HYPERTENSION MANAGEMENT IN PRIMARY CARE: COULD LESS MEAN MORE?

Hypertension management in primary care: could less mean more?

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Panta rhei

Heraclitus, ca. 540-480 v. Chr.

Contents

Chapter 1

General Introduction

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Relevance of research in hypertension

This thesis is yet another on the topic of hypertension. With 65,200,000 hits in Google and 343,883 in Pubmed (22nd of April 2012) it has been an intensely studied subject for decades. One can wonder: are more citations really needed? In many of these citations the introductory words vary on the following theme:

"Hypertension is the most relevant risk factor for cardiovascular disease. Its worldwide prevalence is reported to be 20-26%. [1]Diagnosis is relatively straightforward and treatment options are multiple, cheap and widely available.[2;3] Treatment is worthwhile, each 10 mmHg reduction in systolic blood pressure results in 21% reduction of coronary heart disease and 37% reduction of stroke.[4;5] However, despite this knowledge the rates of diagnoses (50-70%) and control (30-50%) have remained suboptimal over the last decades.[6;7]"

While often these citations addressed the dismal control of hypertension, this constant repetition seems to have numbed the minds of doctors. Although some population studies demonstrate that control rates do improve [6;8], this improvement is still modest and we should not accept that results are not better than they are.

The question then rises: how to improve hypertension control?
One option could be to intensify screening in order to find all those patients with unrecognised hypertension. Additional options are the use of stricter targets, the development of new, more effective drugs, improvement of practice performance indicators and the creation of incentives to follow guidelines.
Paradoxically, the research as described in this thesis is not about "more" but about "less" and is an attempt to reduce false positive labelling of hypertension and to contribute to the exploration of a more efficient use of the available medication by personalised antihypertensive medicine.

Hypertension management in primary care

Optimal control of hypertension starts with a correct determination of the blood pressure status of a patient and a subsequent correct diagnosis of hypertension. The correctly determined blood pressure should then be interpreted in the context of the total cardiovascular risk profile. This will result in a conclusion about the type of hypertension (primary or secondary), on whether or not to start medical treatment and if so, with what class of antihypertensive medication.
These steps are described in depth in guidelines on hypertension management which serve as support for clinicians and as the professional standard of care.[2;3;9] It is assumed that a guideline and its revisions (update with most recent scientific knowledge) will improve hypertension control. Adherence to guidelines by physicians is needed to actually achieve this improvement. The rather modest improvement of hypertension control rates over the last decades suggests that suboptimal physician adherence may be one of the factors to explain mediocre control of hypertension.

We wanted to enhance our understanding of hypertension management in primary care by exploring how the process and outcome of hypertension management was influenced by the Dutch guideline on hypertension management and its revisions.

Diagnosis

The apparent simplicity of a blood pressure measurement is deceptive; compared to other cardiovascular risk factors, assessment of blood pressure is probably the most complicated.
Factors impeding correct determination of blood pressure
Until now, office blood pressure measurement (OBPM) has been the cornerstone for diagnosis and management of hypertension.[2;3;9] Unfortunately, OBPM is prone to different types of error, which in daily practice often will lead to an overestimation of the true blood pressure level. Therefore, guidelines include extensive protocols on how to measure blood pressure in a standardized way to eliminate most types of measurement error. This error can occur on the level of the observer, the patient, the measurement device and the environment of measurement.[10;11] Several studies have shown that blood pressure as measured by usual practice overestimates true systolic blood pressure by 10-14 mmHg as compared to blood pressure measured strictly according to guidelines.[12;13]

Blood pressure is subject to substantial biological variability both short term (minutes-hours) and long term (weeks-months).[14-17] This variability introduces noise in the assessment of the usual or “true” blood pressure of a patient and requires determination of a mean blood pressure based on multiple measurements over a prolonged period of time. It is this mean blood pressure that is considered to be the most important predictor of cardiovascular disease.[2;3;9]

