these measurements was calculated and was regarded as the mean-office BP.

4.2. 24h Ambulatory Blood Pressure Monitoring

24h-ABPM measures BP of the subjects living their normal daily life and during their sleep. The ambulatory BP was recorded with oscillometric Space-Labs 90217 and 90217A monitors (SpaceLabs Inc., Redmond, Washington, USA)[69]. The cuff of the BP monitor was fitted on the non-dominant arm. The devices were programmed to obtain BP readings at 15-minute intervals from 08:00 to 22:00 and at 30-minute intervals for the remainder of the day. Daytime and nighttime ambulatory BP's were calculated as the actual awake and sleep time means of the readings obtained. ABPM was scheduled on visit 1 after office BP measurement and after filling in the questionnaires and occurred outside the hospital. The device was attached on visit 1 and on visit 3 and was removed after 24h, i.e. on visit 2 and visit 4.

Following parameters were calculated: mean 24h SBP, mean 24h DBP, mean 24h mean BP; mean daytime SBP, mean daytime DBP, mean daytime mean BP; mean nocturnal SBP, mean nocturnal DBP, mean nocturnal mean BP; mean SBP dipping, mean DBP dipping, mean BP dipping.

4.3. Telemonitoring based Home Blood Pressure Monitoring

On visit 2 and on visit 4 a tele-HBPM was started. The patients had to measure their BP during 7 consecutive days, trice in the morning and trice in the evening, in the sitting position, and after 5 minutes of rest. For the self-measurement of BP at home, the patients used a validated automated sphygmomanometer (Stabil-O-Graph mobil, IEM, Germany) equipped for BP telemonitoring. This automated oscillometric device measures brachial artery pressure and has successfully passed validation according to the protocol of the British Hypertension Society[70]. At enrolment, the co-investigator, a physician trainee, or the study nurse instructed the patients how to use the telemonitoring equipment and provided written guidelines for their operation at home. The patients measured their BP in the morning (between 06:00 and 10:00, before breakfast and before taking any

medication) and in the evening (between 18:00 and 22:00, before dinner and before taking evening medication) during the week immediately following the ABPM; the same non-dominant arm was used. Self-measured BP values were transmitted automatically by mobile phone to a website and could be checked by the physician and/or study nurse who could enquire about circumstances in case of exceptionally high or low readings.

All measurements during the first day (3 in the morning and 3 in the evening) as well as every first measurement in the following sets of three measurements were excluded and mean-tele-HBPM was calculated on the second and third measurement of each set from day 2 to day 7.

For all types of BP measurement, the same cuff size was used. Standard cuffs have a 24 x 14 cm inflatable bladder. If arm circumference exceeded 31 cm, larger cuffs with a bladder size of 32 x 15 cm were used.

Blood pressure control for conventional BP was defined as a BP threshold <140/ 90 mmHg, for self-measured home BP as a BP threshold <135/ 85 mmHg. Optimal values for ABPM were <135/ 85 mmHg when subjects are awake and <120/ 70 mmHg during sleep, or overall a BP <130/ <80 mmHg. The white-coat effect was defined as the difference between conventional and daytime ambulatory BP or the difference between conventional and average home BP.

4.4. Questionnaires

We analysed the medication adherence as well as the general wellbeing of the patients to evaluate if psychological and emotional conditions may influence the BP values, BP control, compliance to the antihypertensive treatment and the appreciation of the BP measurement techniques. Furthermore we looked into the satisfaction of patients with the different measurement techniques to evaluate if the method itself can influence BP values.

Medication adherence was evaluated by the Morisky Medication Adherence Scale (MMAS-8). It is a self-report questionnaire with 8 questions. The first 7 response choices are yes/no, where 'yes' indicates bad adherence and is rated as '0' and 'no' indicates good adherence and is rated as '1'. The last question is a 5-point Likert scale. Bad adherence corresponds to '0' and good adherence to '1', responses in between are rated as '0.25'; '0.50' and '0.75'. The total score of the MMAS-8 can range from 0 tot 8 with 8 indicating high adherence, 6-7 medium adherence and <6 low adherence. Normotensive subjects had a maximum score of 8 as they don't take any antihypertensive drugs.[71,72,73]

To evaluate the general wellbeing of the patient, we used 2 different questionnaires. The first questionnaire defines the anxiety and depression status of the patient (Hospital Anxiety and Depression Scale – HADS). It consists of twice 7 questions, the first 7 concerning anxiety and the last 7 concerning depression. Each question can be answered by a score ranging between 0 – 3, so possible scores are ranged from 0 – 21 for anxiety and depression, respectively. A score of 0 – 8 corresponds to being in the 'normal range', a score of 9-10 corresponds to 'suggestive for anxiety or depression', and a score of 11 or higher corresponds to 'probable presence of anxiety or depression'.[74]

The second questionnaire (EQ-5D-3L) is a standardised measure of health status. It consists of 2 pages; the EQ-5D descriptive system and the EQ visual analogue scale (VAS). The EQ-5D descriptive system comprises 5 dimensions representing the health status: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each item has 3 options: no problems, some problems and extreme problems. The EQ VAS is a self-rated health status on a visual analogue scale with '0' analogous with the worst health state and '100' with the best health state according to the patient.

5. Statistical analysis

All data relevant to the study were kept in a password protected Excel Data file. After the data had been collected completely and verified, data were imported in the Statview, version 5.0.1 (SAS Institute Inc.) Statistics and Data Analysis Software.

Demographic and clinical disease characteristics were summarized. BP values (office BP, ABP and tele-HBP) and BP changes were summarized and compared to each another, as well as global wellbeing, anxiety and depression, medication adherence and satisfaction concerning the type of BP measurement.

For comparison of the BP values obtained with the different methods, the BP values measured at the same arm were used.

T-test for continuous variables and chi-square-tests for categorical variables were used in the analysis.

Difference between the different out-of-office techniques was explored by using two different statistical analyses. First we compared the techniques by using a paired t-test to see if there is a difference between the methods on the first and the second visit. Secondly we compared the different

techniques by using the Bland-Altman-Method for multiple measurements. This is a method of data plotting used in analysing the agreement between two different assays. The underlying idea is that two methods that are designed to measure the same parameter should have good correlation when a set of samples is chosen such that the parameter varies considerably. A high correlation for two methods designed to measure the same parameter could imply that one has chosen a wide spread sample and thus does not automatically imply that there is good agreement between the two methods. There are two different Bland-Altman-Methods described. The first one is validated for single measurements whereas the second method is used for multiple measurements. Since we are comparing repeated measurements by two methods we first used the second Bland-Altman-Method, using daytime-ABPM as the reference method.[75,76]

Results

At this time we report intermediary results, as the study is still ongoing.

1. Baseline characteristics

Out of the 49 initially included patients, 3 patients (6.1%) withdrew before starting the study, 2 patients only participated the first time and results for visit 3 and 4 are still pending. All data from 46 patients were evaluated in this study; only the data of two patients, whose results of visit 3 and 4 are still pending, and one patient, whose therapy was modified between visit 2 and visit 3, were excluded to compute reproducibility.

Table 6 shows the baseline characteristics of the study population. We included 15 (32.6%) normotensive volunteers, 10 patients (21.7%) with hypertension without CKD and 21 patients (45.7%) with hypertension and CKD. The latter group can be subdivided in 5 hypertensive patients (10.9%) with CKD stage 3, 2 hypertensive patients (4.4%) with CKD stage 4 and 14 hypertensive patients (30.4%) with CKD stage 5.

The group comprised 26 men (56.5%) and 20 women (43.5%), had a mean age of 57.5 years; 95.7% were Caucasian, 2.2% were African and 2.2% were Mediterranean. The average body mass index was 25.7 ± 5.0 kg/m^2 and mean abdominal circumference was 96.2 ± 16.4 cm. Hypertensive patients took an average of 3.2 ± 1.7 antihypertensive drugs per day. Antihypertensive therapy varied in the study population (table 7) from no medication in the normotensive volunteers to hexatherapy in some patients known with hypertension and advanced stage CKD.

Baseline characteristic	Patients (n=46)	Range (min-max)
Study sample		
Normotensive	15 (32.6%)	
Hypertensive without CKD	10 (21.7%)	
Hypertensive with CKD	21 (45.7%)	
CKD stage 3	5 (10.9%)	
CKD stage 4	2 (4.4%)	
CKD stage 5	14 (30.4%)	
Age (years) (mean ± SD)	**57.5 ± 16.2**	**24 – 82**
Normotensive	45.5 ± 16.9	24 – 65
Hypertensive without CKD	57.2 ± 7.2	47 – 67
Hypertensive with CKD	66.1 ± 13.4	29 – 82
CKD stage 3	70.4 ± 5.9	62 – 77
CKD stage 4	61.0 ± 7.1	56 – 66
CKD stage 5	65.4 ± 15.8	29 - 82
Sex		
Male	**26 (56.5%)**	
Normotensive	7 (15.2%)	
Hypertensive without CKD	4 (8.7%)	
Hypertensive with CKD	15 (32.6%)	
CKD stage 3	5 (10.9%)	
CKD stage 4	1 (2.2%)	
CKD stage 5	9 (19.6%)	
Female	**20 (43.5%)**	
Normotensive	8 (17.4%)	
Hypertensive without CKD	6 (13.0%)	
Hypertensive with CKD	6 (13.0%)	
CKD stage 3	0 (0%)	
CKD stage 4	1 (2.2%)	
CKD stage 5	5 (10.9%)	
Ethnicity		
Caucasian	44 (95.7%)	
African	1 (2.2%)	
Mediterranean	1 (2.2%)	
Body Mass Index (kg/m²) (mean ± SD)	**25.7 ± 5.0**	**17.9 – 36.3**
Normotensive	24.5 ± 4.0	19.9 – 36.3
Hypertensive without CKD	29.3 ± 3.6	25.5 – 33.8
Hypertensive with CKD	25.2 ± 5.6	17.9 – 36.1
CKD stage 3	27.5 ± 4.6	20.0 – 31.5
CKD stage 4	28.6 ± 9.1	22.1 – 35.0
CKD stage 5	24.0 ± 5.4	17.9 – 36.1
Abdominal circumference (cm) (mean ± SD)	**96.2 ± 16.4**	**69 – 138**
Normotensive	87.1 ± 11.2	70 – 109
Hypertensive without CKD	106.8 ± 10.4	96.3 – 127
Hypertensive with CKD	98.8 ± 18.6	69 – 138
CKD stage 3	102.7 ± 16.2	74.3 – 113
CKD stage 4	106.3 ± 29.4	85.5 – 127
CKD stage 5	95.9 ± 19.2	69 - 138
Antihypertensive drugs (mean ± SD)	**2.1 ±2.1**	**0 – 6**
Normotensive	0 ± 0	0
Hypertensive without CKD	2.4 ± 1.0	1 – 4
Hypertensive with CKD	3.5 ± 1.9	1 – 6
CKD stage 3	2.8 ± 2.2	1 – 6
CKD stage 4	2.5 ± 0.7	2 – 3

CKD stage 5	3.9 ± 1.9	1 - 6
Type of antihypertensive drugs		
Diuretic	13 (15.1%)	
BB	20 (23.3%)	
CCB	14 (16.3%)	
ACE-I	12 (14.0%)	
ARB	12 (14.0%)	
Other	15 (17.4%)	

Table 6: Baseline characteristics of subjects enrolled in the study.

Abbreviations: ACE-I, Angiotensin Converting Enzyme-Inhibitor; ARB, Angiotensin Receptor Blocker; BB, Beta-Blocker; CCB, Calcium Channel Blocker; CKD, Chronic Kidney Disease (CKD stage 3: eGFR (MDRD) 60 – 30 ml/min/1.73m^2; CKD stage 4: eGFR (MDRD) 30 – 15 ml/min/1.73m^2; CKD stage 5: eGFR (MDRD) <15 ml/min/1.73m^2; eGFR, estimated glomerular filtration rate; MDRD, Modified diet renal disease); n, number of patients; Other, Alpha-Blocker, Central acting agents, hemodialysis; SD, Standard Deviation.

Type of antihypertensive drugs	**Patients (n)**
Monotherapy	**5 (16%)**
BB	1 (3.2%)
ACE-I	2 (6.5%)
ARB	1 (3.2%)
Other	1 (3.2%)
Combination therapy	**26 (84%)**
Bitherapy (n, 9)	
BB + CCB	1 (3.2%)
BB + ACE-I	2 (6.5%)
BB + ARB	1 (3.2%)
BB + other	1 (3.2%)
Diuretic + ARB	1 (3.2%)
Diuretic + other	1 (3.2%)
CCB + other	1 (3.2%)
2 others	1 (3.2%)
Tritherapy (n, 6)	
BB + CCB + ARB	3 (9.7%)
Diuretic + ACE-I + ARB	1 (3.2%)
Diuretic + BB + ARB	1 (3.2%)
CCB + ACE-I + other	1 (3.2%)
Quadritherapy (n, 3)	
BB + CCB + ACE-I + other	1 (3.2%)
Diuretic + BB + CCB + ARB	2 (6.5%)
Pentatherapy (n, 3)	
Diuretic + BB + ACE-I + 2 others	2 (6.5%)
Diuretic + CCB + ARB + 2 others	1 (3.2%)
Hexatherapy (n, 5)	
Diuretic + BB + ACE-I + 3 others	1 (3.2%)
Diuretic + BB + CCB + 3 others	1 (3.2%)
Diuretic + BB + CCB + ACE-I + 2 others	1 (3.2%)
Diuretic + BB + CCB + ARB + 2 others	1 (3.2%)
BB + CCB + ACE-I + 3 others	1 (3.2%)

Table 7: Type of antihypertensive treatment taken by the patients.

Abbreviations: ACE-I, Angiotensin Converting Enzyme-Inhibitor; ARB, Angiotensin Receptor Blocker; BB, Beta-Blocker; CCB, Calcium Channel Blocker; n, number of patients; Other, Alpha-Blocker, Central acting agents, hemodialysis.

2. Blood pressure measurements

Mean office BP was 133.7 ± 23.2/ 75.5 ± 11.4 mmHg on visit 1 and 2, and was 129.7 ± 17.5/ 73.3 ± 10.9 mmHg on visit 3 and 4. Significant differences were seen, especially for SBP, when we compared office BP between the different groups. On visit 1 and 2 as well as on visit 3 and 4 SBP had tendency to increase from normotensive subjects to hypertensive patients without CKD to hypertensive patients with CKD. The first time (V1 + V2) this difference was significant between these 3 patient groups (normotensive vs HT without CKD, $p = 0.0344$; normotensive vs HT with CKD, $p < 0.0001$; HT without CKD vs HT with CKD, $p = 0.0241$). The second time (V3 + V4) this difference was only significant between normotensive and hypertensive patients with CKD ($p < 0.0001$). The first time DBP was only significantly lower in normotensive subjects compared to hypertensive patients without CKD ($p = 0.0437$), but the second time even this difference was no longer significant. No other significant differences were seen for office SBP or DBP.

Investigating reproducibility of office BP there was a significant higher overall SBP ($p = 0.0412$) the first time, overall DBP showed no significant difference. The overall significant higher SBP was mainly attributable to a considerably higher SBP in patients with HT and CKD stage 5 ($p = 0.0404$). Overall DBP showed good reproducibility, but in patients with HT and CKD stage 3 and stage 5 we found significant difference in diastolic office BP ($p = 0.0168$ and 0.0108, respectively).

Mean daytime-ABP on the first and second 24h-ABPM was respectively 129.7 ± 17.2/ 76.9 ± 9.4 mmHg and 127.7 ± 14.4/ 74.8 ± 8.3 mmHg. Mean-daytime-systolic-ABP increased between groups, with lowest values in normotensive subjects and highest values in patients with HT and CKD. These differences were only significant between normotensive subjects and patients with HT and CKD ($p = 0.0014$ and 0.0089, respectively on visit 1 and 3). On the first visit this difference was only due to significant difference with patients on hemodialysis; the second time patients with CKD stage 3 also had their part in this significant difference. Mean-daytime-diastolic-ABP showed no significant differences between normotensive and hypertensive patients, either with or without CKD.

Evaluating the reproducibility, we found that daytime-ABP was overall very good reproducible for both SBP and DBP. It only showed a significant difference for SBP as well as for DBP in patients with HT and CKD stage 5, suggesting that daytime-ABPM is not reproducible in patients on hemodialysis.

Mean tele-HBP during the first week was 128.9 ± 19.5/ 77.4 ± 11.3 mmHg and during the second week was 127.2 ± 13.5/ 75.5 ± 8.6 mmHg. During the first week hypertensive patients with CKD had significantly higher SBP values than normotensive subjects and HT patients without CKD. During the

second week this difference persisted, but was only significant between hypertensive patients with CKD and normotensive subjects. During the first week DBP values were significantly higher in patients on hemodialysis compared to normotensive subjects, but this difference did not persist on the second series of measurements.

Tele-HBP showed very good reproducibility as no significant differences for SBP and DBP were observed between the first and second measurement.

Average BP values for each measuring method at all visits are given in table 8.

Blood pressure	Visit 1 + 2		Visit 3 + 4	
	SBP (mean ± SD)	DBP (mean ± SD)	SBP (mean ± SD)	DBP (mean ± SD)
Office blood pressure (mmHg)	**n = 46**	**n = 46**	**n = 43**	**n = 43**
All patients	**133.7 ± 23.3**	**75.5 ± 11.4**	**129.7 ± 17.5***	**73.3 ± 10.9**
Normotensive	116.7 ± 12.5	72.3 ± 10.5	115.6 ± 13.3	72.4 ± 10.5
Hypertensive without CKD	128.7 ± 13.7	80.4 ± 6.9	128.8 ± 16.7	79.3 ± 9.5
Hypertensive with CKD	148.2 ± 24.1	75.5 ± 13.2	139.5 ± 13.8*	71.7 ± 11.3
CKD stage 3	142.6 ± 11.2	68.6 ± 10.6	144.6 ± 14.9	74.8 ± 12.4*
CKD stage 4	130.9 ± 14.7	74.6 ± 3.0	132.5 ± 2.5	77.4 ± 2.3
CKD stage 5	152.7 ± 27.5	78.0 ± 14.3	138.6 ± 14.4*	69.7 ± 11.7*
24h-ABP (mmHg)	**n = 46**	**n = 46**	**n = 44**	**n = 44**
All patients	**124.7 ± 18.2**	**72.8 ± 9.1**	**123.4 ± 15.6**	**71.3 ± 7.4**
Normotensive	113.0 ± 10.0	71.3 ± 6.1	115.1 ± 10.0	72.8 ± 6.0
Hypertensive without CKD	120.5 ± 10.5	75.3 ± 6.9	118.6 ± 10.4	71.9 ± 5.5
Hypertensive with CKD	135.1 ± 20.0	72.8 ± 11.6	131.1 ± 17.2	70.0 ± 8.9
CKD stage 3	129.6 ± 7.7	68.4 ± 3.6	132.8 ± 13.9	68.8 ± 6.6
CKD stage 4	126.0 ± 7.1	67.0 ± 1.4	136.5 ± 16.3	73.0 ± 4.2
CKD stage 5	138.4 ± 23.5	75.1 ± 13.6	129.7 ± 19.1*	70.1 ± 10.3*
Daytime-ABP (mmHg)	**n = 46**	**n = 46**	**n = 44**	**n = 44**
All patients	**129.7 ± 17.2**	**76.9 ± 9.4**	**127.7 ± 14.4**	**74.8 ± 8.3**
Normotensive	119.4 ± 11.2	76.7 ± 7.1	120.6 ± 10.4	76.9 ± 5.9
Hypertensive without CKD	126.6 ± 10.7	80.2 ± 7.9	124.8 ± 9.1	76.0 ± 6.3
Hypertensive with CKD	138.6 ± 19.0	75.5 ± 11.4	133.8 ± 16.2	72.8 ± 10.1
CKD stage 3	130.4 ± 5.3	69.8 ± 3.1	136.0 ± 14.8	71.2 ± 7.4
CKD stage 4	134.0 ± 8.5	72.5 ± 2.1	138.5 ± 19.1	76.0 ± 8.5
CKD stage 5	142.1 ± 22.3	78.0 ± 13.3	132.4 ± 17.3*	72.9 ± 11.5*
Nighttime-ABP (mmHg)	**n = 46**	**n = 46**	**n = 42**	**n = 42**
All patients	**114.3 ± 22.0**	**64.6 ± 10.5**	**114.7 ± 19.8**	**64.3 ± 7.3**
Normotensive	99.6 ± 8.4	60.1 ± 5.5	102.1 ± 8.1	62.8 ± 5.2
Hypertensive without CKD	108.4 ± 11.8	65.9 ± 7.5	108.5 ± 14.2	64.1 ± 5.5
Hypertensive with CKD	127.5 ± 24.7	67.3 ± 13.4	126.1 ± 21.3	65.4 ± 9.0
CKD stage 3	128.2 ± 16.2	65.6 ± 7.8	128.0 ± 12.9	65.8 ± 7.5
CKD stage 4	114.5 ± 5.0	58.5 ± 0.7	141.0 ± 0.0	65.0 ± 0.0
CKD stage 5	129.1 ± 28.8	69.1 ± 15.5	124.4 ± 24.3	65.2 ± 10.1
Tele-HBP (mmHg)	**n = 46**	**n = 46**	**n = 42**	**n = 42**
All patients	**128.9 ± 19.5**	**77.4 ± 11.3**	**127.2 ± 13.5**	**75.5 ± 8.6**
Normotensive	115.7 ± 11.9	72.5 ± 9.6	117.6 ± 12.0	74.5 ± 9.2
Hypertensive without CKD	123.3 ± 11.4	77.1 ± 8.8	125.5 ± 9.3	77.3 ± 8.3
Hypertensive with CKD	141.1 ± 20.0	81.1 ± 12.6	134.7 ± 11.6	75.4 ± 8.7
CKD stage 3	130.7 ± 9.2	74.1 ± 5.8	135.5 ± 10.2*	76.1 ±6.9
CKD stage 4	127.5 ± 9.4	75.9 ± 2.6	125.0 ± 7.9	75.8 ± 1.6
CKD stage 5	146.7 ± 21.8	84.3 ± 14.1	135.9 ± 12.5	75.0 ± 10.2*

Table 8: Overview of office BP, ambulatory BP and home BP.

Abbreviations: ABP, ambulatory blood pressure; CKD, Chronic Kidney Disease (CKD stage 3: eGFR (MDRD) 60 – 30 ml/min/1.73m²; CKD stage 4: eGFR (MDRD) 30 – 15 ml/min/1.73m²; CKD stage 5: eGFR (MDRD) <15 ml/min/1.73m²); DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; MDRD, Modified diet renal disease; n, number of patients; SBP, systolic blood pressure; SD, standard deviation; Tele-HBP, telemedicine-guided home blood pressure.