Box 1: Definitions [3;25]

White coat effect:
Condition of increased blood pressure measured by clinical staff in a clinical setting compared to blood pressure measured at home or during daily life. It is attributed to an alerting reaction, anxiety and/or conditioned response

White coat hypertension:
Condition when office blood pressure is persistently elevated (≥ 140/90 mmHg) while daytime, 24-hour or home blood pressure is within the normal range

Masked hypertension:
The reverse phenomenon of white coat hypertension, patients with normal (< 140/90 mmHg) office blood pressure but with elevated ambulatory or home blood pressure (≥ 135/85 mmHg)

Besides measurement error the phenomenon of "white coat effect" (Box 1) also results in overestimation of true blood pressure. Unfortunately, this effect cannot be overcome with a fully standardized auscultatory blood pressure measurement. The prevalence of white coat effect is reported to be around 25%, depending on the studied population.[18;19] Although some individual studies have shown that prognosis of patients with white coat effect is slightly worse compared to normotensive patients [20;21], data from a recent meta-analysis suggest that prognosis is the same.[22] The introduction of automated, oscillometric blood pressure measurement devices enabled two seemingly straightforward methods of diagnosing the white coat effect: 24-hour ambulatory blood pressure measurement (24-hour ABPM) and home blood pressure measurement (HBPM).[3;10;23;24]

In HBPM patients ideally take two consecutive measurements both in the morning and the evening for seven days in a row of which the mean of the last six days is used as outcome.[3;23] With 24-hour ABPM, blood pressure is measured each 15-20 minutes in the daytime and each 30-60 minutes at night and results in several variables of which mean daytime, 24-hour and night time seem to be the most important.[3;24]
These methods, however come with some disadvantages. 24-hour ABPM is costly, not suitable for all patients and because sleep is often disturbed many patients do not like to have 24-hour ABPM more than once.[26] HBPM is prone to measurement error, patients need to be able to understand and execute the measurement protocol and some patients may cheat with measurements or measurement results.[27;28]

Conception of the idea to validate serial automated OBPM (AOBPM)
Ideally, a simple method in the office would be able to overcome measurement bias and detect the white coat effect, thus avoiding overdiagnosis and overtreatment. In addition this measurement should be standardised, easy to execute correctly by all types of health care staff, patient friendly and straightforward to implement in daily practice.
We were inspired by outpatient hypertension clinics that used a blood pressure measurement lasting 30 minutes in supine patients alone in a quiet and comfortable room to estimate "basal" or "true" blood pressure. A purpose built measurement device was used for these serial, automated blood pressure measurements. Because of its costs wide scale use of this device in general practice seemed unlikely. In addition, proper validation of this measurement method was lacking. We therefore decided to validate a 30-minute AOBPM using a 24-hour ABPM device. These devices have become routine equipment for most Dutch general practices or are readily available in most primary care diagnostic centres.

Study of the literature at the time of conception of our idea revealed that data on AOBPM were exceptionally scarce. Some research had shown the use of ABPM in shorter time periods from 12 to 4 hours, but not shorter.[29-31] One research group had just started to study AOBPM with the use of a purpose built device (BPTru) able to measure blood pressure five times consecutively at one or two minute intervals.[32;33] This device was also expensive and the short measurement time conflicts with data suggesting that blood pressure in serial measurements reaches a steady state not before 10 minutes.[34]

Treatment

Personalized medicine

Once a patient is correctly diagnosed with essential hypertension and the indication for medical treatment is set, lack of adherence to relevant guidelines by physicians and lack of adherence to prescribed treatment by patients are the two most important causes of suboptimal hypertension control.[8;35]

Personalised medicine is suggested to be one of several approaches that could improve treatment adherence of patients and as such might be useful in hypertension management. In this thesis we define personalised medicine as an approach where individual patient characteristics are used to identify the best possible treatment for that particular patient. This approach assumes that one or more patient characteristics have the ability to predict the response to treatment and enable selection of the drug of first choice for a given patient. This selected drug should have the best efficacy with the lowest risk of adverse events. As a consequence patients will be more motivated to continue treatment.[36] This should then result in a reduction of the number of drugs needed to reach treatment goals.

Data from several studies suggest that patient tailored treatment is indeed possible in hypertension management. In primary care, physicians choose from four different classes of antihypertensive drugs to start treatment: angiotensin converting enzyme inhibitors (ACEi), angiotension receptor blockers (ARB), β blockers, calcium channel blockers (CCB) and/or diuretics. Although meta-analyses have concluded that these different classes of antihypertensive medication are on average equally efficacious in blood pressure reduction,[37;38] several other studies have shown that at the patient level large intra-individual differences in blood pressure response to these different classes exist.[39-41]

The most widespread explanation for these intra-individual differences in response comes from a simplified pathophysiological model of essential hypertension in which patients can be positioned on a scale ranging from high renin, vasoconstriction-driven hypertension to low renin, salt-sensitive/volume-driven hypertension.[42] This model was formulated only some years after the discovery of renin-angiotensin-aldosterone-system (RAAS) around 1960.[43;44]

In combination with knowledge on the working mechanism of the different classes of antihypertensive drugs in theory this model could be the key to successful personalised hypertension management in patients with essential hypertension. After all, ACEi, ARB and beta-blockers suppress the RAAS and therefore might work best in high renin hypertension. In contrast, diuretics and CCB reduce sodium and volume and might work better in volume driven (low renin) hypertension. Based on this theory plasma renin, but – as proven or assumed surrogates for renin status – also age, ethnicity, BMI and waist circumference have been studied as potential predictive variables (table 1).

Besides this renin based model, alternative concepts are less well described and have a limited evidence base. Both the role of sex, through hormonal influences on blood pressure regulation [45] and NT-proBNP, in relation to obesity driven down regulation [46;47], in theory could have predictive potential.

Previous research on predictors and its limitations

The search for predictors has been limited to a relatively small number of studies which have had conflicting results as can be seen in Table 1. Only the role of ethnicity as predictor of treatment response has been acknowledged by all international guidelines.[2;3;9;48]

Many of the studies addressing personalised hypertension management came with serious methodological and practical limitations. First of all the correct measurement of renin has long been subject of debate. Although current assays of plasma renin activity and plasma renin concentration are now reliable, previous assays had low inter-laboratory reproducibility [69-71] which is likely to have contributed to the inconclusive results of previous studies. In addition, laborious demands of previous plasma renin activity assays, particularly if sodium profiling was required, were never successfully implemented in routine primary care. Second, in most studies women were heavily underrepresented. Third, quite a number of studies seemed to be rather underpowered [50;54;59;63-65] to draw firm conclusions. Fourth, only a small number of studies was primarily aimed at identifying predictors of treatment response. Finally, many studies presented data of diastolic blood pressure as opposed to current guidelines that advocate management based on systolic blood pressure.

Moreover only a very limited number of studies involved patients included in primary care. The patient selection from often specialised hypertension clinics may have introduced bias which limits generalisability to the general practice population.[72] Selection of patients in these specialised clinics is prone to include more complicated types of hypertension. The relative low mean age of patients in many of these studies points in that direction. This age was often considerably lower than the mean age of diagnosis of hypertension in general practice populations, which lies around 55-60 years.[73;74]

Therefore we developed a study with the primary objective to identify predictors of the antihypertensive response to two classes of antihypertensive drugs with different mechanisms of action (ARB and diuretic) in a representative sample of the general practice population and with a set of potential predictors that are feasible to implement in the general practice setting.