Legend
*P < 0.05 compared to visit 1+2
24h-ABP: mean values of ambulatory blood pressure monitoring over 24 hours
Daytime-ABP: mean values of ambulatory blood pressure monitoring during the day
Nighttime-ABP: mean values of ambulatory blood pressure monitoring during the night
Office blood pressure: mean values of blood pressure measured in the outpatient clinic
Tele-HBP: mean values of telemedicine-guided home blood pressure monitoring

3. Effectiveness of office BP, 24h-ABPM and tele-HBPM in assessing BP control

We compared the different BP measuring methods to one another to evaluate BP control in the 28 patients with hypertension (for the second tele-HBPM we analysed results of only 27 patients instead of 28, as the results of one patient were lost in the online network for telemedicine guided HBPM). Percentages of patients with their BP at goal are shown in table 9. Furthermore we evaluated the prevalence of masked HT in normotensive subjects and hypertensive patients (table 10 and 11).

Blood pressure control rates range between 46.4% (first office BP) and 66.7% (second tele-HBPM). Comparing BP control in office BP with daytime-ABPM or tele-HBPM showed no significant difference, neither the first time nor the second time. This indicates that the percentage of patients categorised as normotensive, and thus having good BP control, by office BP was similar to daytime-ABPM and tele-HBPM. Comparing tele-HBPM with daytime-ABPM we found a significant difference on the first visit ($p = 0.0087$) but this was no more significant on the second visit.

BP measurement	BP at goal (%)	BP not at goal (%)	Uncontrolled SBP (%)	Uncontrolled DBP (%)	Uncontrolled SBP and DBP (%)
Mean-office BP					
Visit 1 and 2	46.4	53.6	46.4	0.0	7.1
Visit 3 and 4	60.7*	39.3*	32.1	0.0	7.1
Mean-24h-ABP					
24h-ABPM 1	50.0	50.0	35.7	0.0	14.3
24h-ABPM 2	57.1*	42.9*	28.6	3.6	10.7
Mean-daytime-ABP					
Daytime-ABPM 1	57.1	42.9	28.6	3.6	10.7
Daytime-ABPM 2	60.7*	39.3*	28.6	3.6	7.1
Mean-nighttime-ABP					
Nighttime-ABPM 1	50.0	50.0	17.9	7.1	25.0
Nighttime-ABPM 2	51.9*	48.2*	22.2	0.0	25.9
Mean-tele-HBP					
Tele-HBPM 1	53.6	46.4	21.4	7.1	17.9
Tele-HBPM 2	66.7*	33.3*	22.2	3.7	7.4

Table 9: The proportion of patients with controlled and uncontrolled BP according to office BP, 24h-ABPM and tele-HBPM.

Abbreviations: ABP, Ambulatory Blood Pressure; BP, Blood Pressure; DBP, Diastolic Blood Pressure; SBP, Systolic Blood Pressure; Tele-HBP, telemedicine guided Home Blood Pressure.

Legend
*P < 0.05 compared to the first measurement
24h-ABP: mean values of ambulatory blood pressure monitoring over 24 hours
Daytime-ABP: mean values of ambulatory blood pressure monitoring during the day
Nighttime-ABP: mean values of ambulatory blood pressure monitoring during the night
Office blood pressure: mean values of blood pressure measured in the outpatient clinic
Tele-HBP: mean values of telemedicine-guided home blood pressure monitoring

We also evaluated the percentage of normotensive subjects and hypertensive patients who had consistent normotension, white coat HT (WCHT), masked HT (MHT) and sustained HT (table 10 and 11). In the normotensive group we had 15 subjects on the first visit (V1 + V2) and respectively 14 and 13 subjects for the comparison between office BP versus ABPM (24h, daytime and nighttime) and tele-HBP on the second visit (V3 + V4). We compared the BP values of the 28 hypertensive patients on the first visit (V1 + V2) and for ABPM on the second visit (V3 + V4), but we had only 27 hypertensive patients in the second tele-HBPM as the results of 1 patient were lost in the online network for telemedicine guided HBPM.

One normotensive volunteer had uncontrolled BP according to each BP measurement technique, except with nighttime-ABP. He was unaware of his hypertensive status.

Normotensive subjects		**24h-ABP 1**		**Daytime-ABP 1**		**Nighttime-ABP 1**		**Tele-HBP 1**	
		NT (%)	**HT (%)**	**NT (%)**	**HT (%)**	**NT (%)**	**HT (%)**	**NT (%)**	**HT (%)**
Office BP 1	**NT (%)**	93.3	0.0	80.0	13.0	93.3	0.0	93.3	0.0
	HT (%)	0.0	6.7	0.0	6.7	6.7	0.0	0.0	6.7
		24h-ABP 2		**Daytime-ABP 2**		**Nighttime-ABP 2**		**Tele-HBP 2**	
		NT (%)	**HT (%)**	**NT (%)**	**HT (%)**	**NT (%)**	**HT (%)**	**NT (%)**	**HT (%)**
Office BP 2	**NT (%)**	92.9	0.0	92.9	0.0	85.7	7.1	84.6	7.7
	HT (%)	0.0	7.1	0.0	7.1	7.1	0.0	0.0	7.7

Table 10: Evaluation of the agreement on BP control between different BP measuring techniques in normotensive subjects.

Abbreviations: ABP, Ambulatory Blood Pressure; HT, Hypertensive – blood pressure not at goal; NT, Normotensive - blood pressure at goal; Tele-HBP, telemedicine guided Home Blood Pressure.

Hypertensive subjects		**24h-ABP 1**		**Daytime-ABP 1**		**Nighttime-ABP 1**		**Tele-HBP 1**	
		NT (%)	**HT (%)**	**NT (%)**	**HT (%)**	**NT (%)**	**HT (%)**	**NT (%)**	**HT (%)**
Office BP 1	**NT (%)**	35.7	10.7	42.9	3.6	28.6	17.9	35.7	10.7
	HT (%)	14.3	39.3	14.3	39.3	21.4	32.1	17.9	35.7
		24h-ABP 2		**Daytime-ABP 2**		**Nighttime-ABP 2**		**Tele-HBP 2**	
		NT (%)	**HT (%)**	**NT (%)**	**HT (%)**	**NT (%)**	**HT (%)**	**NT (%)**	**HT (%)**
Office BP 2	**NT (%)**	50.0	10.7	50.0	10.7	40.7	18.5	48.1	11.1
	HT (%)	7.1	32.1	10.7	28.6	11.1	29.6	18.5	22.2

Table 11: Evaluation of the agreement on BP control between different BP measuring techniques in hypertensive patients.

Abbreviations: ABP, Ambulatory Blood Pressure; HT, Hypertensive – blood pressure not at goal; NT, Normotensive - blood pressure at goal; Tele-HBP, telemedicine guided Home Blood Pressure.

We can conclude that none of the normotensive subjects presented with WCHT; and that MHT in these subjects ranged between 0 (0%) and 2 (13%) patients depending on the BP measuring method that was used (table 10).

Some HT patients, although treated with antihypertensive drugs, still presented with uncontrolled BP. The second measurement more patients were consistent normotensive, which corresponded with the higher percentages of BP control during the second measurement. White coat HT varied between 7.1% and 21.4%; MHT between 3.6% and 18.5%, again according to the method used.

4. Satisfaction with different types of BP measurement

We evaluated satisfaction with different types of BP measurement by using a questionnaire with a 5-point Likert-scale for 24h-ABPM and tele-HBPM and one additional question asking the preferred BP measuring method for further follow-up.

Study subjects overall preferred tele-HBPM over 24h-ABPM. The first time and the second time 24h-ABPM had a mean score analogous with '*neither satisfied, neither unsatisfied*' and tele-HBPM had a score that was analogous with '*satisfied*'. This difference was present in all groups (normotensive, hypertensive with and without CKD) without any significant difference in satisfaction amongst the different groups. The better score for tele-HBPM was significantly in the overall study population ($p < 0.0001$) on both visits.

Looking into the difference of satisfaction subdivided by age class (subjects in their 20's, 30's, 40's, 50's, 60's, 70's and 80's) we found no difference in satisfaction, neither on the first time nor on the second time.

Moreover subjects were consistent in rating their satisfaction, as no difference was observed between the first and second series of measurements, in any group.

In the evaluation of the preferred method for further follow-up was tele-HBPM preferred over 24h-ABPM in the overall study population as well as in every group, without significant differences between the groups. Follow-up also showed good reproducibility, as there was no difference in choice between the first and second series of measurements. Looking into the preferred method subdivided by age class (subjects in their 20's, 30's, 40's, 50's, 60's, 70's and 80's) showed that younger people had more tendency to chose for 24h-ABPM than elderly people. Only 50% of the younger people chose tele-HBPM over 24h-ABPM and this percentage increased to 70-80% in patients aged in their sixties and seventies; although this difference appeared to be not significant.

5. Effect of intensive BP monitoring on medication adherence

The MMAS-8 value the first time and the second time was 7.6 ± 0.9, indicating high adherence in the majority of the patients. No significant differences were seen between the different groups of patients. Adherence was slightly better the second time but this difference was not significant in the overall study population, neither when we subdivided the study population by stages of CKD.

Overall -, first - and second MMAS-8 scores are shown in table 12.

Patients	Patients (n)	MMAS-8-score (mean ± SD)	Range (min – max)
First MMAS-8	**30**	**7.6 ± 0.9**	**4.5 – 8.0**
Hypertensive without CKD	10	7.7 ± 0.8	5.5 – 8.0
Hypertensive with CKD	20	7.5 ± 0.9	4.5 – 8.0
CKD stage 3	5	7.5 ± 0.7	6.5 – 8.0
CKD stage 4	2	7.4 ± 0.5	7.0 – 7.8
CKD stage 5	13	7.5 ± 1.1	4.5 – 8.0
Second MMAS-8	**27**	**7.6 ± 0.9**	**4.5 – 8.0**
Hypertensive without CKD	7	7.6 ± 0.7	6.3 – 8.0
Hypertensive with CKD	20	7.6 ± 0.9	4.5 – 8.0
CKD stage 3	5	7.8 ± 0.5	7.0 – 8.0
CKD stage 4	2	8.0 ± 0.0	8.0 – 8.0
CKD stage 5	13	7.4 ± 1.1	4.5 – 8.0

Table 12: Overview of the overall -, first measurement – and second measurement MMAS-8 scores.

Abbreviations: CKD, Chronic Kidney Disease (CKD stage 3: eGFR (MDRD) 60 – 30 ml/min/1.73m^2; CKD stage 4: eGFR (MDRD) 30 – 15 ml/min/1.73m^2; CKD stage 5: eGFR (MDRD) <15 ml/min/1.73m^2); eGFR, estimated glomerular filtration rate; MDRD, Modified diet renal disease); MMAS-8, Morisky Medication Adherence Scale-8; n, number of patients; SD, Standard Deviation.

6. Effect of intensive BP monitoring on BP control

Blood pressure control rate has already been discussed above. We also evaluated the effect of intensive BP monitoring on BP control by comparing the percentages of BP control during the first series of measurements with the second series of measurements (table 9).

All methods had significant better BP control on the second visit (office BP: $p = 0.0159$; tele-HBPM: $p = 0.0010$; 24h-ABPM: $p = 0.0023$; daytime-ABPM: $p < 0.0001$; nighttime-ABPM: $p < 0.0001$).

7. Effect of intensive BP monitoring on the general wellbeing of the patient

All patients except hypertensive patients with CKD stage 3 scored in the normal range for HADS-anxiety and HADS-depression with overall values for HADS-anxiety of 3.9 ± 2.4 and 3.7 ± 2.7 on respectively the first and third visit and overall values for HADS-depression of 4.5 ± 3.6 and 5.0 ± 4.0 on respectively the first and third visit. Hypertensive patients with CKD stage 3 was the only group scoring worse on the HADS-depression. The first time their values were categorised between normal and suggestive for depression whereas the second time their values were categorised between suggestive and probable presence of depression.

The HADS-anxiety values of the normotensive group on the first visit were significantly better than hypertensive patients. On visit 3 this difference was still present but it was no longer significant. The HADS-depression values on the first visit were also significantly better in normotensive subjects than hypertensive patients (with and without CKD) and on visit 3 we still found better values in normotensive subjects but they were only significantly different from hypertensive patients with CKD and not from hypertensive patients without CKD.

Intensive BP monitoring showed no difference in either anxiety or depression as results of the first and second visit showed no significant difference and were very good reproducible.

Table 13 provides an overview of the mean-HADS-anxiety and mean-HADS-depression scores.

Patients	Visit 1			Visit 3		
	n	Mean ± SD	Range (min-max)	n	Mean ± SD	Range (min-max)
HADS-Anxiety						
All patients	**45**	**3.9 ± 2.4**	**0 – 10**	**45**	**3.7 ± 2.7**	**0.0 – 12.0**
Normotensive	15	2.3 ± 1.8	0 – 6	15	2.7 ± 2.5	0 – 8
Hypertensive without CKD	10	4.3 ± 2.4(1)	1 – 9	10	4.0 ± 3.4	0 – 12
Hypertensive with CKD	20	4.9 ± 2.3(1)	0 – 10	20	4.4 ± 2.5	0 – 9
CKD stage 3	5	6.2 ± 1.6(1)	5 – 9	5	4.8 ± 3.0	2 – 8
CKD stage 4	2	3.5 ± 0.7	3 – 4	2	3.0 ± 4.2	0 – 6
CKD stage 5	13	4.5 ± 2.4(1)	0 - 10	13	4.4 ± 2.2	1 - 9
HADS-Depression						
All patients	**44**	**4.5 ± 3.6**	**0.0 – 15 .0**	**42**	**5.0 ± 4.4**	**0.0 – 16.0**
Normotensive	15	2.7 ± 2.5	0 – 8	14	2.4 ± 2.2	0 – 7
Hypertensive without CKD	10	5.1 ± 3.4(1)	1 – 10	9	5.1 ± 4.4	0 – 12
Hypertensive with CKD	19	5.7 ± 4.0(1)	0 – 15	19	6.7 ± 4.8(1)	0 – 16
CKD stage 3	5	8.2 ± 4.6(1)	3 – 15	5	10.4 ± 5.1(1)	4 – 16
CKD stage 4	2	5.0 ± 4.2	2 – 8	2	6.5 ± 0.7(1)	6 – 7
CKD stage 5	12	4.8 ± 3.7(1)	0 - 11	12	5.3 ± 4.4(1)	0 - 12

Table 13: Overview of the mean-HADS-anxiety and mean-HADS-depression scores.

Abbreviations: CKD, Chronic Kidney Disease (CKD stage 3: eGFR (MDRD) 60 – 30 ml/min/1.73m²; CKD stage 4: eGFR (MDRD) 30 – 15 ml/min/1.73m²; CKD stage 5: eGFR (MDRD) <15 ml/min/1.73m²); eGFR, estimated glomerular filtration rate; HADS, Hospital Anxiety and Depression Scale; MDRD, Modified diet renal disease; n, number of patients; SD, Standard Deviation.

Legend: (1) $p < 0.05$ compared to normotensive subjects

Normotensive subjects appeared to have a better health status as they scored better on every aspect of the EQ-5D descriptive system on both the first and third visit. Worst values were found in hypertensive patients with stage 5 CKD, on hemodialysis, on both visits. Normotensive subjects had significantly better scores than hypertensive patients on mobility and pain, but no difference was found between hypertensive patients according to their kidney function. Patients on hemodialysis were significantly more limited in their daily activities than other patients on the first visit; on the second visit all hypertensive patients had lower scores than normotensive subjects, but no difference was seen in between the hypertensive patients. No difference was seen for self-care and anxiety/depression between the groups. On both visits the item with the most problems was pain/discomfort, with 40% and 47.6% of the patients, respectively on visit 1 and visit 3, mentioning having problems.

Comparing the EQ-5D descriptive system we found slightly worse values on visit 3. Mobility, self-care and anxiety/depression showed good reproducibility but in daily activities and pain/discomfort we found significant worse values on visit 3 ($p = 0.0235$ and 0.0441, respectively).

Table 14 and 15 describe the results of the EQ-5D-3L questionnaire of first and second time.

EQ-5D-3L Visit 1	Patients (n)	Mobility (%)			Self-care (%)			Usual activities (%)			Pain/ discomfort (%)			Anxiety/ depression (%)		
		Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3
Normotensive	15	100	0	0	100	0	0	100	0	0	93.3	6.7	0	93.3	6.7	0
HT without CKD	10	70.0	30.0	0	100	0	0	90.0	10.0	0	50.0	50.0	0	100	0	0
HT with CKD 3	5	80.0	20.0	0	100	0	0	100	0	0	40.0	60.0	0	100	0	0
HT with CKD 4	2	100	0	0	100	0	0	100	0	0	50.0	50.0	0	100	0	0
HT with CKD 5	13	69.2	30.8	0	92.3	7.7	0	46.2	53.8	0	38.5	53.8	7.7	76.9	23.1	0
All patients	**45**	**82.2**	**17.8**	**0**	**97.7**	**2.3**	**0**	**82.2**	**17.8**	**0**	**60.0**	**37.8**	**2.2**	**91.1**	**8.9**	**0**

Table 14: Overview of the EQ-5D-3L questionnaire on visit 1.

Abbreviations: CKD, Chronic Kidney Disease (CKD stage 3: eGFR (MDRD) 60 – 30 ml/min/1.73m²; CKD stage 4: eGFR (MDRD) 30 – 15 ml/min/1.73m²; CKD stage 5: eGFR (MDRD) <15 ml/min/1.73m²); eGFR, estimated glomerular filtration rate; HT, Hypertensive; MDRD, Modified diet renal disease; n, number of patients.

EQ-5D-3L Visit 3	Patients (n)	Mobility (%)			Self-care (%)			Usual activities (%)*			Pain/ discomfort (%)*			Anxiety/ depression (%)		
		Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3
Normotensive	15	100	0	0	100	0	0	100	0	0	93.3	6.7	0	100	0	0
HT without CKD	8	62.5	37.5	0	100	0	0	62.5	37.5	0	25.0	50.0	25.0	87.5	12.5	0
HT with CKD 3	4	100	0	0	100	0	0	50.0	50.0	0	25.0	75.0	0	100	0	0
HT with CKD 4	2	50.0	50.0	0	100	0	0	100	0	0	0	100	0	100	0	0
HT with CKD 5	13	69.2	30.8	0	92.3	7.7	0	46.2	46.2	7.7	38.5	53.8	7.7	76.9	23.1	0
All patients	**42**	**81.0**	**19.0**	**0**	**97.6**	**2.4**	**0**	**71.4**	**26.2**	**2.4**	**52.4**	**40.5**	**7.1**	**90.5**	**9.5**	**0**

Table 15: Overview of the EQ-5D-3L questionnaire on visit 3.

Abbreviations: CKD, Chronic Kidney Disease (CKD stage 3: eGFR (MDRD) 60 – 30 ml/min/1.73m²; CKD stage 4: eGFR (MDRD) 30 – 15 ml/min/1.73m²; CKD stage 5: eGFR (MDRD) <15 ml/min/1.73m²); eGFR, estimated glomerular filtration rate; HT, Hypertensive; MDRD, Modified diet renal disease); n, number of patients.

Legend: * $P < 0.05$ Values are significantly different in these classes compared with the results of visit 1.

The second part of the EQ-5D-3L questionnaire is the visual analogue scale (table 16). We found an overall health status of 75.3% the first time and 72.5% the second time. There was significant difference between normotensive subjects and hypertensive patients, without CKD and with CKD, but no difference was found between hypertensive patients; even when subdivided by class of kidney disease.

Visual analogue scale-values showed very good reproducibility in every category of patients, as no significant differences were found between the first and second VAS-score.

Patients	Patients (n)	VAS (mean ± SD) (%)
VAS 1 total	**45**	**75.3 ± 12.7**
Normotensive	15	84.3 ± 10.4
Hypertensive without CKD	10(1)	76.3 ± 6.8
Hypertensive with CKD	20(1)	68.2 ± 12.4
CKD stage 3	5(1)	72.0 ± 13.0
CKD stage 4	2(1)	65.0 ± 7.1
CKD stage 5	13(1)	67.2 ± 13.2
VAS 2 total	**43**	**72.5 ± 17.8**
Normotensive	15	84.2 ± 9.5
Hypertensive without CKD	8(1)	63.4 ± 28.2
Hypertensive with CKD	20(1)	67.3 ± 13.0
CKD stage 3	5	74.2 ± 8.4
CKD stage 4	2(1)	55.0 ± 7.1
CKD stage 5	13(1)	66.5 ± 13.9

Table 16: EQ-5D Visual Analogue Scale for visits 1 and 3.

Abbreviations: CKD, Chronic Kidney Disease (CKD stage 3: eGFR (MDRD) 60 – 30 ml/min/1.73m^2; CKD stage 4: eGFR (MDRD) 30 – 15 ml/min/1.73m^2; CKD stage 5: eGFR (MDRD) <15 ml/min/1.73m^2); eGFR, estimated glomerular filtration rate; MDRD, Modified diet renal disease; n, number of patients; SD, Standard Deviation; VAS, Visual Analogue Scale.

Legend: (1) $p < 0.05$ compared to normotensive subjects

8. Daytime-ABPM versus nighttime-ABPM

We also evaluated absolute differences between daytime-ABP and nighttime-ABP (table 8 and 9), the day- and night dipping profile (table 17) and investigated the percentages of dippers and non-dippers (table 18).

	Visit 1			Visit 3		
	n	Dip-SBP (mmHg)	Dip-DBP (mmHg)	n	Dip-SBP (mmHg)	Dip-DBP (mmHg)
All subjects	**46**	**12.3 ± 8.6**	**15.9 ± 9.1**	**42**	**10.4 ± 7.9**	**13.6 ± 7.6***
Normotensive	15	16.4 ± 4.8	21.6 ± 5.0	14	14.5 ± 5.2	17.6 ± 4.4*
Hypertensive without CKD	10	14.4 ± 6.0	17.6 ± 8.7	8	13.3 ± 6.6	15.5 ± 6.7
Hypertensive with CKD	21	8.2 ± 10.0(1)	11.1 ± 9.2(1)	20	6.3 ± 8.3(1) (2)	10.1 ± 8.2(1)
Hypertensive with CKD 3	5	1.8 ± 11.7(2)	5.9 ± 12.4(1)	5	5.6 ± 7.4(1)(2)	7.1 ± 11.2(1)
Hypertensive with CKD 4	2	14.6 ± 1.8	19.4 ± 3.3	1	7.3 ± 0.0	20.8 ± 0.0
Hypertensive with CKD 5	14	9.6 ± 9.3(1)	11.8 ± 7.8(1)	14	6.5 ± 9.1(1)	10.3 ± 6.9(1)

Table 17: Systolic and diastolic dipping in mmHg.