Objectives of this thesis

Our first objective was to improve the understanding of the process and outcome of hypertension management in relation to the publication of the guidelines on hypertension of the Dutch College of General Practitioners. Our research question was:

What is the impact of guideline revisions on the process and outcome of hypertension management in primary care? (Chapter 2)

Second, we aimed to improve the diagnosis of hypertension by validating the concept of an AOBPM in a primary care population using an ABPM device. Such type of measurement would be much quicker than ABPM and HBPM, easier and more patient-friendly in repeat measurements and suitable for patients not willing or able to use ABPM or HBPM. Our research questions were:

Is there agreement between the sitting 30-minute AOBPM and standardized OBPM? (Chapter 3)

What is the reproducibility of the sitting 30-minute AOBPM? (Chapter 3)

Is there agreement between the sitting 30-minute AOBPM and daytime ABPM? (Chapter 4)

Is there agreement between the supine 30-minute AOBPM and daytime ABPM? (Chapter 5)

Third, we questioned whether we could identify patient characteristics that predict blood pressure response to two classes of antihypertensive drugs, each interfering with a different pathophysiological pathway of hypertension. We purposely selected patient characteristics that have been validated, are reproducible and can easily be used in primary care. Results of this study may help to improve hypertension treatment and control. Our research question was:

Are there patient characteristics that can predict the response to either hydrochlorothiazide (diuretic) or valsartan (ARB) in the treatment of newly diagnosed hypertensive patients in primary care? (Chapter 6)

Finally, we have put the results of our findings in the perspective of changes in society and the medical profession. Our research tried to contribute to reduction of false positive diagnoses and overtreatment of hypertension. However, we have noticed that medico-legal changes, pay for performance, societal perception on health, autonomy and risk seems to put pressure on doctors to overdiagnose and treat rather than vice versa. In our essay we propose a change for the better. (Epilogue)

Table 1. Overview of available evidence for and against potential predictors of treatment response to the four major classes of antihypertensive medication

	ACEi	β-blocker	CCB	Diuretic
Renin				
Predictive	41;49-52	39;52-55	50;56	57
Not predictive	39;40	40;41;58	39-41;59	40;41;58
Age				
Predictive	-	60;61	-	62
Not predictive	39-41;50;63; 64	39-41;61;62;65	39-41;50;59;63; 66;67	40;41;64
BMI				
Predictive	68	-	-	-
Not predictive	41	41	41	41;57
Sex				
Predictive	64	-	-	57;64
Not predictive	-	-	-	-

All numbers refer to references;
BMI = body mass index;
ACEi = angiotensin converting enzyme inhibitor;
CCB = calcium channel blocker

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Chapter 2

The influence of guideline revisions on the process and outcome of hypertension management in general practice: A descriptive study

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Abstract

Background: Blood pressure does not reach guideline targets in the majority of hypertensive patients. Longitudinal data from general practice records on trends in hypertension management and the influence of guideline changes are lacking.

Objective: To describe the longitudinal impact of guideline revisions on the process and outcome of hypertension management in a primary care based database.

Methods: We extracted data from the Nijmegen Monitoring Project (NMP), an academic practice-based research network with 50.000 patients listed. Based on the years of publication of the first Dutch guideline on hypertension (1991) and two revisions (1997 and 2003), we formed three cohorts of patients newly diagnosed with hypertension. We compared data such as patient characteristics, 2-year blood pressure course, type of first-choice antihypertensive drugs, and number of medications after 2 years of treatment.

Results: Both the mean age at time of diagnosis of hypertension and pulse pressure rose between cohorts. In agreement with revisions in the guidelines, the use of diuretics as first-choice drugs increased significantly from the first to the last cohort. The percentage of patients with three or more antihypertensive drugs remained equal. The relative 2-year systolic blood pressure decline did not differ with clinical relevance between the cohorts.

Conclusion: Our study has demonstrated that general practitioners achieve substantial and prolonged blood pressure reduction. However, guideline revisions do not seem to influence the amount of reduction, despite clear formulation of stricter treatment goals. In addition to qualitative research to identify the causes of this phenomenon, research to evaluate the effect of expert support systems on risk awareness and risk gain by additional treatment is necessary.