Abbreviations: CKD, Chronic Kidney Disease (CKD stage 3: eGFR (MDRD) 60 – 30 ml/min/1.73m²; CKD stage 4: eGFR (MDRD) 30 – 15 ml/min/1.73m²; CKD stage 5: eGFR (MDRD) <15 ml/min/1.73m²); DBP, Diastolic Blood Pressure; Dip, dipping; eGFR, estimated glomerular filtration rate; MDRD, Modified diet renal disease; n, number of patients; SBP, Systolic Blood Pressure.

Legend
* P < 0.05 Values are significantly different in these classes compared with the results of visit 1
(1) p < 0.05 compared to normotensive subjects
(2) p< 0.05 compared to hypertensive patients without CKD
Dip-SBP or Dip-DBP in mmHg, the absolute decrease in mmHg during nighttime-ABPM

	Visit 1			Visit 3		
	n	Dip-SBP (%)	Dip-DBP (%)	n	Dip-SBP (%)	Dip-DBP (%)
All subjects	**46**	**67.3**	**70.1**	**42**	**57.1**	**71.4**
Normotensive	15	93.3	100	14	78.6	100
Hypertensive without CKD	10	70.0	70.0	8	62.5(1)	75.0
Hypertensive with CKD	21	47.6(1)	47.6(1)	20	40.0(1)	50.0(1)
Hypertensive with CKD 3	5	20.0(1)(2)	40.0(1)	5	40.0(1)	40.0(1)
Hypertensive with CKD 4	2	100	100	1	0.0	100
Hypertensive with CKD 5	14	50.0(1)	42.9(1)	14	42.9(1)	50.0(1)

Table 18: The percentage of subjects that has > 10% SBP- or DBP-dip during nighttime-ABPM.

Abbreviations: CKD, Chronic Kidney Disease (CKD stage 3: eGFR (MDRD) 60 – 30 ml/min/1.73m²; CKD stage 4: eGFR (MDRD) 30 – 15 ml/min/1.73m²; CKD stage 5: eGFR (MDRD) <15 ml/min/1.73m²); DBP, Diastolic Blood Pressure; Dip, dipping; eGFR, estimated glomerular filtration rate; MDRD, Modified diet renal disease; n, number of patients; SBP, Systolic Blood Pressure.

Legend
(1) p < 0.05 compared to normotensive subjects
(2) p< 0.05 compared to hypertensive patients without CKD
Dip-SBP or dip-DBP, % of subjects that has > 10% dipping of their SBP or DBP during nighttime-ABPM

Of all subjects and patients, 67.3% and 70.1% showed normal nighttime dipping during the first 24h-ABPM for respectively SBP and DBP. During the second 24h-ABPM these percentages were 57.1% and 71.4%, for SBP and DBP respectively. More normotensive subjects than HT patients showed normal dipping profile on both 24h-ABPM. Among HT patients, the patients suffering from CKD exhibited the least dipping. Although these differences were present, they were not significant between all groups.

During both 24h-ABPM the normotensive subjects significantly had greater SBP-dipping than hypertensive patients with CKD ($p = 0.0058$ and 0.0027, respectively). During the second 24h-ABPM HT patients without CKD also had significantly greater SBP-dipping percentages than HT patients with CKD. For DBP we only found significant difference on the first as well as on the second 24h-ABPM between normotensive subjects and HT patients with CKD ($p = 0.0003$ and 0.0040, respectively).

Evaluating reproducibility showed that SBP-dipping was good reproducible without any significant different amongst the different groups. We found a significant difference in the overall population in DBP-dipping between the first and second series of measurements ($p = 0.0330$). Diastolic BP-dipping was reproducible in the HT population, but in normotensive subjects DBP-dipping showed significantly lower values ($p = 0.0335$) and thereby was not reproducible.

The mean systolic difference between daytime-ABP and nighttime-ABP was 15.5 ± 11.4 mmHg and 12.8 ± 10.6 mmHg, respectively during the first and second 24h-ABPM. The mean diastolic difference between daytime-ABP and nighttime-ABP was 12.3 ± 7.3 mmHg and 10.3 ± 5.9 mmHg, respectively during the first and second 24h-ABPM. Normally BP should be lower during the night. In 6.5% of the patients nighttime-ABP was even higher than daytime-ABP during the first measurement and 9.5% for SBP and 4.8% for DBP had higher values the second measurement. The increase of percentage higher nighttime-ABP was significant for SBP ($p = 0.0005$), but was not significant for DBP.

Overall mean 24h-ABP control was respectively 50.0% and 57.1% for the first and second ABPM. As described above, BP control improved significantly in daytime- and nighttime-ABPM. The BP control by daytime-ABPM was 57.1% and 60.7% on respectively the first and second visit. Blood pressure control was better during daytime than during nighttime. Blood pressure control by nighttime-ABPM was 50.0% and 51.9% on respectively the first and second visit. The first time there was no significant difference in BP control by daytime- or nighttime-ABP (57.1% and 50.0%, respectively), but the second time this difference (60.7% and 51.9%, respectively) was significant ($p = 0.0037$).

9. Blood pressure measurement with two different out-of-office techniques

We also investigated if there was a correlation/ agreement/ difference between the two out-of-office BP measurement techniques

9.1. Paired t-test

The mean SBP measured by tele-HBPM showed no significant difference with the mean SBP measured by daytime-ABPM in the overall population on the first visit, neither on the second visit. Analysing SBP measured by both methods in the different patient groups also showed no significant difference.

The mean DBP in the overall study population was a little higher when measured by tele-HBPM than measured by daytime-ABPM, but this difference was not significant. When we looked into the differences in the subgroups we found that normotensive subjects had lower DBP values the first time as well as the second time when BP was measured by tele-HBPM, but this difference was only significant the first time ($p = 0.0028$). On the contrary DBP in hypertensive patients with CKD was significantly higher when using tele-HBPM on both measurements ($p = 0.0035$ and 0.0370, respectively the first and the second time).

9.2. Bland-Altman-Method

Both Bland-Altman-Plots for multiple measurements for SBP as well as for DBP showed good agreement between the two different out-of-office techniques, i.e. daytime-ABPM and tele-HBPM.

The mean SBP by tele-HBPM was only 0.7 mmHg lower than the mean daytime-systolic-ABP. The 95% confidential interval (CI) was + 24.7 and – 26.1 mmHg (figure 4). Apart from one value, all measurements fell within the limits of the 95% CI.

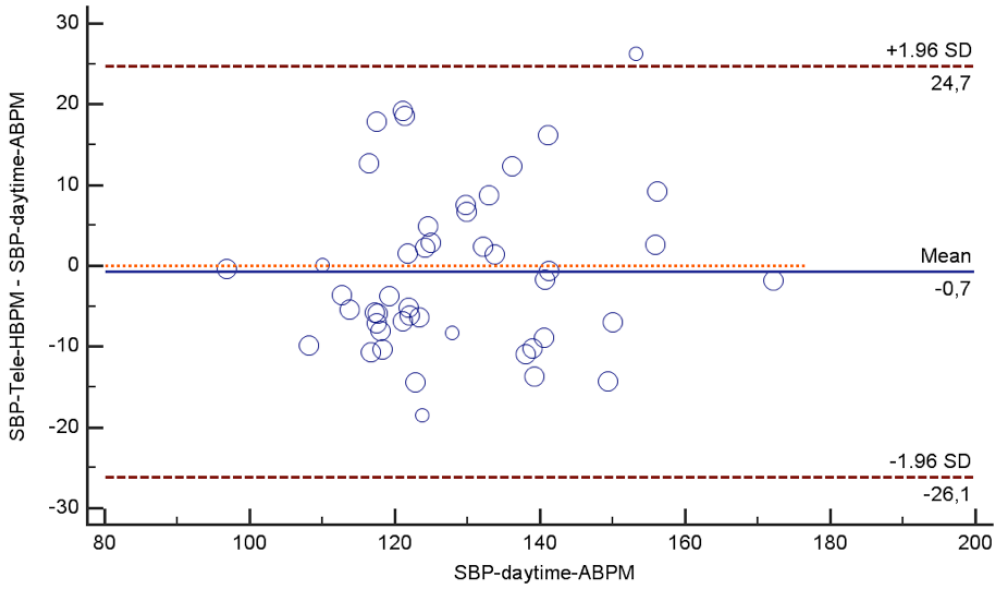


Figure 4: Bland-Altman-Plot for multiple SBP measurements by tele-ABPM and daytime-ABPM.

On the other hand, mean DBP measured by tele-HBPM was 0.7 mmHg higher than the mean daytime-diastolic-ABP and the 95% CI was + 17.0 and – 15.7 mmHg. All DBP values fell within the 95% CI (figure 5).

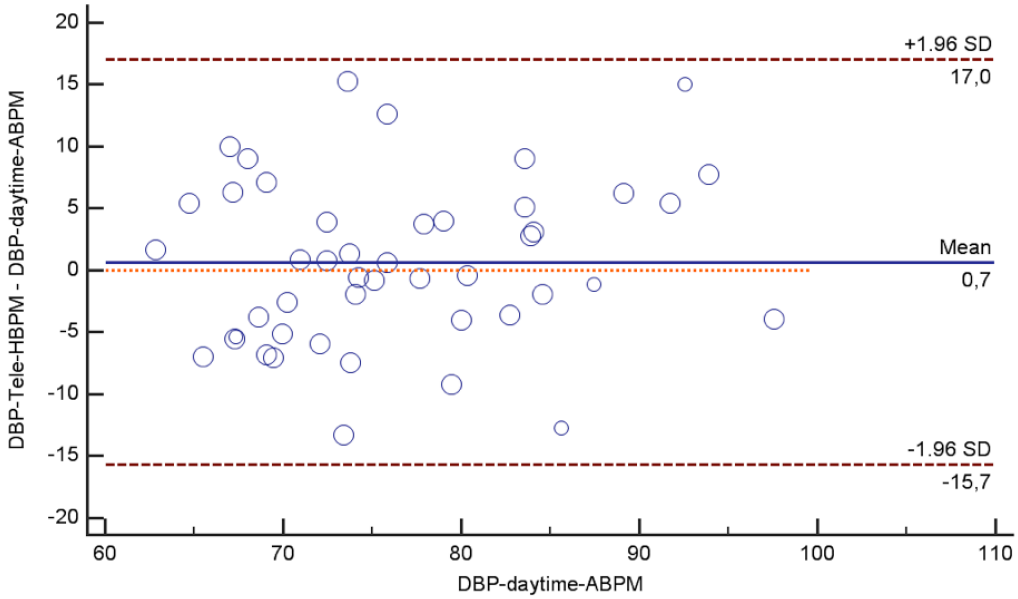


Figure 5: Bland-Altman-Plot for multiple DBP measurements by tele-ABPM and daytime-ABPM.

Linear regression for SBP and DBP was computed by using the Bland-Altman-Method for single measurements (figure 6 and 7).

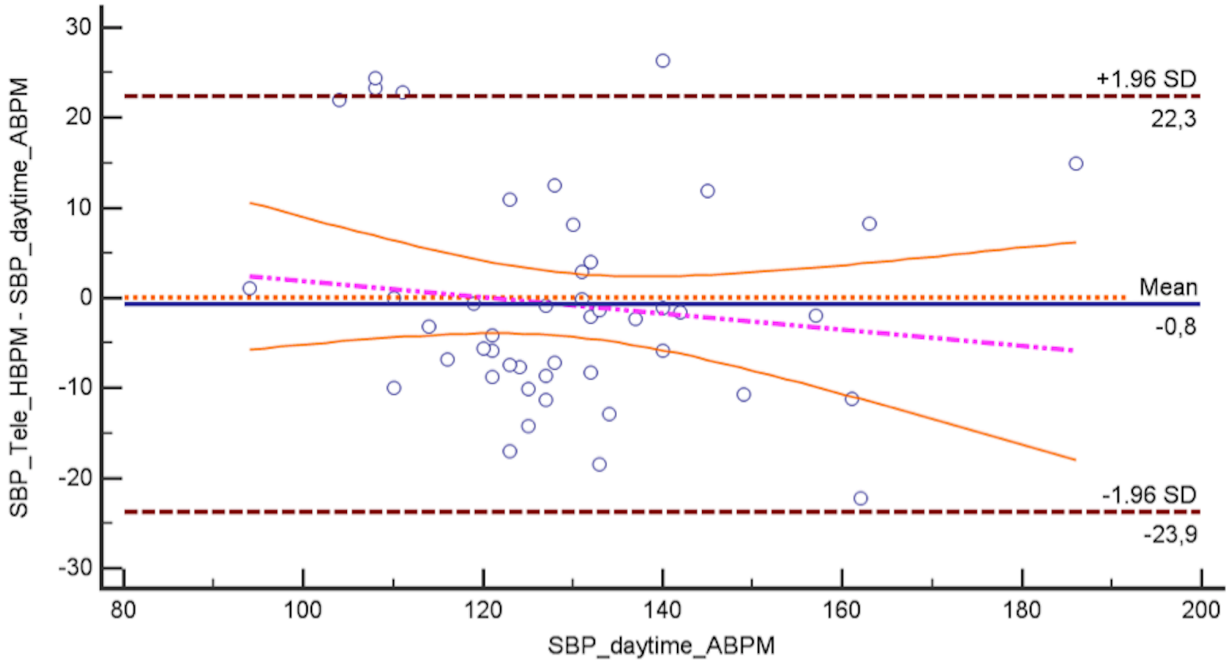


Figure 6: Bland-Altman-Plot for SBP measurements by tele-ABPM 1 and daytime-ABPM 1.

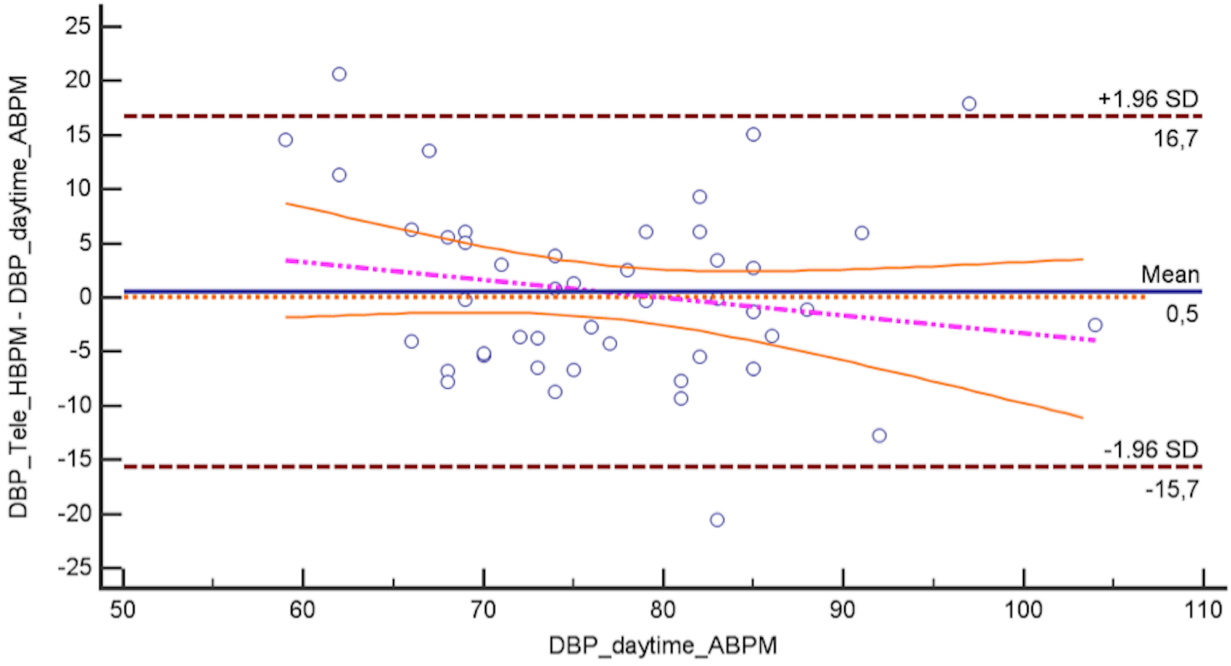


Figure 7: Bland-Altman-Plot for DBP measurements by tele-ABPM 1 and daytime-ABPM 1.

Regression for the first series of measurements is shown in figure 6 and 7, but Bland-Altman-Plot and regression for the second series of measurements was very similar. Both Bland-Altman-plots provided a declining linear regression line, indicating a systematic error. The confidence interval (CI) was the narrowest around respectively 120 – 140 mmHg SBP and 75 – 80 mmHg DBP. When BP values became lower or higher the CI became wider. This indicates that lower and higher values showed greater diversification.

Discussion

At this moment the study comprises 46 subjects of whom we analysed BP values and questionnaires. Although this number of subjects is in accordance with the a priori computed study sample, some groups consist of very few subjects (e.g. HT patients with CKD stage 3 consist of 5 patients and HT patients with CKD stage 4 consist of 2 patients). This implies that the analysis of the results of these subgroups may be biased due to the small amount of enrolled patients and that consequently we should be cautious when interpreting the results of these subjects.

Blood pressure control

Our primary objective is to evaluate the effectiveness of different BP measurement techniques in assessing BP control in different patient groups, with special attention to the newer technique of telemedicine-guided HBPM.

The BP control rates in hypertensive patients in our study range between 46.4% and 66.7%, which is in line with the better BP control rates in the literature. Pereira et al. find that 29.7% of Western European men and 44.5% of Western European women have good BP control.[3] Van der Niepen et al. find an overall BP control of 21.5% in patients in primary care in Belgium.[9] The effectiveness of the three methods to objectify BP control is very comparable in our study as office BP has analogous BP control as daytime-ABPM and tele-HBPM. Daytime ABPM shows better BP control rates the first time but is analogous the second time compared to tele-HBPM. Better agreement between daytime-ABP and tele-HBP the second time suggests that there is less stress-induced HT when patients are more familiar with the technique.

In our study the different techniques, including the newer technique of tele-HBPM, show similar BP control rates (with BP control defined as office BP < 140 / 90 mmHg, and daytime-ABP and tele-HBP < 135/ 85 mmHg). The results are therefore in line with the recommendations in the ESH/ESC guidelines.[1] Some studies evaluate BP control by storage-HBPM and find good correlation between storage-HBPM and ABPM.[59,61,63] Few studies have been done concerning telemedicine guided HBPM and to our knowledge the use of tele-HBPM to evaluate BP control has not previously been done.

Similar BP control rates also imply that all measurements, positioning of the patients, cuff positioning,… have been done according to the recommended guidelines. Therefore, an 'ideal situation' was created to measure office BP: a study nurse or medical student, but not the doctor, measured the office BP in a different room than the consultation room; BP was measured with an automatic BP

measuring device[24] (thereby excluding interobserver and intraobserver bias); good positioning of patient and cuff was ensured; at least 5 minutes rest before measuring office BP was taken into account, and multiple measurements were taken (thereby increasing reproducibility, decreasing WCHT). Subjects also received good information and were well instructed how to act during ABPM and how HBPM should be measured.

Blood pressure measurement

Although all HT patients are treated with antihypertensive drugs, SBP appears to be higher in treated hypertensive patients than in normotensive subjects and is even higher in patients suffering chronic kidney disease compared to HT patients without CKD, irrespective of the BP measurement technique that is used. Diastolic BP values show fewer discrepancies than SBP. We find some differences between the different groups, but they turn out to be not reproducible.

Systolic and diastolic BP frequently turn out to be significantly higher in patients with CKD stage 5, irrespective of the BP measurement technique that is used. Moreover systolic and diastolic BP values are often significantly different between two series of measurements. This indicates that measuring and evaluating BP and the HT status in patients on hemodialysis is very difficult, which corresponds with earlier publications on BP measurement in patients on hemodialysis[45,46,47,48]

Tele-HBPM appears to be as good as ABPM for follow-up in the overall population as their reproducibility is good for systolic and diastolic BP. Office BP appears to be less reproducible (significant difference in SBP) and is therefore less appropriate for follow-up.

Yet measurements in patients with HT and CKD stage 5 show no reproducibility for SBP and DBP in office BP and daytime-ABP, and even for DBP in tele-HBPM. Low reproducibility in patients with CKD stage 5 has also been described by Cohen et al.[45]

Intensive BP monitoring

Our study shows that an intensive BP monitoring significantly increases BP control, as BP control percentages are significantly better the second time, irrespectively of the technique used to evaluate BP. Our findings correspond to published studies that show that BP control is better when patients have an intensive follow-up. The TASMINH2 study by McManus et al. shows that an intensive follow-up in combination with self-management leads to better BP control.[54] Margolis et al. describe a significant decrease in BP by usual care (i.e. office BP) and an even greater decrease in BP by tele-HBPM at 6 and 12 months follow-up compared to usual care.[53] The 2010 Cochrane review concludes

that an organised system for regular follow-up and review of HT patients is needed to overcome barriers to optimal HT control.[52]

Possible reasons for better BP control are: better medication adherence (although the questionnaire evaluating the medication adherence (MMAS-8) finds no significant difference between the first and second series of measurements - will be discussed below), decrease in anxiousness as firstly patients are monitored closely and this could improve their general wellbeing (will be discussed below) or secondly there is a factor of habituation to the method which results in less stress on the moment of measurement and better sleeping pattern and therefore may account for better BP control the second time.

Daytime- and nighttime-ABPM

As mentioned above BP control significantly improves from the first time to the second time in both daytime- and nighttime-ABPM. Daytime-ABPM consistently has better BP control than nighttime-ABPM, although this difference is only significant on the second series of measurements. There are only small changes in the absolute number of patients categorised as controlled or uncontrolled BP according to daytime- or nighttime-ABP. Probably the small number of patients is accountable for significance during the second ABPM.

Daytime- and in particular nighttime-ABP are important variables in the clinical practice as studies have shown that organ damage (OD) correlates with ABPM more closely than with office BP.[1] In our study most normotensive subjects, who have lower CV-risk, have at least 10% nighttime dipping. Dipping in HT patients, who are at higher CV-risk, is lower than normotensive subjects; which corresponds to the underlying theory.[1] Furthermore it is well known that HT patients with CKD have an even lesser or no drop in nighttime-ABP, which reflects in our study by lesser nighttime-ABP drop. Studies have shown that these patients have an increased CV-risk compared to HT patients without CKD.[44,45,46] Blood pressure load (defined as the percentage of readings in a given period that exceeds a predefined threshold value, usually thresholds as defined in the recommended guidelines[26]) is higher by nighttime-ABP compared to daytime-ABP (50% vs 43% and 48% vs 39%, respectively the first and second time), suggesting that nighttime-ABP is a more sensitive predictor of patients with higher CV-risk and confirming findings in previous studies.[1]

Masked and white coat HT

In our study none of the normotensive subjects appear to have WCHT and MHT ranges between 0% and 13.0% in normotensive subjects, depending on the BP monitoring method used. The overall prevalence of WCHT and MHT averages 13% in population-based studies, i.e. normotensive and hypertensive subjects.[1] We can assume that percentages are little lower in normotensive subjects than

the overall population but probably not 0% and therefore this is an extra argument in favour of the good measurement conditions. The procedure of office BP was well explained, the patient rested at least 5 minutes, we used an automatic BP measurement device, the study nurse or medical student measured the BP, … The fact that there is a decrease in MHT by daytime-ABPM in normotensive subjects could be explained by habituation to the method, although in HT patients instead of a decrease we find an increase in MHT.

White coat HT in HT patients in our study ranges between 7.1% and 21.4% and MHT ranges between 3.6% and 18.5%, depending on the used method. According to the literature WCHT in HT patients is estimated at 32%, which is higher than percentages in our study.[1] Percentages of WCHT or MHT change from the first to the second series of measurements but in absolute numbers only one or two patients change groups. As mentioned earlier in this discussion the number of patients enrolled in the study is not very high, so a shift of 1 or 2 subjects can already cause considerate changes in percentages. This is probably also the cause of large changes in percentages of WCHT and MHT in HT patients.

In the normotensive group we detect 1 patient that consistently, except when measured by nighttime-ABP, has sustained HT (i.e. HT according to office BP as well as out-of-office BP). This patient was unaware of his hypertensive status. In the literature 25.2% to 75% of the world population is unaware of his/her HT status.[2] Hypertension awareness in Western Europe ranges between 46.4% in men and 63.0% in women.[3] Only one subject out of our 15 (7%) young and healthy volunteers presents with undiagnosed HT. This is, once again, an argument to measure BP on a regular basis, even when people are feeling well and do not present symptoms directly linked to HT.

Satisfaction

Overall study subjects, regardless of their HT status or their kidney function or their age, are more satisfied with tele-HBPM than 24h-ABPM. Lower satisfaction rates for 24h-ABPM may be explained by the frequency of BP measurement (every 15 minutes during the day and every 30 minutes during the night), additional measurements are taken when the arm is not held still or there is a nod in the cable (and thus measurement interval is shorter than 15 minutes and 30 minutes, respectively). The 24h-ABPM may also interfere with daily activities and BP measurement during the night can consequently interfere with sleeping pattern. Staessens et al. and Elliot et al. account sleep disturbance as an important reason for dissatisfaction with 24h-ABPM.[77,78] Furthermore Elliot et al. find that patients are dissatisfied with 24h-ABPM because it makes a rather loud noise and the device is too heavy. This study dates from 2003 and at that time devices were indeed larger and heavier than they are today. Although devices are smaller, lighter and make less noise today, they still consist of a small case that inflates the cuff and makes some noise.

Preference for further follow-up in the overall population is tele-HBPM, regardless of their HT status or their kidney function, but younger people are less unanimous. Although all younger people are also more satisfied with tele-HBPM than 24h-ABPM, only half of the younger people prefer tele-HBPM to 24h-ABPM for further follow-up compared to 70-80% of the elderly people. The fact that younger people (20's to 50's) have less tendency to choose tele-HBPM for further follow-up may be explained by the assumption that on the one hand younger people are part of the working class and/or have young children to look after and consequently have less time, and on the other hand elderly people are retired and do not mind spending some extra time on measuring BP thrice in the morning and in the evening. We think that these arguments surpass the greater satisfaction with tele-HBPM in their choice for further follow-up.

Medication adherence

In our study patients are highly adherent to their antihypertensive treatment (MMAS-8 = 7.6 ± 0.9 on the first and second time). We have to take into account that the overall adherence is already very high from the start and by consequence obtaining a significant improvement in medication adherence is very hard, especially in a small number of patients. Being highly compliant may be explained by two reasons. The first one is that the patients who agreed on participating in the study are included in the hypertension outpatient clinic, they are aware of their HT situation, they already receive a good follow-up and most of them have a stable antihypertensive treatment. Moreover they receive some supplementary information on HT and its possible consequences on organ damage by means of an informed consent. The second reason is that patients participating in a study may be more motivated and may also alter their behaviour, which is also known as the Hawthorne effect (HE). The HE is defined as an alteration in behaviour as a consequence of research participation and the consequent awareness of being studied, and the possible impact on behaviour. Although the HE has been disputed in the past, a recent review confirms that behavioural changes because of research participation do exist, but there is little known about the exact conditions under which they operate, their mechanisms of effects or their magnitudes.[79]

General wellbeing of the patient

General wellbeing was evaluated by two different questionnaires.

Analysing *Hospital Anxiety and Depression Scale* (HADS) reveals good overall wellbeing of the patients (HADS-A 3.9 ± 2.4 and 3.7 ± 2.7 on respectively the first and second time; HADS-D 4.5 ± 3.6 and 5.0 ± 4.0 on respectively the first and second time). Since patients had to come twice three times to the hospital we selected patients who were mobile and able to come several times to the hospital. This may reflect in the general wellbeing of the patient. So the study setup may influence general wellbeing

of the patients. Furthermore anxiety and depression is more likely to be present in HT patients than in normotensive subjects, which may be explained by the fact that they do not need to worry about their health status, medication adherence, BP control,… This was also found in the HOT-study, where Wiklund et al. investigate if a BP lowering treatment is associated with an improvement of the mood by means of the Psychological General Well-Being index. Their study shows that a more intensive treatment is associated with an improvement in patients' wellbeing.[80]

Only patients with CKD stage 3 have values that are little worse. As this group of patients only comprises 5 patients, we are well aware that concluding that these patients suffer more anxiety and depression might be wrong.

The *EQ-5D-3L questionnaire* also reveals better wellbeing of normotensive subjects, especially for mobility and pain, as well as better overall health scores in the Visual Analogue Scale. Hayes et al. report that having HT and being aware of it, is related to lower quality of life, which is identical to our study.[81]

Patients with HT and CKD stage 5 have worst scores and are more restricted in daily activities. This is a logic conclusion, as these patients have to come to the hospital thrice a week for at least 4 hours to receive hemodialysis. Soni et al. report similar findings. Hypertensive patients have a lower quality of life than normotensive subjects and HT patients with co-existent disease (e.g. CKD) have an even lower quality of life than 'normal' HT patients, as they are more restricted in physical domains.[82] In our study HT patients with CKD present with lowest health-rates, measured by means of a Visual Analogue Scale.

Out-of-office measurements

We compare the two out-of-office BP monitoring techniques (tele-HBPM and daytime-ABPM) to evaluate if these methods are equivalent in defining HT. We find a very good agreement between both methods in normotensive subjects, as well as in HT patients without or with CKD, with only a small systematic error between both measurements. We can therefore conclude that both techniques are equivalent for evaluating SBP and DBP. Our results are not in agreement with the results found by Robberechts et al. as they find significant higher BP values when BP is measured by tele-HBPM in comparison with ABPM.[56] However their small study focuses on a population of only HT patients with CKD stage 5 on hemodialysis. As mentioned earlier in this discussion, patients with CKD stage 5 on hemodialysis show low reproducibility of their BP measurements and therefore they are not ideal patients to evaluate difference or agreement between two techniques. Reviewing the literature we find several studies with larger number of patients enrolled, that also find higher HBPM values than daytime-ABPM values.[57,58,59,60] But we also find several studies that are in agreement with our findings. Our results correspond with the data found by Den Hond et al.[61], Hara et al.[62], Stergiou et al. (1)[63] and (2)[64], Mansoor et al.[65], Shimbo et al.[66] and Jula et al[67].

Strengths and limitations

Our study has several *strengths*. This is a prospective study in normotensive volunteers and in different hypertensive patients. The design is made in that way that we have several office BP measurements, measured according to the recommended guidelines and thereby increasing reproducibility and reliability. The same accounts for 24h-ABPM and tele-HBPM.

On the other hand our study has some *limitations*. Firstly, this analysis includes for the moment only a limited number of patients. Secondly, measuring 24h-ABPM and tele-HBPM has several limitations. The 24h-ABPM is bound to some technical difficulties as BP is remeasured when there is a nod in the cable, when the patient does not hold his arm still enough, … Furthermore some patients did not want to wear the device during the night as this interferes with their sleep. Telemedicine-guided HBPM is also linked to several technical difficulties, maybe even more than 24h-ABPM. We encountered mistakes in the pre-set date of the device, the mobile phone was not always fully charged and therefore patients did not always measure BP as requested when the mobile phone was out of service, the company responsible for telemedicine performed an upgrade of the system without informing us and data were not transmitted after the upgrade (after several phone calls we succeeded in retrieving the BP values). In tele-HBPM there is great participation of the patient. This may have positive effects on the awareness of his HT status, but we are also more dependent on the patients' collaboration. Some patients had very few measurements; because they did not take the device with them when not coming home, they forgot, it was not compatible with their social life, … It also requires very accurate explanation how to measure tele-HBPM. Thirdly, we only have 4 devices for telemedicine guided HBPM, which creates a bottleneck for the study as only 4 patients per week can participate at the same time in the study.

Conclusion

In summary, we conclude that the effectiveness of the three BP measuring techniques is very comparable since office BP, daytime-ABP and tele-HBP show analogous results for BP control, if office BP is measured in a standardized way. Intensive BP monitoring shows to improve BP control.

Out-of-office techniques are the techniques best used for further follow-up as they have good reproducibility and office BP is less reproducible. Moreover patients prefer to have a follow-up by tele-HBPM rather than by 24h-ABPM.

Patients known with HT and suffering CKD stage 5 are a class apart. Their systolic and diastolic BP turns out to be higher than other patients, irrespectively of the used technique. Moreover the results appear to have low reproducibility.

We do not observe a difference between the two out-of-office techniques (daytime-ABPM and tele-HBPM) as we find good agreement between both methods in normotensive subjects as well as in hypertensive patients without and with CKD.

Expanding the study population, we hope to confirm these preliminary results.

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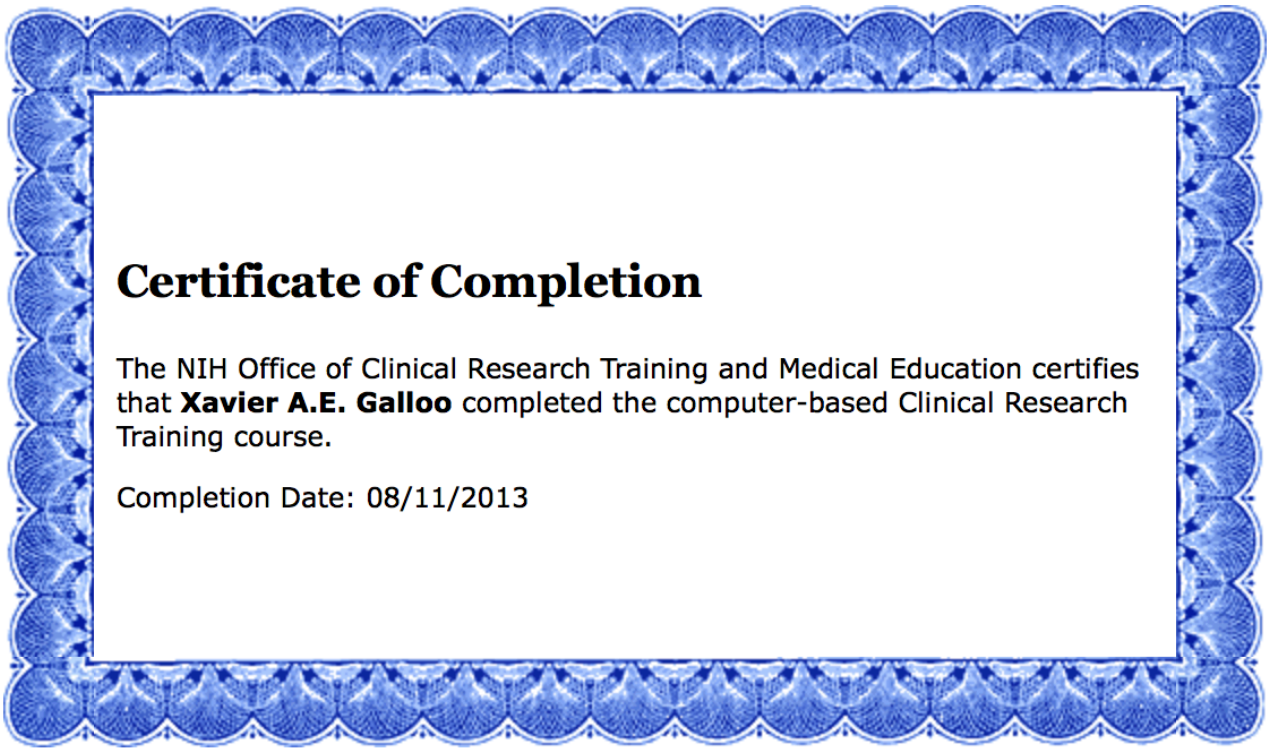
Appendices

Appendix 1: Certificate of NIH-GCP training course



Certificate of Completion

The NIH Office of Clinical Research Training and Medical Education certifies that **Xavier A.E. Galloo** completed the computer-based Clinical Research Training course.

Completion Date: 08/11/2013

Appendix 2: Physiology

1. Hemodynamics

Physiology of the blood pressure and the vessels is based upon a simplified model of the circulatory system upon which the classical hydrodynamic laws can be applied. The most important law is an analogous to Ohm's law of electricity; modified so it is applicable for fluids:

$$\Delta P = F \times R$$

The difference in pressure (ΔP) between an upstream point (P_1) and a downstream point (P_2) is equal to the product of the flow (F) and the resistance (R) between these points. In reality the pressure difference (ΔP) in the human systemic circulation appears to be quite constant over time. The flow is variable in time and it depends on physiologic circumstances. Resistance varies also in time, just like the flow, but in addition it also varies with the location within the body.

Applying this formula on the human circulatory system it provides the following definition: blood pressure (BP) is the result of the cardiac output (CO) increased by the total peripheral resistance (TPR).

$$BP = CO \times TPR$$

Cardiac output is defined as the volume of blood being pumped out of the heart in one minute and equals the product of the stroke volume (SV) and the heart rate per minute (HR): CO = SV x HR. In healthy adults CO at rest should be between 4–6 L/min. Stroke volume is the difference between end-diastolic volume (EDV) and end-systolic volume (ESV).

Total peripheral resistance is subject to the blood vessels (diameter, sum, …) and the viscosity of the blood.

According to the laws of physics pressure is measured in Pascals, however physiologists depict BP by the height it can drive a column of liquid (usually water or mercury):

$$P = \rho \times g \times h$$

In this formula P equals pressure, ρ is the density of the liquid, g is the gravitational constant and h is the height of the column. The blood pressure is expressed in cm H_2O or mm Hg.

A movement of a mechanical system can only be defined by the difference between two forces. The reference pressure in human physiology is the atmospheric or barometric pressure (P_B). Blood pressure measurements express the difference between the pressure inside the blood vessel and the atmospheric pressure.

2. Regulation of the arterial blood pressure

Arterial BP is regulated by two different systems; the first system regulates BP on short-term (seconds to minutes), the second system regulates BP on intermediate and long-term (hours to days). Some systems only influence BP on a short-term base or long-term base but others influence BP by both mechanisms.

2.1. Short-term regulation

A quick response of the human body to changes in the BP is mainly mediated via neural pathways (negative feedback) and triggers blood vessels, heart and adrenal medulla and so influencing the cardiac output as well as total peripheral resistance. Neural pathways consist of stimuli triggering two types of receptors (baroreceptors and chemoreceptors), sending signals via afferent nerves to the central nervous system (CNS), which in return will send signals via efferent nerves to effector cells.

Besides neural pathways there are mechanisms intrinsic and extrinsic to the heart that influence either the heart rate or the stroke volume and thus influencing the cardiac output on a short-term base.

A. Baroreceptors

The primary sensors are the baroreceptors, which are actually stretch receptors, as they do not sense difference in pressure but they sense distention of the vascular wall. The two most important stretch receptors are located on high-pressure-sites: *the carotid sinus* (just cranial to the carotid bifurcation) and *the aortic arch*. An increase of the blood pressure will cause an expansion in vascular diameter, which results in a deformation (stretch) of the receptor.

In response to the deformation of the baroreceptor it will generate receptor potentials via afferent nerves. The carotid sinus sends its signals via the *carotid sinus reflex* and the baroreceptors in the aortic arch send their signals via the *n. vagus*.

Both signals reach the *medullary cardiovascular center* in the central nervous system via the nucleus tractus solitarius (NTS). The medullary cardiovascular center consists of a vasomotor area, a cardioinhibitory area and a cardioacceleratory area. The vasomotor area, which produces a tonic output that promotes vasoconstriction, is inhibited by the NTS, resulting in a vasodilatation. The NTS will also stimulate the cardioinhibitory area and inhibit the cardioacceleratory area resulting in a bradycardia.

The medullary cardiovascular center sends efferent signals to the effector cells. These efferent pathways include the sympathetic (OSy) and parasympathetic (PSy) division of the autonomic nervous system (ANS). The sympathetic system is part of the vasomotor area and the parasympathetic system is part of the cardioinhibitory area.

Sympathetic system: Preganglionic OSy efferent neurons release acetylcholine (Ach) that interacts at N_2-nicotinic-acetylcholine-receptors located in:

(1) the adrenal medulla and so stimulating epinephrine (and in minor degree norepinephrine) secretion by chromaffin cells resulting in systemic vasoconstriction.

(2) postganglionic sympathetic neurons, located in the ganglia of the paravertebral and prevertebral sympathetic chain. Postganglionic sympathetic neurons will innervate the heart and blood vessels. By a release of norepinephrine it increases the rate and contractility of the heart (β_1-adrenergic-receptor) and it stimulates the vasoconstrictor response of arterioles and venules.

Parasympathetic system: Preganglionic PSy neurons depart in the cardioinhibitory area, run along with the nervus vagus and target the postganglionic PSy neurons located in the heart and blood vessels. By a release of Ach onto N_2-nicotinic-Ach-receptors they will stimulate the postganglionic efferents. Postganglionic neurons release Ach onto M_2-muscarin-receptors located in the:

(1) heart, resulting in a decrease of the rate and contractility.

(2) the arterioles and venules, resulting in a stimulation of the vasodilator response.

To summarize: in response to an elevated blood pressure, baroreceptors will be triggers and will send afferent signals to the medullary cardiovascular center where the OSy system in the vasomotor area will be inhibited and the PSy system in the cardioinhibitory area will be stimulated and therefore resulting in a vasodilatation and bradycardia (Figure 2).

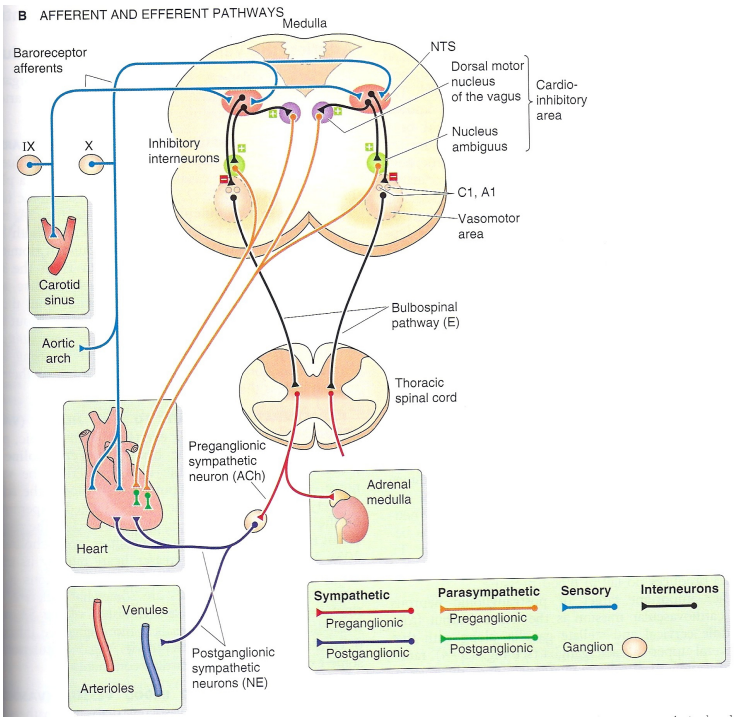


Figure 2: Afferent and efferent neural pathways in short-term blood pressure control. [ii]

B. Chemoreceptors

Chemoreceptors react to changes in PO_2, PCO_2 and pH. The two types of peripheral chemoreceptors (carotid bodies/glomus caroticum and aortic bodies) are more sensitive to changes in PO_2, while central chemoreceptors are more sensitive to changes in pH (and thus in CO_2). Stimulated chemoreceptors will induce vasoconstriction by a positive feedback via the vasomotor area and bradycardia by a positive feedback via the cardioinhibitory area. The peripheral chemoreceptors only play a role during severe hypoxia. However under real-life conditions stimulation of the peripheral chemoreceptors by sever hypoxia will not induce bradycardia, on the contrary it will induce tachycardia as it stimulates the medullary respiratory center and stimulate ventilation.

C. Cardiac output

Mechanisms intrinsic and extrinsic to the heart also influence the blood pressure by modulating the cardiac output.

Intrinsic mechanisms: Potassium and calcium concentration are both intrinsic factors modulating the heart rate. Both factors influence the ionic currents responsible for sino-atrial node pacemaker activity. Stroke volume is the difference between EDV and ESV. Filling pressure, filling time and ventricular compliance are intrinsic factors modulating EDV, whereas preload, afterload, heart rate and contractility modulate ESV.

[ii] Boron W. F., Boulpaep E. L., *Medical physiology: A Cellular and Molecular Approach, updated edition*, Elsevier, 2003, p539.