Introduction

International guidelines on hypertension and cardiovascular risk management stress the importance of strict blood pressure regulation, defining targets that have become increasingly demanding over the last few decades.[1-5] Despite these guidelines, blood pressure decrease - often expressed as control rates - appears to be insufficient. In addition, these rates have improved little in recent decades.[6] Control rates can easily be misinterpreted or misused, because they depend highly on the population and hypertension guideline under study.[7,8] Therefore, research data on quality of care solely based on control rates need to be scrutinized with caution. The current approach to hypertension in the context of cardiovascular risk management demonstrates a lack of cost effectiveness in ''controlling'' all hypertensive (≥ 140/90 mmHg) patients in primary care or the open population.[3,4] Of course, hypertension management in general practice could be improved. Both patient-related factors (e.g., comorbidity, poor treatment adherence) and doctor-related factors (e.g., lack of knowledge of guideline content, disagreement with guidelines) contribute to substandard treatment of population-based blood pressure[7]. However, it is hard to accept that all the efforts of both researchers and guideline developers to improve blood pressure outcomes seem to have been of little value. We hypothesized that interpretation of the progress (or lack thereof) of blood pressure management over the last few decades is biased by comparing data of different populations in different settings using different types of guidelines (or using current guideline definitions retrospectively). Therefore, we studied the impact of guideline revisions on the process and outcome of hypertension management in one primary care based database that has continuously and structurally monitored hypertension management since 1986: the Nijmegen Monitoring Project, the Netherlands.

Methods

Database

We extracted data from the Nijmegen Monitoring Project (NMP), a research database involving nine practices. The practices were fully computerized and had approximately 50.000 patients listed in total, with a sex and age distribution representative for the general Dutch population. The historical background of the NMP has been described in further detail in the editorial of this issue. The database was founded in 1986 to monitor the management of three common chronic conditions: hypertension, diabetes mellitus, and chronic obstructive pulmonary disease. A specific data extraction form was filled in for each condition-related consultation. In the case of hypertension, several aspects were recorded: the diagnostic process; cardiovascular risk factors; type of treatment (with or without medication); initiation of drug treatment; type of medication; changes in medication or dosage; and control/evaluation moments. The quality of the data was ascertained by monthly meetings of representatives of all nine practices on quality control, knowledge, and protocol development, and annual feedback on process and outcome.

Blood pressure management

Practice protocols for blood pressure measurement and management (including diagnosis) of hypertension are based on the guidelines of the Dutch College of General Practitioners (most recent guideline: ''Cardiovascular Risk Management'', 2006). [9] Over the last few decades,

protocols have been adjusted when guideline updates contained relevant changes. Since the start of the NMP, the first hypertension guideline and two guideline updates have been published.[1-3]

Population and data collection

Based on the year of publication of the original 1991 and revised (1997 and 2003) hypertension guidelines, we formed three cohorts of patients newly diagnosed with hypertension. Patients for cohort 1 were selected in the period 1992-1996; for cohort 2 in the period 1998-2002; and for cohort 3 in the period 2004-2006. Not all hypertensive patients of the NMP practices were included in the study cohorts. Only patients treated with medication, with follow-up data covering a minimum of 2 years, and at least one blood pressure related consultation per year were included. In Table 1, we have summarized the key points of the guidelines used in this study according to four domains. Based on these domains, we have formulated several hypotheses about the expected change in actual diagnosis and management of hypertension in daily practice during the periods under study. For domain 1, we hypothesized an increase in the prevalence of hypertension and a decrease in the mean age of the cohorts. For domain 2, we expected an increase in the number of people treated with medication (increase in cohort size) and no change in the mean blood pressure at time of diagnosis. For domain 3, we expected an increase in the achieved systolic blood pressure reduction. For domain 4, we hypothesized an increase in the use of diuretics and beta-blockers as first-choice drugs; in addition, we hypothesized an increase in the percentage of patients on two or more types of antihypertensive drugs.

Analysis

Descriptive statistics were used where applicable. We used Mantel-Haenszel chi-square tests to determine significance in trends for variables expressed in percentages. Analysis of variance (ANOVA) testing was used to compare cohorts for differences in continuous variables such as age and blood pressure. All statistical analyses were performed with SAS software, version 9.1.

Results

In the studied period of 1992-2006, 2251 patients were registered with newly diagnosed hypertension by general practitioners (GPs) working in the NMP practices. Of these patients, 2021 (90%) started on medication at the time of diagnosis or the first blood pressure control thereafter. The mean blood pressure was 176/102 mmHg compared to 165/99 mmHg in the 10% of patients without medication. Two or more years of follow-up data were lacking for 945 patients. In 56% of these patients, the diagnosis of hypertension was made in the last 2 years of cohort period 3, so that it was not possible to obtain 2 years of follow-up data; in 30% of patients, control frequency was irregular and therefore did not meet the inclusion criteria. Other reasons were: patient died (4.1%), patient moved (4.8%), and miscellaneous (5.2%). An overview of the patient characteristics for each of the three studied cohorts is given in Table 2. The mean age rose significantly ($p < 0.0001$); the mean diastolic blood pressure at time of diagnosis decreased significantly ($p < 0.0001$). The age-adjusted prevalence of registered hypertension

in the NMP practices increased in the last decade, from 5.5% in 1995 and 6.1% in 2000 to 7.0% in 2005. Table 3 depicts the 2-year course of blood pressure for all three cohorts. In addition to the absolute decline, the table denotes the relative decline, correcting for the influence of an initial higher blood pressure on the potential of blood pressure decrease. The relative 2-year decline in systolic blood pressure was significantly lower in the first cohort compared to the other two cohorts. In contrast, the diastolic blood pressure decline was significantly lower in the last cohort as opposed to the other two. The effect of guidelines on the prescription of types of antihypertensive medication at initiation of treatment can be derived from Table 4. While in cohort 1, beta-blockers were the first choice of treatment, in cohort 3 this had changed in favour of diuretics. In all three cohorts, approximately one-third of all patients were using one hypertensive medication after 2 years of treatment (Table 5), and the number of patients on three or more medications was constant ($p = 0.743$).

Discussion

Summary of main results

Patients in cohort 3 were significantly older and had a significant higher pulse pressure than patients in cohort 1. In accordance with guideline revisions, diuretics became the first-choice drugs. Despite stricter and more clearly formulated treatment goals, the percentage of patients on three or more medications remained constant in all three cohorts. No clinically relevant changes were noted in blood pressure outcome, with 2-year systolic blood pressure reduction ranging from 13.3 to 15.7% (24 to 29 mmHg) between cohorts.

Interpretation of results

To our knowledge, no previous study has longitudinally evaluated hypertension management in general practice based on 15 years of data from the same general practice research network. The changed perspective from focus on diastolic (1991 guideline) to systolic blood pressure in the context of 10-year absolute cardiovascular risk (2003 guideline) may explain the significant rise in mean age from cohort 1 to cohort 3.[1,3] In hindsight, applying current knowledge and guidelines of cardiovascular risk management, it could be that part of the (younger) population of cohort 1 was overtreated. The rise in the age-adjusted prevalence of hypertension in our study has also been demonstrated in population-based surveys.[10,11] Part of this rise may be explained by the lower cut-off levels used to define hypertension over the last 15 years. In theory, every lower cut-off level to define hypertension should result in a substantial rise in prevalence. However, general practitioners will often not register a patient to be hypertensive before he or she wants to initiate medical treatment. Therefore, our reported prevalence is substantially lower than those derived from the open population by screening and does not rise steeply.[10,11] Stricter hypertension definitions do not automatically imply that treatment is initiated sooner. With the introduction in recent years of cardiovascular risk functions, the use of cardiovascular risk factors other than hypertension in the assessment whether antihypertensive medication is indicated has become more refined. However, in essence, this approach was already applied in the 1991 guideline (see Table I). The outcome of blood pressure management, expressed in terms of relative 2-year systolic blood pressure reduction, did not differ substantially between