Extrinsic mechanisms: The neural pathways, described above, are important extrinsic factors modulating the cardiac output and peripheral resistance. Besides the baroreceptors located in high-pressure sites there are also low-pressure baroreceptors that influence the cardiac output. They are located at low-pressure sites (atria, ventricles, pulmonary arteries,…). An example of an extrinsic factor in the atria influencing cardiac output is atrial natriuretic peptide (ANP), which is released by atrial myocytes in reaction to stretching and resulting in vasodilatation and natriuresis.

2.2. Intermediate and long-term regulation

The intermediate and long-term control of the blood pressure is a humoral control by endocrine and paracrine compounds contributing to the homeostasis of the circulation (renal fluid volume regulation mechanism) acting on a time scale of hours or days. Humoral control can be divided into two groups:

A. Vasoactive substances released in the blood or near vascular smooth muscle cells.

B. Non-vasoactive substances interacting with targets controlling the effective circulation volume.

Some substances have vasoactive as well as non-vasoactive effects and therefore this division in vasoactive and non-vasoactive substances is rather arbitrary.

A. Vasoactive substances

The vasoactive substances influence the vasomotor tone of the blood vessels and so modulating the blood pressure and blood flow. The vasoactive compounds can be amines (epinephrine, serotonin), peptides (angiotensin II, arginine vasopressin (AVP), endothelins, atrial natriuretic peptide, kinins), prostaglandins and gases (nitric oxide).

Not all vasoactive substances will be discussed as this is to detailed for this paper. A brief summary of epinephrine and angiotensin II will be discussed, as there are various pharmacotherapeutics that are widely used, acting on these systems.

Epinephrine has already been addressed in the section handling the baroreceptors. Epinephrine is produced by the adrenal medulla and binds to α_1-receptors causing vasoconstriction and β_2-receptors causing vasodilatation. Adrenergic β_2-receptors are located in the blood vessels of the skeletal muscles, heart, liver and adrenal medulla and therefore the vasodilator function is rather restricted. Furthermore epinephrine also binds β_1-receptors in the heart resulting in an increase of heart rate and contractility.

A decrease in circulating volume will trigger the *renin-angiotensin-aldosterone system (RAAS)* and consequently modulate renal Na^+-excretion. The liver synthetizes angiotensinogen and releases it in the systemic circulation. A decrease in circulation volume triggers the granular cells of the juxtaglomerular apparatus (JGA) of the kidney who synthetize renin and as a result renin will be released in the circulation. The JGA is stimulated by three different mechanisms:

(1) CNS senses a decrease in circulation volume and will increase sympathetic outflow to the JGA, thus increasing renin-release.
(2) Change in the NaCl-concentration is sensed by the macula densa and modulates renin-release.
(3) Stretch-receptors (renal baroreceptors), located in the granular cells of the afferent arterioles, sense decreased renal perfusion pressure and will increase renin-release.

Renin catalyzes the conversion of angiotensinogen in angiotensin I (Ang I). Angiotensin-converting-enzyme (ACE) present on the luminal surface of vascular endothelia catalyzes the conversion of the physiologic inactive Ang I into angiotensin II (Ang II). The proximal tubule secretes Ang II into the lumen so it cannot be cleaved by aminopeptidases present in the systemic circulation. Ang II has several actions to regulate the blood pressure:

(1) Stimulation of aldosterone-release from glomerulosa cells in the adrenal cortex and thus promoting Na^+-reabsorption in the collecting ducts
(2) Vasoconstriction
(3) Enhancing tubuloglomerular feedback
(4) Enhancing Na-H exchange in order to promote Na^+-reabsorption
(5) Stimulating thirst and AVP-release

Angiotensin II in the systemic circulation is cleaved by aminopeptidases into angiotensin III (Ang III), which is physiologically inactive. Figure 3 provides an overview of the RAAS.

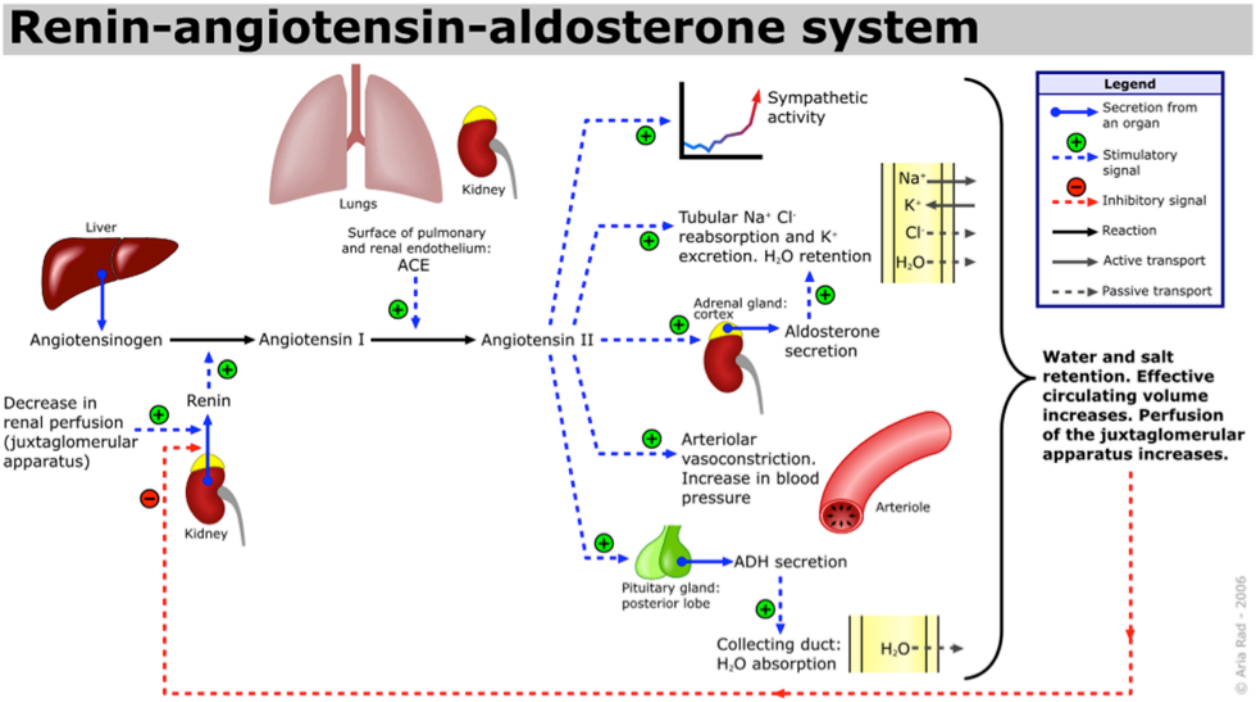


Figure 3: The Renin-Angiotensin-Aldosterone system.[iii]

B. Non-vasoactive substances

Non-vasoactive substances modulate blood pressure not by influencing the heart or blood vessels, but they control the effective circulating volume. There are four main pathways to modulate effective circulating volume.

(1) RAAS
(2) Sympathetic division of the ANS
(3) Arginine vasopressin (antidiuretic hormone)
(4) Atrial natriuretic peptide

This will not be further discussed as this goes beyond the objectives of this paper.

PHYSIOLOGY – References

Boron WF, Boulpaep EL. Medical physiology: A Cellular and Molecular Approach, updated edition. *Elsevier* 2003, 534-557.

[iii] http://commons.wikimedia.org/wiki/File:Renin-angiotensin-aldosterone_system.png, Rad A, Renin-angiotensin-aldosteron system, Wikimedia Commons, consulted on 20/apr/2014.

Appendix 3: Study protocol

PROTOCOL of "Effectiveness of clinic blood pressure monitoring, home blood pressure telemonitoring and ambulatory blood pressure monitoring in evaluating blood pressure control in hypertensive patients with and without chronic kidney disease."

TABLE OF CONTENTS

1. INTRODUCTION AND BACKGROUND

Hypertension (HT) is a worldwide problem and a leading cause of morbidity and mortality. Several clinical studies have shown that optimal control of blood pressure (BP) reduces cardiovascular (CV) risk such as heart failure, myocardial infarction and stroke.[1]

The European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) define hypertension as a systolic blood pressure (SBP) value above 140 mmHg and/or diastolic blood pressure (DBP) value above 90 mmHg (table 1). This classification is applicable in young, middle-aged and elderly adults. Different cut-off values, based on percentiles, are used in children and adolescents.[2]

Category	Systolic (mm Hg)		Diastolic (mm Hg)
Optimal	< 120	And	< 80
Normal	120 - 129	And/or	80 - 84
High normal	130 - 139	And/or	85 - 89
Grade 1 hypertension	140 - 159	And/or	90 - 99
Grade 2 hypertension	160- 179	And/or	100 - 109
Grade 3 hypertension	≥ 180	And/or	≥ 110
Isolated systolic hypertension	≥ 140	And	< 90

Table 1. Definitions and classification of office blood pressure levels.

The prevalence of HT varies a lot between countries. Worldwide prevalence is estimated at 26% with a HT control varying from 5 to 58%.[3] In the USA approximately 1 in 3 individuals deals with HT.[1] The prevalence of HT in Europe is estimated around 30-45% of the general population and increases significantly with age.[2] According to a review by Pereira et al. HT prevalence in Western European men and women is respectively 42.4% and 29.3%.[3]

These figures demonstrate the importance of hypertension control. Although a good control of BP reduces the CV risk considerably, control of HT is been achieved in barely 50.1% of the North-American patients according to data of the National Health and Nutrition Examination Survey (NHANES).[1] According to the National Center for Health Statistics 53.3% of North-American people with HT had a good control of their BP in 2009 – 2010.[5] Pereira et al. conclude that 29.7% of the Western European men and 44.5% of the Western European women have a good BP control.[3] According to Van der Niepen et al. only 21.5% of the treated HT patients in Belgium had a good BP-control in 2004.[4]

Different barriers to optimal hypertension control have been defined. There are three major categories: patient-related, physician-related and medical environment/health care system factors. Patient-related barriers are the most common and most important reasons for a bad HT control. These barriers include poor medical adherence, patients' beliefs about HT and its treatment, depression, cognitive dysfunction, low health literacy, comorbidity, coping, patient motivation etc. The principal reason of all these is poor medical adherence. The most important physician-related barrier is clinical inertia. This is a failure of the physician to initiate or intensify drug therapy and it's caused by 1) overestimation of the administered care; 2) lack of training; 3) the use of soft reasons to avoid treatment intensification by a 'wait and see-policy'. The reasons associated with the medical environment and the health care system are the least important. They include lack of access to care, cost of medication, low socioeconomic status, etc.[6]

In the guidelines published by the ESH several methods to improve BP control are suggested. Information about BP and its possible consequences has to be given to the patient, either in an individual meeting or in group sessions. The patient should self-monitor his BP and there should be room for self-management either with simple patient-guided-systems or supervised by a health care provider (doctor, pharmacist, nurse).[7] On health care level intensification of care by good BP monitoring, telemedicine, involving pharmacists in the drug therapy, etc.[2]

The diagnostic evaluation of HT should consist of confirming the diagnosis, uncovering secondary causes of HT and an assessment of the CV risk, organ damage and clinical condition. To confirm the diagnosis of HT, different techniques are used:

A. Office or clinic BP: a health care provider measures the BP in the doctor's office.

B. Out-of-office BP: usually it consists of self-measurement. There are two types of out-of-office BP measurement: 24h ambulatory BP measurement and home BP measurement.

1. 24h Ambulatory BP monitoring (ABPM): BP is measured for a 24h period. The patient wears a portable BP measuring device, usually on the non-dominant arm. During daytime measurements are performed with an interval of 15 minutes and overnight every 30 minutes. ABPM has an important prognostic significance because it has a stronger correlation with morbidity and mortality than office BP. ABPM is also used to diagnose white-coat and masked hypertension and hypertension at night. In these cases, ABPM will be performed to evaluate BP control.

2. Home BP monitoring (HBPM): it generally consists of daily self-measurements, preferably 7 consecutive days, twice in the morning as well as in the evening. Home BP is the average of these readings, with exclusion of the first monitoring day. These values are communicated to a health care provider or clinic either in person or recently it's possible to transmit values via telephone or an e-Health-related technology (telemonitoring). Different studies have shown that HBPM correlates stronger with CV morbidity and mortality than office BP and that HBPM is at least as well correlated with morbidity and mortality compared with ABPM

Office BP is usually higher than out-of-office BP, so different cut-off values are used in out-of-office BP monitoring to define HT (Table 2).[2]

Category	**SBP** (mmHg)		**DBP** (mmHg)
Office BP	≥ 140	And/or	≥ 90
Ambulatory BP			
Daytime (or awake)	≥ 135	And/or	≥ 85
Nighttime (or asleep)	≥ 120	And/or	≥ 70
24-h (or mean)	≥ 130	And/or	≥ 80
Home BP	≥ 135	And/or	≥ 85

Table 2. Cut-off values defining HT in office BP, ABPM and HBPM.

As described in table 2, office BP is usually higher than out-of-office BP. The alerting response, anxiety and/or conditional response to an unusual situation are some of the reasons accountable for this difference. The difference between office BP and out-of-office BP is referred to as white-coat HT (WCHT) or masked HT (MHT) depending on which values are elevated. Isolated office HT or isolated clinic HT are synonyms of WCHT and isolated ambulatory HT is a synonym of MHT. WCHT is defined as elevated office BP at repeated visits and normal BP during out-of-office measurements. The contrary, when office BP is normal and out-of-office BP measurements (ABPM or HBPM) are elevated, is called MHT.[2]

Office BP measurement still remains the 'gold standard' for screening, diagnosis and management of hypertension, but out-of-office BP measurements are an important added value to conventional office BP measurements. HBPM supported by telemonitoring is an effective method to decrease BP in patients with uncontrolled HT in primary care.[8] HBPM is more suitable in primary care and ABPM is more suitable in specialist care, but availability, ease, cost of use and patient preference will determine if either ABPM or HBPM will be chosen. Since ABPM is currently considered the reference for out-of-office BP, it is advisable that abnormalities on HBPM are confirmed with ABPM.[2]

Many interventions have been designed to help patients improve their BP control. On the one hand there are 'simple interventions' where different measurement techniques are compared to one another without investigating other influencing factors. [9,10] On the other hand there are 'complex interventions' where besides the measuring technique also other influencing factors (patient education, counseling on medication adherence by health care providers, adaptation of the antihypertensive treatment, etc.) are examined. [9, 11-13] Since the methods, inclusion criteria, etc. of all

these studies vary a lot, it is difficult to compare these studies to each other.

Most investigations compared office BP with ABPM or HBPM. Few studies have been done to compare ABPM with HBPM. In a previous study by our department, where the effect of hyponatremic and isonatremic dialysate in patients with intradialytic hypertension was investigated, a significant discrepancy between ABPM and HBPM with telemonitoring was seen in nearly every patient (at wash out p-values for mean systolic BP and mean diastolic BP were respectively 0.0323 and 0.0452). In total 11 patients with CKD on hemodialysis were enrolled in a prospective randomized cross-over study. ABPM and HBPM were measured in every patient. Mean awake ABPM at wash-out was 133.8 / 71.1 mmHg and mean HBPM at wash-out was 144.3 / 76.4 mmHg.[14]

Since the ESH uses the same cut-off values for daytime ABPM and HBPM, we want to verify this discrepancy. Reviewing the literature, we conclude that there are very few comparative studies between ABPM en HBPM.

Gaborieau et al. performed a study to investigate the correlation of ABPM and HBPM with target organ damage. They used the ESH-guidelines to define HT. Their population consisted of hypertensive patients referred to a cardiology department. Office BP, ABPM and HBPM (without telemonitoring) were measured in 302 of the initially 325 included patients. They concluded there was a significant 5 mmHg systolic BP difference between daytime (or awake) ABPM and mean HBPM. A value of 135 mmHg mean daytime ABPM corresponded to 140 mmHg mean HBPM. To their knowledge this was the first report in the literature where such a discrepancy has been reported and they recommend further investigation because it may have important consequences in the definition of target values for HT. [15]

This trend can also be seen in a study performed by *Martinez et al*, who also investigated if ABPM and HBPM correlated with target organ damage. In all 225 included patients office BP, ABPM and HBPM was measured. Mean daytime ABPM was 139/82 mmHg and mean HBPM was 144/84 mmHg.[16]

In a study by *Bayo et al.* the same trend was observed. They examined the role of HBPM in the diagnosis of white-coat HT in four primary health care centers. All 190 included patients underwent HBPM for 3 consecutive days (without telemonitoring; patients themselves had to enter the BP-values in the device), followed by ABPM. ESH-guidelines were used to define HT. Although the difference was not statistically significant, mean HBPM was higher than mean daytime ABPM, respectively 137.4 ± 14.3 / 82.1 ± 8.3 mmHg and 134.8 ± 11.3 / 81.3 ± 9.5 mmHg.[17]

Den Hond et al. performed a subanalysis of the THOP trial, a randomized controlled trial, to see if HBPM could be an alternative to ABPM to diagnose white-coat HT. They included 247 untreated hypertensive patients who all underwent office BP, ABPM and HBPM (without telemonitoring). Their values don't follow the trend in the studies mentioned above: mean daytime ABPM is 148.1 ± 14.2 / 95.0 ± 9.3 mmHg and mean HBPM 143.1 ± 16.1 / 91.5 ± 9.0 mmHg.[18]

Hara et al. investigated the correlation of cerebrovascular disease with office BP, ABPM and HBPM. A total of 1007 patients were included in the study. They all had office BP measurement, ABPM and HBPM (no telemonitoring was used). Their results also don't support the trend described above: mean daytime ABPM was higher (129 ± 13 / 76 ± 8 mmHg) than mean HBPM = 122 ± 14 / 73 ± 9 mmHg.[19]

Another study investigated the diagnostic value of ABPM and HBPM as alternatives to office BP for the diagnosis of HT. This study, performed by *Stergiou et al.*, contained a direct comparison between ABPM and HBPM (without telemonitoring). In total 133 patients, either untreated with diastolic office BP of 90-115 mmHg or treated for HT but whose diagnosis of HT was questionable, were enrolled in the study. Findings showed no significant difference between mean daytime ABPM and mean HBPM (mean difference 0.6 ± 11.8 / 1.8 ± 6.7 mmHg). Mean daytime ABPM was 139.3 ± 12.8 / 91.1 ± 9.9 mmHg and mean HBPM was 138.7 ± 15.6 / 89.3 ± 8.6 mmHg. Stergiou et al. mention that there is uncertainty regarding reference values for these BP measurement techniques.[20]

The data of all these studies are summarized in table 3.

Study	n	Mean-daytime-ABPM		Mean-HBPM		HBPM + telemonitoring
		Systolic (mm Hg)	Diastolic (mm Hg)	Systolic (mm Hg)	Diastolic (mm Hg)	
Robberechts et al.[14] *	11	133.8 ± 17.8	71.1 ± 10.9	144.3 ± 17.1	76.4 ± 13.7	yes
Gaborieau et al.[15] *	302	130 ± 18	78 ± 9	135.5 ± 14	77 ± 9	no
Martinez et al.[16]	225	139	82	144	84	no
Bayo et al.[17] *	190	134.8 ± 11.3	81.3 ± 9.5	137.4 ± 14.3	82.1 ± 8.3	no
Den Hond et al.[18]	247	148.1 ± 14.2	95.0 ± 9.3	143.1 ± 16.1[a]	91.5 ± 9.0[a]	no
Hara et al.[19]	1007	129 ± 13	76 ± 8	122 ± 14	73 ± 9	no
Stergiou et al.[20] *	133	139.3 ± 12.8	91.1 ± 9.9	138.7 ± 15.6	89.3 ± 8.6	no

Table 3. Comparison of the values in the studies where ABPM was compared to HBPM
Abbreviations: n, number of patients included in the study;
[a] Mean-HBPM-values in a graph (142.4 / 91.0 mmHg) differ from the readings in the table (143.1 ± 16.1 / 91.5 ± 9.0 mmHg).
* In these studies significance between ABPM and HBPM was calculated. Robberechts et al. and Gaborieau et al. had significant differences; Bayo et al. and Stergiou et al. had non-significant values.

2. RATIONALE

Although the number of studies debating this subject is very small, we found a few studies comparing HBPM to ABPM. We conclude there is a discrepancy in the literature. Most values are obtained from studies where the difference between ABPM and HBPM isn't part of the objectives and so it isn't further discussed. All studies were performed in hypertensive patients. The study by Robberechts et al. was performed in patients with CKD in dialysis. To investigate the discrepancy between HBPM with a telemonitoring system and ABPM we would like to broaden this population and investigate if this trend persists in normotensive individuals and patients with HT with or without CKD.

3. STUDY OBJECTIVES

3.1 Primary Objectives:

To evaluate the effectiveness of office blood pressure measurement, home blood pressure telemonitoring and 24h ambulatory blood pressure monitoring in assessing blood pressure control (defined as office BP <140/<90 mm Hg and for home/ ambulatory daytime BP as <135/<85 mm Hg)

3.2 Secondary Objectives:

a) To evaluate the satisfaction with the different types of blood pressure measurement
b) To evaluate the effect of intensive blood pressure monitoring on medication adherence
c) To evaluate the effect of intensive blood pressure monitoring on blood pressure control
d) To evaluate the effect of intensive blood pressure monitoring on the general wellbeing of the patient
e) To evaluate the percentage of patients with a higher blood pressure at night than during daytime.

4. INVESTIGATIONAL PLAN

4.1 Overall Study Design

The study will consist of 2 periods of 1 week of BP monitoring

Visit 1 Visit 2 Visit 3 Visit 4

/----------/----------/----------/

Visit 1 (day 1): - Informed consent
- Baseline characteristics
- Office BP measurement (3x) in sitting position after 5 minutes of rest
- Questionnaires on overall wellbeing and medication adherence (EQ-5D-3L, HADS, Morisky)
- Start 24h ambulatory BP monitoring till visit 2

Visit 2 (day 2): - Office BP measurement (3x) in sitting position after 5 minutes of rest
- Start home BP telemonitoring during 7 consecutive days, twice in the morning and twice in the evening, in the sitting position, after 5 minutes of rest, before eating and before taking medication.
- Questionnaire on satisfaction concerning type of BP measurement

Visit 3 (after 4 weeks): - Office BP measurement (3x) in sitting position after 5 minutes of rest
- Questionnaires on overall wellbeing and medication adherence (EQ-5D-3L, HADS, Morisky)
- Start 24h ambulatory BP monitoring till visit 2

Visit 4 (1 day after V3): - Office BP measurement (3x) in sitting position after 5 minutes of rest
- Start home BP telemonitoring during 7 consecutive days, twice in the morning and twice in the evening, in the sitting position, after 5 minutes of rest, before eating and before taking medication.
- Questionnaire on satisfaction concerning type of BP measurement

4.2 Duration of Subject Participation and Study
6 weeks

5. SELECTION AND WITHDRAWAL OF SUBJECTS
5.1 Number of Subjects
73 - 80 patients

5.2 Inclusion Criteria
- ✓ Normal volunteers
- → who are at least 18 yrs
- → who have provided the appropriate written informed consent before any study-specific procedure is performed

- ✓ Subjects with hypertension
  - Without CKD
  - With CKD

- → who are on a stable antihypertensive treatment
- → who are at least 18 yrs
- → who have provided the appropriate written informed consent before any study-specific procedure is performed

5.3 Exclusion Criteria
- ✓ Subjects with recent cardiovascular or cerebral event
- ✓ Subjects with severe hypertension (>180/110 mm Hg)
- ✓ Subjects with atrial fibrillation

- ✓ Simultaneous participation in another clinical study except observational trials
- ✓ Subjects with acute kidney failure
- ✓ Subjects with debilitating illness: liver failure, instable patients, active bleeding, active infection, active neoplasm, …
- ✓ Subjects with impossibility to measure BP in a standardized way
- ✓ Pregnancy
- ✓ Subjects with any kind of disorder that compromises the ability of the subject to provide written informed consent and/or to comply with study procedures.

5.4 Withdrawal of Subjects
Subjects may withdraw from the study at any time.
Subjects will be withdrawn if their mean blood pressure exceeds 180/110 mm Hg

6. STUDY TREATMENT
No investigational treatment.
Investigation of different BP monitoring systems

7. BENEFITS/RISKS/PRECAUTIONS

- ➢ Benefit to the patient:

The study has the potential benefit to identify patients with suboptimal control of arterial hypertension.
Participation in the study therefore has the potential benefit to improve hypertension control and lower cardiovascular risk.

- ➢ Benefit to the hypertensive community:

The study might validate the use of home blood pressure telemonitoring to improve blood pressure control
in hypertensive patients with and without CKD.

- ➢ Risks/Discomforts for the patients:

The study does not implicate a pharmacological intervention. Patients will continue their antihypertensive medication. The risk of uncontrolled severe hypertension will be minimal as these patients are treated and closely monitored. Due to the cuff of the 24h ABPM patients can eventually experience at the arm some pain or redness, seldom a bruise.

8. STUDY PROCEDURES
8.1 Description of Study Assessments

- ➢ Standardized BP measurement: BP is measured with an automated oscillometric BP device (Omron HEM-705CP digital BP monitor (Omron Corp., Tokyo, Japan)), measuring brachial artery pressure and successfully passed validation according to the protocol of the British Hypertension Society[21], with an appropriate cuff around the upper arm. BP readings will be obtained after the patient had rested for 5 min in the sitting position and are measured at both arms. Blood pressure is taken trice with 1 minute interval. For the analysis the BP values obtained at the non-dominant arm will be used, as this is also the arm used for 24 h ABPM and for selfmeasurement of blood pressure.

- ➢ 24h ABPM: this procedure measures the blood pressure of the subjects living their normal daily life and during their sleep. The ambulatory BP is recorded with oscillometric Space-Labs 90217 and 90217A monitors (SpaceLabs Inc., Redmond, Washington, USA). The cuff of the BP monitor is fitted on the non-dominant arm. The devices are programmed to obtain BP readings at 15-min intervals from 0800 to 2200 h and at 30-min intervals for the remainder of the day. Daytime and night-time ambulatory BPs will be calculated as the actual awake and sleep time means of the readings obtained. ABPM is scheduled on visit 1 after office BP measurement and after filling in the questionnaires and occurs outside the hospital. The device is attached on visit 1 and on visit 3 and is removed after 24h, i.e. on visit 2 and visit 4

Following parameters will be calculated: mean daytime systolic blood pressure, mean daytime diastolic blood pressure, mean daytime mean blood pressure, 24 h systolic blood pressure, 24 h diastolic blood pressure, 24 h mean blood pressure, systolic BP dipping, diastolic BP dipping, mean arterial pressure dipping, mean nocturnal systolic blood pressure, mean nocturnal diastolic blood pressure, mean nocturnal mean blood pressure.
Optimal values for ABPM are <135/85 mm Hg when subjects are awake and <120/70 mm Hg during sleep; or overall a BP <130/<80 mm Hg.

- 1 week telemonitoring of home BP measurement: Telemonitoring is a particular form of chronic disease management. In this telehealth monitoring system patients are given an automated blood pressure monitor to obtain BP data at home. These data are remotely transmitted by a GSM to care providers on a daily basis, allowing close monitoring of the patient's clinical status without office or in-home visits by health personnel. On visit 2 and on visit 4 home BP telemonitoring is started, during 7 consecutive days, trice in the morning and trice in the evening, in the sitting position, after 5 minutes of rest. For the self-measurement of BP at home, the patients use a validated automated sphygmomanometer (Stabil-O-Graph mobil, IEM, Germany)* for BP telemonitoring. This automated oscillometric device measures brachial artery pressure and has successfully passed validation according to the protocol of the British Hypertension Society[22]. At enrolment, the doctor or the study nurse instruct the patients how to use the telemonitoring equipment and provide written guidelines for their operation at home. The patients measure their BP in the morning (between 0600 and 1000 h, before breakfast and before taking any medication) and in the evening (between 1800 and 2200 h, before dinner and before taking evening medication) during the week immediately following the ambulatory BP monitoring. Each measurement session consists of three readings after 5-min rest in the sitting position. Self-measured BP values are transmitted automatically by mobile phone to a website and can be checked by the physician/ study nurse who can enquire about circumstances in case of exceptionally high or low readings.

For all types of BP measurement, the same cuff size is used. Standard cuffs have a 24 x 14 cm inflatable bladder. If arm circumference exceeds 31 cm, larger cuffs with a bladder size of 32 x 15 cm are used.
Blood pressure control is defined as a BP threshold < 135/85 mmHg for daytime ambulatory and self-measured home BP, <140/90 mmHg for conventional BP. The white-coat effect is defined as the difference between conventional and daytime ambulatory BP or the difference between conventional and average home BP.

8.2 Schedule of Assessments
The study consists of 2 periods of 1 week of BP monitoring

Visit 1 Visit 2 Visit 3 Visit 4

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Visit 1 (day 1): - Informed consent
- Baseline characteristics
- Office BP measurement (3x) in sitting position after 5 minutes of rest
- Questionnaires on overall wellbeing and medication adherence (EQ-5D-3L, HADS, Morisky)
- Start 24h ambulatory BP monitoring till visit 2

Visit 2 (day 2): - Office BP measurement (3x) in sitting position after 5 minutes of rest
- Start home BP telemonitoring during 7 consecutive days, twice in the morning and twice in the evening, in the sitting position, after 5 minutes of rest
- Questionnaire on satisfaction concerning type of BP measurement

Visit 3 (after 4 weeks): - Office BP measurement (3x) in sitting position after 5 minutes of rest
- Questionnaires on overall wellbeing and medication adherence (EQ5D, HADS, Morisky)
- Start 24h ambulatory BP monitoring till visit 2

Visit 4 (1 day after V3): - Office BP measurement (3x) in sitting position after 5 minutes of rest
- Start home BP telemonitoring during 7 consecutive days, twice in the morning and twice in the evening, in the sitting position, after 5 minutes of rest
- Questionnaire on satisfaction concerning type of BP measurement

8.2.1 Treatment Procedures
BP monitoring with different automatic devices in different setting

8.2.2 End of Study (or Early Discontinuation) Procedures
Subjects will complete the study after 6 weeks of monitoring (2 periods of 1 week with a 4 week interval)
Subjects may withdraw from the study at any time.
Subjects will be withdrawn if their mean BP exceeds 180/110 mm Hg
Antihypertensive drug treatment will be continued and if necessary adapted.

8.2.3 Follow-up Procedures
All subjects, whether completing the study or withdrawn prematurely, will be followed up as usual.

9. EVALUATION AND RECORDING OF AES AND SAES
The present study is a short trial without a pharmacological therapeutic intervention. The short duration of the trial and an intervention that only focuses on blood pressure measurement and blood pressure control reduces the risk of adverse events to a minimum.

9.1 Definitions
9.1.1 Adverse Event
Any complaint or sign
o Severe hypertension (BP ≥ 180/110 mmHg)
o Pain at the arm
o Redness or bruise at the arm

9.1.2 Serious Adverse Event
Death, hospitalisation or prolonged hospitalisation due to the study

9.2.1 Intensity/Severity Categorisation
Mild/ Moderate/ Severe

9.2.2 Causal Relationship Categorisation
Unlikely/ likely/ probably/ certain

9.2.3 Outcome Categorisation
Recovered/resolved - Recovering/Resolving - Not recovered/not resolved - Fatal - Unknown

9.2.4 Clinical Laboratory Evaluations
Not applicable

9.3 Pregnancy
Not applicable

10. STATISTICAL ANALYSIS

All data relevant to the study will be kept in a password protected Excel Data file. After the data have been collected completely and verified, data will be imported in the Statview, version 5.0.1 (SAS Institute Inc.) Statistics and Data Analysis Software. Data will be rechecked by range and consistency checks. Any errors in the data will be corrected after consulting the source documents. All data corrections will be recorded to keep an auditable workflow of the data. Analysis will be conducted as detailed in the analysis plan.

10.1 Statistical Methods

- Demographic and clinical disease characteristics will be summarized.
- Blood pressure values and blood pressure changes will be summarized and compared.
- Medication adherence, patient satisfaction and wellbeing will be summarized and compared.
- t-tests for continuous variables and chi-square tests for categorical variables will be used
- Correlations between the different BP monitoring systems will be explored.
- Adverse events will be compared descriptively.
- All tests will be at the 0.05 level

10.2 Sample Size and Power Calculations

The sample size for the study is calculated based on the primary efficacy endpoint, which is detecting a difference of <5 mm Hg between home BP telemonitoring and 24h ambulatory monitoring and of < 10 mmHg between office and home BP telemonitoring.
A total of resp. at least 35 and 73 patients are needed to detect a difference of resp. 10 and 5 mmHg.
The probability is 80 percent that the study will detect a difference at a two-sided 0.05 significance level, if the true difference between BP methods is 5 and 10 mm Hg.
This is based on the assumption that the standard deviation of the difference in the response variables is 15. To account for incomplete data collection and 20% drop outs, the overall sample of the study has to include 88 patients.

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11. STUDY ETHICAL CONSIDERATIONS

11.1 Ethical Conduct of the Study

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki.
All investigators have the GCP training and certificate.

Plan for Maintaining Privacy and Confidentiality of Subject Records:
Patient data will be kept in a password protected Excel computer file. Only the investigators and the clinical nurses of the Nephrology department will have access to the file. Only initials of the name will be kept in the data file. Date of birth will be indicated by month and year. Information linking the patient identifier in the data file with patient information and file number will be kept separately. No individual patient data or any information likely to identify patients having participated in the study will be shown in presentations or publication manuscripts prepared from the analysis of the data.

Plan for Research Use and Storage of Human Samples, Specimens or Data
All BP measurements and procedures will be done by the in-hospital investigators and study nurses of the Universitair Ziekenhuis Brussel (VUB). The study will not imply storage and use of biological samples. All results of office BP, 24h blood pressure monitoring and of the home BP telemonitoring will be stored in the "Electronisch Medisch Dossier - EMD" of the patient and retrieved by the investigators as indicated in the Data

Management Section
Renumeration/Compensation
Participation in the study is voluntary. Patients will not receive financial incentives to participate in the

study. Investigations that are not part of the standard medical follow up will be covered by the Department of Nephrology & Hypertension.

11.2 Informed Consent
All potentially eligible patients will receive a written informative document and will have the opportunity to discuss all relevant questions with the investigators. A written informed consent will be obtained from all participants before any study procedure will be done. The patient information and informed consent documents are provided as an attachment to the present protocol

11.3 Institutional Review Board or EC/IEC
The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Ethics Committee/Research Ethics Board (IRB/EC/REB) before study start.

12. ADMINISTRATIVE PROCEDURES
12.1. Insurance
As required by the Belgian law of May 7, 2004 concerning experiments on the human person, the investigators will, even without fault, assume responsibility over the damage caused, either directly or indirectly linked to the study, to a participant or his beneficiaries. The hospital has taken out insurance for this purpose, covering potential fatalities, physical injuries, or damage to health that may occur during the clinical study.

12.2. Investigators' responsibilities
12.2.1 Recording of Data
All data will be identified in a manner designed to maintain patient confidentiality (anonymized) and recorded in a pass word protected excel file.
12.2.2 Source Documentation
All data will be recorded in the EMD of the patient
12.2.3 Records Retention
Following the current legal rules
12.2.4 Site Documentation
All documentation will be kept following Belgian legislation.

LIST OF TABLES
Definitions
Following the ESH/ESC guidelines[2], hypertension is defined as a BP ≥140/90 mm Hg at the office and ≥135/85 mm Hg at home. Blood pressure control is defined as a BP <140/90 mm Hg in the office and <135/85 mm Hg at home.

Qualifications and resources of the investigator:
The study is conducted by the following investigators:
Mr. Xavier Galloo (Medical Student)
Prof. Dr. Patricia Van der Niepen (Promotor)
Mr. Dirk Van Ingelgem (Study coordinator)
Mrs. Nathalie Marmitte (Study Nurse)

Mr. Galloo is a medical student and has 3 months during the 2013-2014 academic year to conduct the study in order to graduate. This is sufficient for patient selection, patient recruitment and conduct of the study. Mr. Galloo will be partly responsible for follow up of the patients, collection and recording of the study data as well as for writing of the final report of the study results.

Prof. Dr. Patricia Van der Niepen is a trained nephrologist and hypertension specialist with experience in the conduct of clinical trials. She contributed to the design of study, and will also supervise the progress of the study, the data collection and the statistical analysis of the study results with the interpretation of the results. She will also interpret the 24h ambulatory blood pressure monitoring recordings and the home blood pressure telemonitorings.

Mrs. Nathalie Marmitte is an experienced clinical nurse and will assist the investigators with the conduct and administrative aspects of the study.

Mr. Dirk Van Ingelgem is an experienced clinical study coordinator and a graduated dialysis nurse, currently responsible for ambulatory and home blood pressure monitoring.

Resources available for the study:
The study is financed by the Nephrology & Hypertension department of the UZ Brussel. The 24 hour blood pressure monitorings and home BP telemonitorings are realized by the hypertension clinic. All investigators and study personnel have a certified GCP training and will conduct the study according to the Good Clinical Practice guidelines

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List of Abbreviations

ABPM: Ambulatory Blood Pressure Monitoring
AE: Adverse Event
BP: Blood Pressure
CKD: Chronic Kidney Disease
DBP: Diastolic Blood Pressure
EC: Ethics Committee
EMD: Electronical Medical Dossier
GCP: Good Clinical Practice
h: hour
ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB: Institutional Review Board
MAP: Mean Arterial Pressure
mmHg: millimeter mercury
REB: Research Ethics Board
SAE: Severe Adverse Event
SBP: Systolic Blood Pressure
yrs: years

Appendix 4: Informed consent

Appendix 4a: Dutch version

Informatiefiche voor deelnemers aan een studie

Titel van de studie
Nagaan van de efficiëntie van een bloeddruk gemeten op de consultatie, een bloeddruk thuis gemeten door middel van een telemonitoringsysteem en een 24-uurs ambulante bloeddruk bij het evalueren van de bloeddrukcontrole bij patiënten met arteriële hypertensie, met of zonder chronische nierziekte.

U wordt uitgenodigd deel te nemen aan een studie rond bloeddrukmeting.
Voor u uw akkoord geeft voor deelname aan deze studie, is het belangrijk eerst dit formulier te lezen. Dit informatie- en toestemmingsformulier beschrijft het doel van de studie, de procedures, de mogelijke voordelen en risico's verbonden aan de studie. Het formulier beschrijft eveneens uw recht om u te allen tijde terug te trekken uit de studie. U hebt steeds het recht om vragen te stellen over eventuele risico's van deze studie.

Doel van de studie
Deze studie heeft als doel na te gaan of de verschillende soorten bloeddrukmeting evenwaardig zijn om de controle van de bloeddruk te evalueren.
Gedurende twee periodes van telkens 1 week zal uw bloeddruk worden gemeten met verschillende methodes van bloeddrukmeting. Tevens zal gepeild worden naar uw tevredenheid met de gebruikte methodes.

De onderzoeker(s)
Prof. dr. P. Van der Niepen Universitair Ziekenhuis Brussel (VUB)
Dienst Nefrologie en Hypertensie
Laarbeeklaan 101, 1090 Brussel, België

Dhr. X. Galloo (student-arts)
Universitair Ziekenhuis Brussel (VUB)
Laarbeeklaan 101, 1090 Brussel, België

Studieverpleegkundigen
Dhr. D. Van Ingelgem
Universitair Ziekenhuis Brussel
Dienst Nefrologie en Hypertensie
Laarbeeklaan 101, 1090 Brussel, België

Mevr. N. Marmitte
Universitair Ziekenhuis Brussel
Dienst Nefrologie en Hypertensie
Laarbeeklaan 101, 1090 Brussel, België

Contactgegevens:
- Tel: 02/477 60 55
  02/476 31 91
  02/477 62 24
- E-mail: Xavier.Galloo@vub.ac.be
  Dirk.Vaningelgem@uzbrussel.be
  Nathalie.Marmitte@uzbrussel.be
  hemovnnp@uzbrussel.be

Beschrijving van de studie

1. Inleiding:

U wordt uitgenodigd deel te nemen aan een studie rond bloeddrukcontrole omdat u lijdt aan een arteriële hypertensie. Arteriële hypertensie wil zeggen dat de bloeddruk gelijk of hoger is dan 140/90 mm Hg. Een verhoogde bloeddruk is schadelijk voor hart, bloedvaten, hersenen en nieren. Om deze redenen wordt een verhoogde bloeddruk behandeld met bloeddrukverlagende middelen. De streefwaarde van de bloeddruk onder behandeling is lager dan 140/90 mm Hg.
Patiënten waarbij de bloeddruk onvoldoende onder controle is (een waarde hoger dan 140/90 mm Hg) blijven een hoger risico op hart- en bloedvatziekten hebben.
Normaal wordt de bloeddruk gemeten bij de dokter in zijn kabinet of thuis door de huisarts. Dit is een eenmalige meting en dus een momentopname, en weerspiegelt niet altijd de werkelijke bloeddruk. Bovendien hebben een aantal patiënten een wittejashypertensie of wittejaseffect. Dit wil zeggen dat de bloeddruk hoger is als deze gemeten wordt door de dokter.
Om een beter idee te hebben van de werkelijke bloeddruk gedurende de ganse dag en nacht, kan er gebruik gemaakt worden van een ambulante 24-uurs bloeddrukmeting. Dit gebeurt als volgt: de patiënt komt naar de arts waar een bloeddrukmeter aan de arm bevestigd wordt, deze is geconnecteerd met een opnamesysteem dat bestaat uit een klein toestel dat rond het middel bevestigd wordt. Het toestel is door de arts geprogrammeerd om gedurende de dag elke 15 minuten automatisch de bloeddruk te meten en elke 30 minuten gedurende de nacht. De volgende dag wordt het toestel teruggebracht naar de arts en uitgelezen.
Een andere mogelijkheid om een beter idee te hebben van de werkelijke bloeddruk gedurende de dag bestaat erin om de patiënt zijn/ haar bloeddruk zelf te laten meten met een automatische bloeddrukmeter, en dit minstens tweemaal per dag ('s ochtends en 's avonds). Dit geeft een goed idee over de bloeddruk overdag in de thuissituatie. Vandaar dat artsen meer en meer aanraden om de bloeddruk ook zelf thuis te meten. Om als arts bij zelfmeting door de patiënt snel te kunnen reageren op abnormale bloeddrukwaardes, bestaan er nu ook systemen die de gemeten bloeddruk onmiddellijk doorseinen naar de arts. Dit wordt een telemonitoringsysteem genoemd.
Wij vermoeden echter dat de dagbloeddruk gemeten met een 24uurs ambulante bloeddrukmeter en deze gemeten door de patiënt met een automatische bloeddrukmeter, die uitgerust is met het telemonitoring systeem, mogelijk niet helemaal overeenkomt.

Om dit te testen wordt de huidige studie uitgevoerd. We zullen de controle van de bloeddruk nagaan ten eerste op de raadpleging met een gewone bloeddrukmeting met een automatische bloeddrukmeter door de arts, ten tweede aan de hand van een 24uurs ambulante bloeddrukmeting en ten slotte met een bloeddruk telemonitoringsysteem voor zelfmeting thuis.

2. Concreet verloopt de studie als volgt:

- Op dag 1 (visite 1): wordt de bloeddruk driemaal gemeten op de raadpleging in zittende houding, na 5 minuten rust. Er zal u ook gevraagd worden naar de huidige bloeddrukverlagende medicatie die u neemt en er zal u gevraagd worden om een vragenlijst in te vullen, die peilt naar uw algemene gezondheid en medicatie inname. Op het einde van de raadpleging wordt een 24-uurs ambulante bloeddrukmeter aangelegd.
- Op dag 2 (visite 2): brengt u de 24-uurs ambulante bloeddrukmeter terug naar de raadpleging. De bloeddruk zal terug driemaal genomen worden in zittende houding. Daarna krijgt u een automatische bloeddrukmeter met telemonitoringsysteem mee naar huis. Er zal u gevraagd worden om de bloeddruk gedurende 1 week (7 dagen) zowel 's ochtends als 's avonds te meten. Telkens tweemaal in zittende houding, na 5 minuten rust. Na de laatste dag, brengt u het toestel terug, en wordt u gevraagd om een vragenlijst in te vullen over de tevredenheid van de verschillende soorten bloeddrukmeting.

- Vier weken later, op visite 3 gebeurt hetzelfde als op dag 1
- Een dag na visite 3, op visite 4, gebeurt hetzelfde als op dag 2

De bloeddrukmeting zal steeds aan dezelfde arm gebeuren, omdat er steeds een klein verschil tussen beide armen kan bestaan.

U hoeft geen andere onderzoeken te ondergaan voor de studie. We vragen wel of u akkoord bent dat we gegevens uit uw medisch dossier mogen gebruiken, zoals de resultaten van bepaalde bloed – en urineonderzoeken.

Deelnemers aan de studie
Deelnemers aan de studie zijn gezonde vrijwilligers, en patiënten met arteriële hypertensie, al dan niet behandeld, en met of zonder chronische nierziekte.
De deelnemers moeten bereid zijn de instructies van de behandelende artsen/onderzoekers goed op te volgen. Patiënten met voorkamerfibrillatie en recente aandoeningen van hart en bloedvaten of andere acute ziekten, komen niet in aanmerking voor deelname. Ook niet degenen die niet bekwaam zijn om de eenvoudige instructies op te volgen.

Procedures
Als u bereid bent deel te nemen aan deze studie, zal u volgende testen ondergaan:

- Bloeddrukmeting op de raadpleging
- Bloeddrukmeting via telemonitoring: De bloeddrukmeting via telemonitoring gebeurt door uzelf aan de hand van een conventionele automatische bloeddrukmeter. Hierbij wordt een bloeddrukmanchet aan de bovenarm bevestigd. De bloeddruk wordt automatisch bepaald. Deze meting is niet pijnlijk. De gegevens worden vervolgens verzonden naar het onderzoekende team via een Gsm-toestel, dat u meekrijgt.
- Bloeddrukmeting met een 24-uurs ambulante bloeddrukmonitoring: Voor deze meting krijgt u een geautomatiseerde bloeddrukmeter ter beschikking. Bij het begin van de meting wordt een bloeddrukmanchet bevestigd aan de bovenarm. Deze manchet dient gedurende het hele verloop van de metingen (m.a.w. 24 uur), inclusief ’s nachts, aanwezig
  te blijven. Deze manchet is verbonden met de eigenlijke bloeddrukmeter: een doosje dat ter hoogte van uw middel kan bevestigd worden. De meter voert automatisch volgens een vast interval (= elke 15 minuten overdag en elke 30 minuten gedurende de nacht) een bloeddrukmeting uit. De meter registreert automatisch de resultaten. Eenmaal de metingen volledig voltooid zijn, dient u de bloeddrukmeter terug in te leveren bij de daartoe aangeduide persoon.
- In te vullen vragenlijsten: een vragenlijst met betrekking tot de algemene gezondheid van de patiënt (EQ-5D-3L en HADS) en een vragenlijst met betrekking tot de inname van de antihypertensieve medicatie (Morisky score).

Risico's en voordelen
Sommige patiënten ervaren de 24-uurs ambulante bloeddrukmeting eerder als lastig omdat deze soms hindert in de dagelijkse bezigheden. Indien de bloeddruk erg hoog is kan het herhaaldelijk meten van de bloeddruk wat roodheid en pijn onder de bloeddrukmanchet veroorzaken.

De voordelen zijn dat u en uw bloeddruk gedurende de hele studie van heel nabij zullen gevolgd worden door een ervaren team. De eventuele risico’s verbonden aan de studie zijn miniem. Er zal steeds medisch personeel ter beschikking staan om eventuele neveneffecten vroegtijdig op te sporen en op te vangen.

Kosten verbonden aan deelname
De kosten van de onderzoeken die voor de studie worden uitgevoerd en die geen deel uitmaken van de normale zorg, worden door de dienst Nefrologie & Hypertensie van het Universitair Ziekenhuis Brussel (VUB) gedragen.

Vergoeding
Er wordt geen vergoeding voor deelname aan de studie voorzien.

Vertrouwelijkheid
In overeenstemming met de Belgische wet van 8 december 1992 en de Belgische wet van 22 augustus 2002, zal uw persoonlijke levenssfeer worden gerespecteerd en zal u toegang krijgen tot de verzamelde gegevens. Elk onjuist gegeven kan op uw verzoek verbeterd worden.

Vertegenwoordigers van de Commissie voor Medische Ethiek en de bevoegde overheden hebben rechtstreeks toegang tot uw medische dossiers om de procedures van de studie en/of de gegevens te controleren, zonder de vertrouwelijkheid te schenden. Dit kan enkel binnen de grenzen die door de betreffende wetten zijn toegestaan. Door het toestemmingsformulier, na voorafgaande uitleg, te ondertekenen stemt u in met deze toegang.

Als u akkoord gaat om aan deze studie deel te nemen, zullen uw persoonlijke en klinische gegevens tijdens deze studie worden verzameld en gecodeerd (hierbij kan men uw gegevens nog terugkoppelen naar uw persoonlijk dossier). Verslagen waarin u wordt geïdentificeerd zullen niet openlijk beschikbaar zijn. Als de resultaten van de studie worden gepubliceerd, zal uw identiteit vertrouwelijke informatie blijven.

Deelname en beëindiging van de studie
De deelname aan deze studie vindt plaats op vrijwillige basis. U kunt weigeren om deel te nemen en u kunt zich op elk ogenblik terugtrekken uit de studie zonder dat u hiervoor een reden moet opgeven en zonder dat dit op enigerlei wijze een invloed zal hebben op uw verdere relatie en/of behandeling met de onderzoeker of de behandelende arts.

Letsels ten gevolge van deelname aan de studie
De onderzoeker voorziet in een vergoeding en/of medische behandeling in het geval van schade en/of letsel tengevolge van deelname aan de klinische studie. Voor dit doeleinde is een verzekering afgesloten met foutloze aansprakelijkheid conform de wet betreffende experimenten op de menselijke persoon van 7 mei 2004. Op dat ogenblik kunnen uw gegevens doorgegeven worden aan de verzekeraar.

Ethisch comité
Deze studie werd geëvalueerd en goedgekeurd door de Commissie Medische Ethiek van het Universitair Ziekenhuis Brussel (VUB).

Contactpersonen bij vragen omtrent de studie
Als u meent schade te ondervinden ten gevolge van deze studie, vragen heeft omtrent de studie of omtrent uw rechten als patiënt, zowel nu, tijdens als na uw deelname aan de studie, kan u steeds het onderzoeksteam contacteren. U vindt hun gegevens bovenaan dit formulier.

Toestemmingsformulier

Nagaan van de efficiëntie van een bloeddruk gemeten op de consultatie, een bloeddruk thuis gemeten door middel van een telemonitoringsysteem en een 24-uurs ambulante bloeddruk bij het evalueren van de bloeddrukcontrole bij patiënten met arteriële hypertensie, met of zonder chronische nierziekte.

Ik, ondergetekende:---------- (Naam en voornaam)

heb het document "informatiefiche voor deelnemers aan een studie" (informed consent IC_nl versie 1.0) pagina 1 tot en met 7 gelezen en er een kopij van gekregen. Ik stem in met de inhoud van het document en stem ook in deel te nemen aan deze studie.

Ik heb een kopij gekregen van dit ondertekende en gedateerde "toestemmingsformulier". Ik heb uitleg gekregen over de aard, het doel, de duur en de te voorziene effecten van de studie en over wat men van mij verwacht. Ik heb uitleg gekregen over de mogelijke risico's en voordelen van de studie. Men heeft me de gelegenheid en voldoende tijd gegeven om vragen te stellen over de studie en ik heb op al mijn vragen, ook medische, een bevredigend antwoord gekregen.

Ik stem ermee in om volledig samen te werken met de onderzoeksarts. Ik zal hem/haar op de hoogte brengen als ik onverwachte of ongebruikelijke symptomen ervaar. Ik bevestig dat ik de toeziende arts zal inlichten over eventuele geneesmiddelen, van welke aard ook, die ik in de maand voorafgaand aan de studie heb gebruikt, momenteel gebruik of van plan ben te gebruiken, ongeacht of ze al dan niet werden voorgeschreven.

Men heeft mij ingelicht over het bestaan van een verzekeringspolis in geval er letsel zou ontstaan dat aan de studieprocedures of aan de toediening van het (de) geneesmiddel(en) is toe te schrijven.

Ik ben me er van bewust dat deze studie werd goedgekeurd door een onafhankelijke Commissie voor Medische Ethiek verbonden aan het UZ Brussel en dat deze studie zal uitgevoerd worden volgens de richtlijnen voor de goede klinische praktijk en de verklaring van Helsinki, opgesteld ter bescherming van mensen deelnemend aan experimenten. Deze goedkeuring was in geen geval de aanzet om te beslissen om deel te nemen aan deze studie.

Ik mag me op elk ogenblik uit de studie terugtrekken zonder een reden voor deze beslissing op te geven en zonder dat dit op enigerlei wijze een invloed zal hebben op mijn verdere relatie met de onderzoeker.
Men heeft mij ingelicht dat zowel persoonlijke gegevens als gegevens aangaande mijn gezondheid, ras en geslacht worden verwerkt en bewaard gedurende minstens 30 jaar. Ik stem hiermee in en ben op de hoogte dat ik recht heb op toegang en op verbetering van deze gegevens. Aangezien deze gegevens verwerkt worden in het kader van medisch-wetenschappelijke doeleinden, begrijp ik dat de toegang tot mijn gegevens kan uitgesteld worden tot na beëindiging van het onderzoek. Indien ik toegang wil tot mijn gegevens zal ik mij richten tot de toeziende arts die verantwoordelijk is voor de verwerking.

Ik begrijp dat vertegenwoordigers van de Commissie Medische Ethiek of bevoegde overheden, mijn gegevens mogelijk willen inspecteren om de verzamelde informatie te controleren. Door dit document te ondertekenen, geef ik toestemming voor deze controle. Te allen tijde zal mijn privacy gerespecteerd worden.

Ik ben bereid op vrijwillige basis deel te nemen aan deze studie.

Naam van de vrijwilliger:

Datum:

Handtekening:

Ik bevestig dat ik de aard, het doel en de te voorziene effecten van de studie heb uitgelegd aan de bovenvermelde deelnemer.
De deelnemer stemde toe om deel te nemen door zijn/haar persoonlijk gedateerde handtekening te plaatsen.

Naam van de persoon die voorafgaande uitleg heeft gegeven:

Datum:

Handtekening:

Appendix 4b: French version

Information au patient

Le titre de l'étude

Examiner l'efficacité de mesurer votre tension artérielle à la consultation, à domicile par télésurveillance ou par un holter tensionnel de 24 h chez des patients hypertendus, sans ou avec une maladie rénale chronique.

Vous êtes invité(e) à participer volontairement à une étude clinique concernant 3 différentes techniques pour mesurer la tension artérielle.
Avant d'accepter votre participation à cette étude, veuillez d'abord lire ce formulaire attentivement. Ce formulaire d'information et de consentement décrit l'objectif de l'étude, les examens demandés, les bénéfices et éventuels risques liés à votre participation à cette étude. Il décrit également votre droit d'arrêter votre participation à tout moment. Vous avez le droit de poser à tout moment toutes les questions concernant les éventuels risques.

L'objectif de l'étude

L'objectif de cette étude est de déterminer si les différentes méthodes pour mesurer la tension artérielle sont équivalentes pour évaluer le bon contrôle de la tension.
Pendant deux périodes d'une semaine votre tension sera mesurée par les 3 différentes méthodes et en même temps votre appréciation des méthodes utilisées sera demandée.

Les investigateurs

Prof. Dr. P. Van der Niepen
Universitair Ziekenhuis Brussel
Service de Néphrologie et d'Hypertension artérielle
Avenue du Laerbeek, 101, 1090 Bruxelles, Belgique

M. X. Galloo (étudiant en médecine)
Universitair Ziekenhuis Brussel
Avenue du Laerbeek, 101, 1090 Bruxelles, Belgique

Infirmi(é)er(e)
Mme N. Marmitte
Universitair Ziekenhuis Brussel
Service de Néphrologie et d'Hypertension artérielle
Avenue du Laerbeek, 101, 1090 Bruxelles, Belgique

M. D. Van Ingelgem
Universitair Ziekenhuis Brussel
Service de Néphrologie et d'Hypertension artérielle
Avenue du Laerbeek, 101, 1090 Bruxelles, Belgique

Contact :
§Tél : 02/477 60 55
02/476 31 91
02/477 62 24

§ E-mail : Xavier.Galloo@vub.ac.be
Dirk.Vaningelgem@uzbrussel.be
Nathalie.Marmitte@uzbrussel.be
hemovnnp@uzbrussel.be

La description de l'étude

1. Introduction

Vous êtes invité(e), comme patient(e) hypertendu(e), à participer à une étude sur le contrôle de la tension artérielle. L'hypertension artérielle est définie comme une tension artérielle égale ou supérieure à 140/90 mmHg.
Une tension artérielle élevée peut être néfaste pour le cœur, les vaisseaux, le cerveau et les reins. C'est pourquoi l'hypertension artérielle doit être traitée par des médicaments (antihypertenseurs). Le but est d'atteindre une tension artérielle inférieure à 140/90 mmHg.
Patients dont la tension artérielle n'est pas bien contrôlée (= supérieur à 140/90 mmHg) sont à risque de maladies cardiaques ou vasculaires.
D'habitude la tension artérielle est mesurée dans le cabinet du médecin ou à domicile. La valeur tensionnelle à un moment précis de la journée ne présente pas nécessairement la vraie tension artérielle. Beaucoup de patients en effet ont une tension artérielle augmentée par l'effet dite de la blouse blanche. Ceci veut dire que la tension artérielle mesurée par le médecin est faussement trop élevée.
La meilleure méthode pour mesurer la tension artérielle réelle en journée et la nuit, est l'holter tensionnel de 24h. La procédure consiste de vous procurer un tensiomètre automatique. Une manchette est attachée autour de votre bras et connectée à l'enregistreur autour de votre ceinture. La tension artérielle sera mesurée toutes les 15 minutes en journée et toutes les 30 minutes la nuit. Le tensiomètre est ramené à l'hôpital le lendemain.
Une autre méthode pour mieux estimer la tension artérielle est l'automesure de la pression artérielle à la maison par le patient même. Avec un système de télésurveillance le patient mesure sa tension artérielle lui-même à la maison par un tensiomètre automatique et les résultats sont envoyés automatiquement par voie électronique aux investigateurs. Les patients reçoivent un tensiomètre automatique et adapté et mesurez la tension artérielle au moins 2 fois par jour (matin et soir). Cette méthode permet les médecins d'observer la tension artérielle des patients à distance. Les médecins peuvent intervenir immédiatement, voire de manière proactive pour ajuster la thérapie et en contrôler la fiabilité.
L'automesure de la tension artérielle permet d'obtenir votre tension artérielle à domicile et elle est de plus en plus conseillée par les médecins comme excellente.
Mais nous pensons que les valeurs de la tension artérielle mesurée par l'holter tensionnel de 24h et la tension artérielle mesurée à domicile par la méthode de télésurveillance ne sont pas égales.

Pour tester cette hypothèse cette étude est performée. Nous contrôlerons la tension artérielle, mesurée par un médecin à l'aide d'un tensiomètre automatique à la consultation, par un holter tensionnel de 24h et par une tensiométrie à la maison avec télésurveillance.

2. En pratique

→ Jour 1 (première visite) : la tension artérielle est mesurée trois fois à la consultation après 5 minutes de repos. Les noms et doses des antihypertenseurs sont registrés et vous êtes demandé de remplir un questionnaire sur votre état de santé générale. A la fin de la consultation le holter tensionnel de 24 h est attaché.
→ Jour 2 (deuxième visite) : quand vous ramenez le holter tensionnel, la tension artérielle est mesurée trois fois après 5 minutes de repos. Ensuite vous recevrez le tensiomètre électronique par

télésurveillance pour mesurer votre tension artérielle à domicile. Vous prenez la tension artérielle matin et soir pendant une semaine (sept jours). A chaque fois vous mesurez votre tension artérielle deux après 5 minutes de repos. Après une semaine vous ramenez le matériel à la consultation. Vous êtes demandés de remplir un questionnaire concernant votre appréciation des différentes méthodes.
→ Après 4 semaines (troisième visite) = jour 1
→ Le jour suivant (quatrième visite) = jour 2
Les mesures seront toujours faites au même bras parce-qu' il y a parfois des différences entre les bras.

Aucun autre examen n'est demandé dans cette étude, mais avec votre accord, des résultats d'autres examens disponibles dans votre dossier médical personnel de l'UZ Brussel, par exemple des résultats de prises de sang et des examens d'urines, pourraient être sollicités.

Les participants à l'étude

Les participants sont des volontair(e)s en bonne santé ou des patients hypertendus (oui ou non traité, sans ou avec une maladie Rénale chronique.
Les patients doivent être en état de comprendre et être d'accord de suivre les instructions du médecin traitant ou des investigateurs (sinon ils sont exclus). Des patients atteints d'une fibrillation auriculaire, d'une maladie cardiaque ou vasculaire récente, d' une autre maladie aiguë et grave, ne peuvent pas participer à l'étude.

Les procédures

Si vous acceptez de participer à l'étude, voici les tests et examens demandés:
→ une tensiométrie à la consultation
→ une tensiométrie par télésurveillance : la tensiométrie par télésurveillance se fait à l'aide d'un tensiomètre conventionnel, automatisé. Vous devez attacher la manchette du tensiomètre autour de votre bras non-dominant. La tension artérielle est mesurée automatiquement. Cette mesure n'est pas douloureuse. Les données sont envoyées à l'équipe de recherche par un GSM que vous est fournis.
→ un holter tensionnel de 24 h : vous obtenez un tensiomètre lors de votre visite. La manchette du tensiomètre est attachée autour de votre bras pour toute la durée de l'examen (24h, y compris la nuit). La manchette est connecté au tensiomètre = une boîte attachée à une ceinture. Le tensiomètre enregistre la tension artérielle automatiquement selon des intervalles fixes (= toutes les 15 minutes en journée et toutes les 30 minutes la nuit). L'appareil mémorise tous ces résultats. Une fois que l'examen est terminé, vous rendez l'appareil à la consultation de l'UZ Brussel.
→ vous devez remplir trois questionnaires (appelés le Morisky score, le HADS et le EQ- 5D-3L).

Les risques et bénéfices

Parfois des patients mentionnent que mesurer de la tension pendant 24h les dérangent pendant leurs activités quotidiennes. Si la tension artérielle est souvent élevée, la peau peut être rouge et sensible (légèrement douloureuse) en dessous la manchette.

Les bénéfices sont que vous et votre tension seront suivis de près pendant toute la durée de l'étude par une équipe spécialisée. Les risques liés à l'étude sont minimales. A tout moment le personnel médical est disponible pour vous assister et aider en cas de problèmes, effets secondaires.

Coûts associés à la participation

Les coûts des traitements et examens menés pour l'étude et qui ne font pas partie des soins habituels, sont à la charge du service de Néphrologie, UZ Brussel.

Compensation

Il n'y a pas de compensation prévue pour la participation à cette étude.

Protection de la vie privée

En concordance avec la loi de 8 décembre 1992 et la loi de 22 août 2002 vos données personnelles et votre participation à cette étude clinique demeureront strictement confidentielles. Vous ne serez pas identifié(e) ni par votre nom ni d'aucune autre manière dans aucun des dossiers, résultats ou publications en rapport avec l'étude.

Conformément aux directives des bonnes pratiques cliniques, votre dossier médical, dans la mesure où il est lié à l'étude clinique, sera examiné par des collaborateurs à cette étude qui sont tenus par le secret médical et par les autorités réglementaires, afin de contrôler les données et procédures de l'étude et de s'assurer que les informations sont exactes. Votre identité demeurera confidentielle, puisque les informations vous concernant seront identifiées uniquement par un numéro de patient unique et seront donc codées.

Les informations codées vous concernant pourront être transmises aux autorités réglementaires, au comité d'éthique, à d'autres médecins en collaboration avec le commanditaire de cette étude. Les informations vous concernant seront traitées électroniquement (c'est-à-dire par ordinateur) ou manuellement, et analysées afin de déterminer les résultats de cette étude. Vous avez le droit à tout moment de demander au médecin responsable de l'étude quelles sont les données collectées à votre sujet et quelle est l'utilité de ces données. Vous avez le droit de demander au médecin responsable de l'étude de vous permettre d'examiner vos informations personnelles et d'y apporter les éventuelles corrections jugées nécessaires.

Votre consentement à participer à cette étude implique que vous consentez également à l'utilisation de vos données médicales codées aux fins décrites ci-dessus et à leur transmission aux personnes et/ou instances susmentionnées.

Les résultats seront donc traités en parfaite compliance avec la Loi Belge sur la protection de la vie privée et la Loi sur les droits des patients.

Participation à l'étude et terminassions de l'étude

Votre participation à cette étude est entièrement volontaire et vous avez le droit de refuser d'y participer. Votre décision de participer ou non à cette étude ou de vous retirer de l'étude n'affectera en aucune manière votre traitement ultérieur par votre médecin responsable de l'étude ou au sein de cet hôpital.

Vous avez également le droit de vous retirer de l'étude à tout moment, même après avoir signé le formulaire de consentement. Vous n'aurez pas à fournir de raison au retrait de votre consentement à participer.

Assurance

Si vous ou vos ayants droit (famille) subissez un dommage lié à cette étude d'investigation, ce dommage sera indemnisé conformément à la loi relative aux expérimentations sur la personne humaine du 7 mai 2004. Vous ne devrez en aucun cas prouver la faute de qui que ce soit. Une assurance couvrant les risques et dommages qui pourraient résulter de cette étude a été contractée. Vous ou vos ayants-droit pouvez assigner l'assureur directement en Belgique.

Comité d'éthique

Cette étude clinique fut évaluée et approuvée par le Comité d'Ethique de l'UZ Brussel de la VUB.

Personnes à contacter si vous avez des questions à propos de l'étude

Si vous estimez avoir subi un dommage lié à l'étude ou si vous avez des questions à propos de l'étude ou à propos de vos droits en tant que patient participant à une étude clinique, maintenant, durant ou après votre participation, vous pouvez contacter l'équipe de recherche. Vous trouvez leurs données en haut de ce formulaire.

FORMULAIRE DE CONSENTEMENT
Partie uniquement destinée au/à la patient(e):

Examiner l'efficacité de mesurer votre tension artérielle à la consultation, à domicile par télésurveillance ou par un holter tensionnel de 24 h chez des patient hypertendus, sans ou avec une maladie rénale chronique.

Je soussigné(e) ---------- (nom, prénom) confirme être informé(e) sur l'étude et avoir reçu une copie de l' "Information au patient" (IC_fr version 1.0 dd 7/10/2013) et du "Formulaire de consentement". J'ai lu les informations et les ai comprises. Je suis d'accord avec le contenu de ce document et confirme de participer à l'étude.

Mon médecin m'a donné suffisamment d'informations à propos des conditions et de la durée de l'étude, ainsi que sur les effets attendus et secondaires de ce traitement. Par ailleurs, il m'a été donné suffisamment de temps pour peser l'information et pour poser des questions auxquelles j'ai reçu des réponses satisfaisantes.

Je consens de mon plein gré à participer à cette étude et à collaborer à tous les examens demandés. Je suis disposé(e) à fournir toute information concernant mes antécédents médicaux, ma consommation de médicaments et ma participation éventuelle à d'autres études.

Ils m'ont informé(e) de l'existence d'une assurance au cas ou moi ou un de mes ayants droit (famille) subissez un dommage lié à cette étude d'investigation.

Je comprends que cette étude clinique a été évaluée et approuvée par le Comité d'Ethique de l'UZ Brussel de la VUB.

J'autorise les responsables de l'étude et les autorités réglementaires à avoir accès à mon dossier médical. Mes données médicales seront traitées en toute confidentialité. Je suis conscient(e) de l'objectif dans lequel ces données sont recueillies, traitées et utilisées dans le cadre de cette étude. Je consens à ce que ces données médicales soient recueillies, traitées et utilisées, comme décrit dans l'information au patient.

J'ai compris que je peux arrêter ma participation à l'étude à tout moment après en avoir informé mon médecin, sans que cela puisse me porter préjudice.

Je participe à l'étude entièrement volontaire et je sais que j'ai le droit de refuser d'y participer.

Nom du volontaire: _____

Date: _____

Signature: _____

Partie uniquement destinée à l'équipe d'investigation
Je confirme que j'ai expliqué(e) la description, la procédure et les risques et bénéfices.
Le/La participant(e) consente à participer à l'étude par sa signature.

Nom de la personne qui a donné les informations : _____
(*Ce n'est pas nécessairement le médecin investigateur qui parcourt les informations et la procédure de consentement éclairé avec le patient, mais parfois un autre membre de l'équipe d'investigation*)

Date: _____

Signature: _____

Appendix 4c: Informed consent procedure

Effectiveness of clinic blood pressure monitoring, home blood pressure telemonitoring and ambulatory blood pressure monitoring in evaluating blood pressure control in hypertensive patients with and without chronic kidney disease
B.U.N. 14320131866

Principal Investigator: Prof. Dr. P. Van der Niepen
Sub-Investigator: Dhr. X. Galloo

Subject Name:

Datum:

Informed Consent getekend op (datum):

Version IC: 1.0/OKT - OCT/2013	IC_nl versie /IC_fr version
Vragen:	Geen vragen werden gesteld/ Alle vragen werden beantwoord
Er werden geen studieprocedures uitgevoerd vooraleer patiënt het IC tekende. Hij/Zij had voldoende tijd had om het IC door te nemen.	JA - NEEN
Kopie van het IC werd aan de patiënt overhandigd:	JA - NEEN

Sub-Investigator's Signature: _____ Date: _____

Principal Investigator's Signature: _____ Date: _____

Appendix 5: EQ-5D-3L questionnaire

Appendix 5a: Dutch version

Gezondheidsvragenlijst

Nederlandse versie voor België

(Dutch version for Belgium)

Zet bij iedere hieronder vermelde groep een kruisje in één hokje achter de zin die het best uw gezondheidstoestand van vandaag weergeeft.

Mobiliteit

Ik heb geen problemen met rondwandelen ❑

Ik heb enige problemen met rondwandelen ❑

Ik ben bedlegerig ❑

Zelfzorg

Ik heb geen problemen om voor mezelf te zorgen ❑

Ik heb enige problemen om mezelf te wassen of aan te kleden ❑

Ik ben niet in staat mezelf te wassen of aan te kleden ❑

Dagelijkse activiteiten *(bijv. werk, studie, huishouden, gezins- of vrijetijdsactiviteiten)*

Ik heb geen problemen met mijn dagelijkse activiteiten ❑

Ik heb enige problemen met mijn dagelijkse activiteiten ❑

Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren ❑

Pijn/klachten

Ik heb geen pijn of andere klachten ❑

Ik heb matige pijn of andere klachten ❑

Ik heb zeer ernstige pijn of andere klachten ❑

Angst/depressie

Ik ben niet angstig of depressief ❑

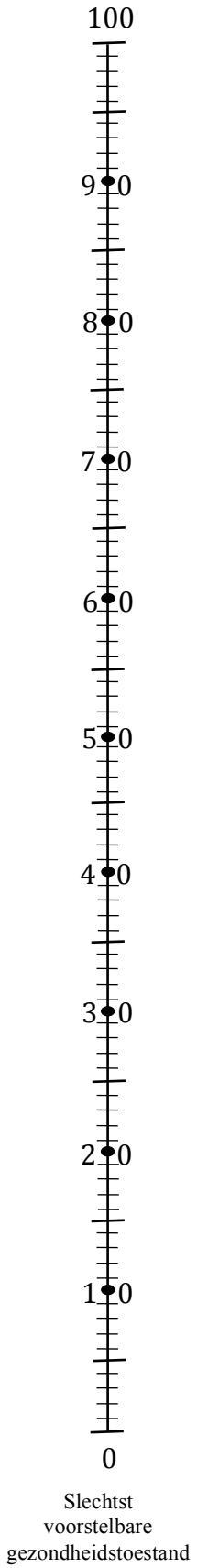
Ik ben matig angstig of depressief ❑

Ik ben erg angstig of depressief ❑

Om mensen te helpen bij het aangeven hoe goed of hoe slecht een gezondheidstoestand is, hebben we een meetschaal (te vergelijken met een thermometer) gemaakt. Op de meetschaal hiernaast betekent “100” de beste gezondheidstoestand die u zich kunt voorstellen, en “0” de slechtste gezondheidstoestand die u zich kunt voorstellen.

We willen u vragen op deze meetschaal aan te geven hoe goed of hoe slecht volgens u uw eigen gezondheidstoestand vandaag is. Trek een lijn van het hokje hieronder naar het punt op de meetschaal dat volgens u aangeeft hoe goed of hoe slecht uw gezondheidstoestand vandaag is.

Uw gezondheidstoestand vandaag



Appendix 5b: French version

Questionnaire sur la santé

Version française pour la Belgique

(French version for Belgium)

Veuillez indiquer, pour chacune des rubriques suivantes, l'affirmation qui décrit le mieux votre état de santé aujourd'hui, en cochant la case appropriée.

Mobilité

Je n'ai aucun problème pour me déplacer à pied ❑

J'ai des problèmes pour me déplacer à pied ❑

Je suis obligé(e) de rester alité(e) ❑

Autonomie de la personne

Je n'ai aucun problème pour prendre soin de moi ❑

J'ai des problèmes pour me laver ou m'habiller tout(e) seul(e) ❑

Je suis incapable de me laver ou de m'habiller tout(e) seul(e) ❑

Activités courantes (*exemples : travail, études, travaux domestiques, activités familiales ou loisirs)*

Je n'ai aucun problème pour accomplir mes activités courantes ❑

J'ai des problèmes pour accomplir mes activités courantes ❑

Je suis incapable d'accomplir mes activités courantes ❑

Douleurs/gêne

Je n'ai ni douleur ni gêne ❑

J'ai des douleurs ou une gêne modérée(s) ❑

J'ai des douleurs ou une gêne extrême(s) ❑

Anxiété/dépression

Je ne suis ni anxieux(se), ni déprimé(e) ❑

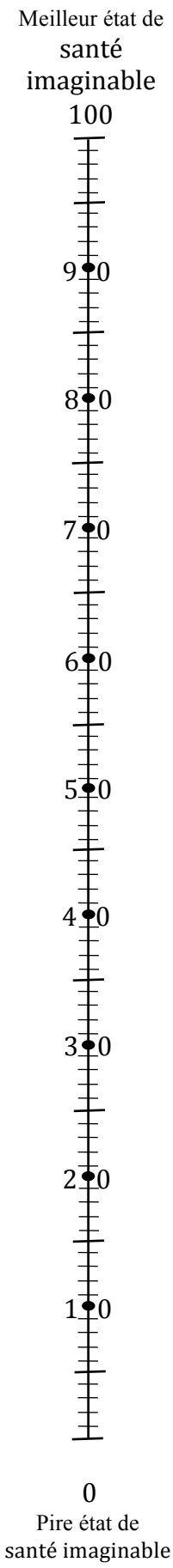
Je suis modérément anxieux(se) ou déprimé(e) ❑

Je suis extrêmement anxieux(se) ou déprimé(e) ❑

Pour vous aider à indiquer dans quelle mesure tel ou tel état de santé est bon ou mauvais, nous avons tracé une échelle graduée (comme celle d'un thermomètre) sur laquelle 100 correspond au meilleur état de santé que vous puissiez imaginer et 0 au pire état de santé que vous puissiez imaginer.

Nous aimerions que vous indiquiez sur cette échelle graduée à quel endroit vous situez votre état de santé aujourd'hui. Pour cela, veuillez tracer une ligne allant du cadre ci-dessous à l'endroit qui, sur l'échelle, correspond à votre état de santé aujourd'hui.

Votre état de santé aujourd'hui



Appendix 6: Hospital Anxiety and Depression Scale (HADS) questionnaire

Appendix 6a: Dutch version

Evaluatie van de angst en depressie

HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

Onderstaande vragenlijst peilt naar uw emotionele toestand en geeft de arts een beeld van uw angst- en depressieniveau. Gelieve elke vraag grondig te lezen en een kruisje te zetten in de kolom met het nummer dat het beste overeenkomt met uw toestand.

0 = Helemaal niet of nooit van toepassing
1 = Een beetje of soms van toepassing
2 = Behoorlijk of vaak van toepassing
3 = Zeer zeker of meestal van toepassing

De items op de vragenlijst die betrekking hebben op angst:

	0	1	2	3
Ik voel me gespannen.				
Ik krijg een soort angstgevoel alsof er iets ergs staat te gebeuren.				
Verontrustende gedachten gaan door mijn hoofd.				
Ik kan op mijn gemak zitten en me ontspannen.				
Ik krijg een soort benauwd, gespannen gevoel, vlinders in de buik.				
Ik voel me rusteloos en moeten in beweging blijven.				
Ik krijg plotseling gevoelens van paniek.				

De items die betrekking hebben op depressie:

	0	1	2	3
Ik geniet nog steeds van dingen waar ik vroeger van genoot.				
Ik kan lachen en de grappige kant van de dingen inzien.				
Ik voel me vrolijk.				
Ik heb het gevoel alsof ik vertraagd ben.				
Ik heb geen interesse meer in mijn uiterlijk.				
Ik kijk met plezier naar dingen.				
Ik kan genieten van een goed boek of een radio-of tv-programma.				

Appendix 6b: French version

Evaluation de l'anxiété et de la dépression

HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

Ce questionnaire a été conçu de façon à permettre à votre médecin de se familiariser avec ce que vous éprouvez vous-même sur le plan émotif. Lisez chaque série de questions et mettez une croix dans la colonne correspondante à la réponse qui exprime le mieux ce que vous avez éprouvé au cours de la semaine qui vient de s'écouler.

3 = Presque toujours
2 = Très souvent
1 = Parfois - rarement
0 = Jamais

Evaluation de l'anxiété:

	0	1	2	3
Je me sens tendu(e) ou énervé(e).				
J'ai une sensation de peur comme si quelque chose d'horrible allait m'arriver.				
Je me fais du souci.				
Je peux rester tranquillement assis(e) à ne rien faire et me sentir décontracté(e).				
J'éprouve des sensations de peur et j'ai l'estomac noué.				
J'ai la bougeotte et n'arrive pas à tenir en place.				
J'éprouve des sensations soudaines de panique.				

Evaluation de la dépression:

	0	1	2	3
Je prends plaisir aux mêmes choses qu'autrefois.				
Je ris et vois le bon côté des choses.				
Je suis de bonne humeur.				
J'ai l'impression de fonctionner au ralenti.				
Je ne m'intéresse plus à mon apparence.				
Je me réjouis à l'idée de faire certaines choses.				
Je peux prendre plaisir à un bon livre ou à une bonne émission de radio ou de télévision				

Appendix 7: Morisky questionnaire

Appendix 7a: Dutch version

©Morisky Medication Adherence Scale (MMAS-8-Item)

Beste Mevrouw, Beste Mijnheer,

Neemt u medicatie tegen hoge bloeddruk?
Uit onderzoek blijkt dat een regelmatige inname van geneesmiddelen tegen hoge bloeddruk niet altijd gemakkelijk is. Patiënten die reeds deelgenomen hebben aan dergelijk onderzoek geven hiervoor zeer verschillende redenen op.
Om u beter te kunnen begeleiden in uw behandeling tegen hoge bloeddruk en om een beter inzicht te krijgen in deze problematiek, zouden we willen weten hoe het in onze praktijk gesteld is met de inname van geneesmiddelen tegen hoge bloeddruk. Wij zijn geïnteresseerd in uw persoonlijke ervaring.
Het is om die reden dat wij u willen vragen de vragenlijst op keerzijde in te vullen en hem ons terug te bezorgen tijdens de consultatie.
Alle gegevens worden anoniem verwerkt en kunnen gebruikt worden voor wetenschappelijke presentaties, publicaties of communicatie naar de media.
Het invullen van deze vragenlijst en het terugbezorgen hiervan aan uw arts, wordt gezien als uw akkoord om uw gegevens te mogen verzamelen.
Uw deelname is uiteraard volledig vrijblijvend.
Uw beslissing om hieraan al dan niet deel te nemen, zal op geen enkele manier een invloed hebben op de relatie met uw arts.
Mogen wij u vragen om de vragenlijst op keerzijde in te vullen en deze aan uw arts te bezorgen.
Beantwoord elke vraag op basis van uw persoonlijke ervaringen met uw geneesmiddelen tegen hoge bloeddruk.
Er zijn geen goede of slechte antwoorden. Vul voor elke vraag maar één kruisje in.
Vergeet niet uw volledig ingevulde vragenlijst terug te bezorgen aan uw arts.

Hartelijk dank voor uw deelname.

Prof. dr. Van der Niepen Patricia

Ingevuld op: _____ (dag) _____ (maand) _____ (jaar) (in te vullen door de patiënt)

1. **Vergeet u soms uw pillen tegen hoge bloeddruk in te nemen?**
   ○ Ja ○ Neen

2. **Soms nemen mensen hun geneesmiddelen niet in, niet omdat ze het vergeten, maar om een andere reden. Denk nu aan de afgelopen twee weken. Hebt u op sommige dagen uw geneesmiddelen tegen hoge bloeddruk niet ingenomen?**
   ○ Ja ○ Neen

3. **Hebt u ooit de dosis verminderd of bent u ooit gestopt met het innemen van uw geneesmiddelen tegen hoge bloeddruk zonder uw arts daarover in te lichten, omdat u zich slechter voelde toen u ze wel innam?**
   ○ Ja ○ Neen

4. **Wanneer u reist of weg bent van huis, vergeet u dan soms om uw geneesmiddelen tegen hoge bloeddruk mee te nemen?**
   ○ Ja ○ Neen

5. **Hebt u gisteren uw geneesmiddelen tegen hoge bloeddruk ingenomen?**
   ○ Ja ○ Neen

6. **Stopt u soms met het innemen van uw geneesmiddelen tegen hoge bloeddruk wanneer u vindt dat u uw symptomen onder controle hebt?**
   ○ Ja ○ Neen

7. **Voor sommige mensen is het een groot ongemak om elke dag geneesmiddelen tegen hoge bloeddruk in te nemen. Vindt u het soms een gedoe om u aan het schema van uw behandeling tegen hypertensie te houden?**
   ○ Ja ○ Neen

8. **Hebt u het moeilijk om u te herinneren al uw geneesmiddelen tegen hoge bloeddruk in te nemen?**
   ○ Nooit/zelden ○ Occasioneel ○ Soms ○ Regelmatig ○ Altijd

Appendix 7b: French version

©Morisky Medication Adherence Scale (MMAS-8-Item)

Chère Madame, Cher Monsieur,

Prenez-vous des médicaments pour traiter l'hypertension ou une autre maladie?
Différentes études montrent que certains patients éprouvent des difficultés à prendre leurs médicaments comme leur médecin le demande et ceci pour différentes raisons.
Afin de vous accompagner au mieux dans votre traitement contre l'hypertension et de mieux comprendre cette problématique, nous souhaiterions connaître votre expérience personnelle en rapport avec les médicaments prescrits.
Dès lors nous vous serions très reconnaissants de remplir le questionnaire au verso et de nous le remettre lors de la consultation.
L'ensemble des données recueillies sera traité de manière anonyme. Elles pourraient être utilisées dans le cadre de présentations scientifiques, de publications ou de communications vers les medias.
Le fait de remplir ce questionnaire et de le remettre à votre médecin est considéré comme marquant votre accord de participer à ce recueil de données.
Votre participation est bien entendu entièrement volontaire.
Votre accord ou refus ne modifieront en rien les soins et l'attention prodigués par votre médecin.
Le questionnaire se trouve au verso.
Merci de bien vouloir répondre à chaque question en fonction de votre expérience personnelle en rapport avec les médicaments prescrits.
Il n'y a ni bonnes, ni mauvaises réponses. Veuillez, s'il vous plait, ne cocher qu'une croix par question.
N'oubliez pas de remettre le questionnaire dûment rempli à votre médecin.

D'avance merci pour votre participation.

Prof. dr. Van der Niepen Patricia

Complété le ___ (jour) ___ (mois) ___ (année) (à remplir par le patient)

1. **Vous arrive-t-il d'oublier de prendre vos médicaments pour l'hypertension ?**
   ○ Oui ○ Non

2. **Il arrive que l'on ne prenne pas ses médicaments pour des raisons autres que l'oubli. En repensant aux deux dernières semaines, y a-t-il eu des jours où vous n'avez pas pris votre médicament pour l'hypertension?**
   ○ Oui ○ Non

3. **Avez-vous déjà réduit votre dose de votre médicament pour l'hypertension ou arrêté de le prendre sans en parler à votre médecin parce que vous vous sentiez moins bien quand vous le preniez?**
   ○ Oui ○ Non

4. **Lorsque vous voyagez ou quittez la maison, vous arrive-t-il d'oublier d'emporter votre médicament pour l'hypertension ?**
   ○ Oui ○ Non

5. **Avez-vous pris votre médicament pour l'hypertension hier?**
   ○ Oui ○ Non

6. **Lorsque vous avez l'impression que vos symptômes sont contrôlés, vous arrive-t-il d'arrêter de prendre votre médicament pour l'hypertension?**
   ○ Oui ○ Non

7. **Pour certaines personnes, prendre un médicament pour l'hypertension tous les jours est gênant. Vous arrive-t-il de trouver ennuyeux de devoir respecter votre plan de traitement contre l'hypertension ?**
   ○ Oui ○ Non

8. **Avez-vous du mal à vous souvenir de prendre tous vos médicaments pour l'hypertension?**
   ○ Jamais/ Rarement ○ Rarement ○ Parfois ○ Fréquemment ○ Toujours

Appendix 8: Questionnaire on satisfaction concerning type of BP measurement

Appendix 8a: Dutch version

Vragenlijst rond tevredenheid van het type bloeddrukmeting

1. 24-uurs ambulante bloeddrukmeting

   O helemaal tevreden
   O tevreden
   O niet tevreden niet ontevreden
   O niet tevreden
   O helemaal niet tevreden

2. Thuismeting met telemonitoring

   O helemaal tevreden
   O tevreden
   O niet tevreden niet ontevreden
   O niet tevreden
   O helemaal niet tevreden

3. Welke bloeddrukmeting zou u verkiezen om opgevolgd te worden (gelieve een kruisje te plaatsen bij de methode die uw voorkeur geniet)

   O Thuismeting met telemonitoring

   O 24-uurs ambulante bloeddrukmeting

Appendix 8b: French version

Questionnaire pour évaluer votre satisfaction concernant les méthodes pour mesurer la tension.

1. Tensiométrie ambulatoire de 24 heures

   O complètement satisfait
   O satisfait
   O ni satisfait ni insatisfait
   O insatisfait
   O complètement insatisfait

2. Tensiométrie à la maison par télésurveillance

   O complètement satisfait
   O satisfait
   O ni satisfait ni insatisfait
   O insatisfait
   O complètement insatisfait

3. Quelle méthode préférerez-vous pour être suivi (cochez la méthode que vous préfèreriez)

   O Tensiométrie à la maison par télésurveillance

   O Tensiométrie ambulatoire pendant 24 heures

Universitair Ziekenhuis Brussel

Vrije Universiteit Brussel

COMMISSIE MEDISCHE ETHIEK (O.G. 016)
Reflectiegroep Biomedische Ethiek
Laarbeeklaan 101
1090 BRUSSEL

el + 32 2 477 55 84
Fax + 32 2 477 55 94
commissie.ethiek@uzbrussel.be

Meeting date: 30-10-2013

Ons Kenmerk : 2013/296

MEMBERS OF THE MEDICAL ETHICS COMMITTEE UZ BRUSSEL - VUB (since 03-10-2013)

Name	Function	Gender	participated in vote	present
Prof. Dr. Em. A. Van Steirteghem, MD	CHAIRMAN UZ BRUSSEL	M	☒	☒
Dr. J. Marchand, MD	VICE- CHAIRMAN Pediatrics UZ BRUSSEL	M	☒	☒
Dr. Y. Adriaenssens, MD	General Practitioner Van Hoeystraat 7, Mechelen	M	☐	☐
Dr. K. Beeckman, PhD	Nursing and Midwifery research group UZ BRUSSEL	F	☒	☒
Dr. Apr. V. Caveliers, PhD	Pharmacist UZ BRUSSEL	F	☐	☐
Prof. Dr. H. De Boeck, MD	Pediatric Orthopedics UZ BRUSSEL	M	☒	☒
Prof. Dr. J. De Grève, MD	Medical Oncology UZ BRUSSEL	M	☒	☒
Prof. Dr. E. De Groot, MD, Mr. of Laws	General practitioner and Lawyer - Tuyaertstraat 30, Boom	M	☐	☐
Prof. Dr. J. De Mey, MD	Radiology UZ BRUSSEL	M	☒	☒
Mrs. M. De Win	External Member	F	☐	☐
Mr. D. Danschutter	Head Nurse UZ BRUSSEL	M	☐	☐
Prof. Dr. P. Haentjens, MD	Faculty of Medicine and Pharmacy VUB	M	☒	☐
Prof. Dr. P. Lacor, MD	Internal Medicine UZ BRUSSEL	M	☒	☒
Prof. Dr. J. Poelaert, MD	Anesthesiology UZ Brussel	M	☒	☐
Prof. Dr. J. van der Werff ten Bosch, MD	Pediatrics UZ BRUSSEL	F	☒	☒
Prof. Dr. T. Vanhaecke, MD	Toxicology - Faculty of Medicine and Pharmacy VUB	F	☐	☐

If member of the Ethics Committee, the investigator does not participate to the vote