cohorts. We would like to highlight two possible interpretations of this result. First, although changes in cut-off levels to define hypertension have caused more patients to be labelled as hypertensive, indications for medical treatment have only changed moderately throughout the years, and, for younger patients in particular, seem to even have become less strict. Second, treatment goals have been defined more clearly and have become stricter in the course of guideline revisions. Therefore, although medical treatment should in subgroups of patients be initiated at a later stage than in previous years, if treatment is indicated, it should reach stricter targets. In this respect, the unchanged blood pressure reduction as reported in our study is disappointing. Our results, as shown in Table 5, are in agreement with previous studies and show that somehow doctors are reluctant to prescribe three or more antihypertensive medications, even when treatment goals are not reached.[12,13] However, it is important to stress that the reported blood pressure reduction that was achieved in all three cohorts matches or exceeds that of results in the severely controlled environment of selected patients in randomized controlled trials (RCTs). [14-16]

Limitations

It is essential for optimal interpretation of our presented results to realize that data were derived from a well-described part of the hypertensive population of the NMP practices. We have not described patients registered with hypertension but not using medication, or the group of patients known to have high blood pressure but not yet registered by their GP as being hypertensive. The NMP practices form an academic research network. The mere fact that these practices monitor chronic diseases will have enhanced the quality of care. As a consequence, our results may not fully represent average general practice in the Netherlands and may overestimate the quality of the process and outcome of hypertension management. The last study cohort was relatively small compared to cohorts 1 and 2. In addition, compared to the first two cohorts, the number of patients in cohort 3 for whom the new guideline could be best applied were lacking. We assume it takes 1-2 years after the introduction of a new guideline before any kind of homeostasis is reached with regard to the application of new guideline recommendations in daily practice. In this respect, the results of cohort 3 could change for the better with two additional follow-up years (equal to cohorts 1 and 2).

Conclusion

Our study demonstrates the relevance of longitudinal data recording in understanding the management of chronic conditions. This type of data recording in one research network forms the basis of truly comprehending and interpreting medical outcomes in the context of the inevitable revisions in guidelines and protocols. Guidelines and guideline revisions do result in changes in the process of hypertension management, but the resultant blood pressure outcome has not changed with any clinical relevance over the last 15 years. General practitioners achieve substantial and prolonged blood pressure reduction, which equals or exceeds reductions achieved in RCTs. However, despite the clear formulation of stricter treatment goals in the revised guidelines, general practitioners appear to be reluctant to subscribe three or more antihypertensive medications. In addition to qualitative research to identify the causes of this

phenomenon, research to evaluate the effect of expert support systems on risk awareness and risk gain by additional treatment is necessary.

Acknowledgements

We would like to thank all collaborators of the NMP practices for their contribution to monitoring hypertension management.

Table 1. Summary points of hypertension guidelines in studied period

	Guideline 1 (1991) [1]	Guideline 2 (1997) [2]	Guideline 3 (2003) [3]
Diagnosis	DBP ≥ 95 mmHg	DBP 95 mmHg ≥ or SBP ≥ 160 mmHg	SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg
Indications medical treatment	DBP criterion for diagnosis and treatment - DBP < 100 mmHg: no medication - DBP 100-104 mmHg: medication if two more risk factors present - DBP ≥ 105 mmHg: always start medication	Both DBP and SBP criteria for diagnosis and treatment - DBP < 100 and/or SBP < 160 mmHg: no medication - DBP 100-104 and/or SBP 160-180 mmHg: medication if one or more other risk factors present - DBP ≥ 105 and/or SBP ≥ 180 mmHg: always start medication	Both DBP and SBP criteria for diagnosis and SBP criterion for treatment - Based on risk function; medication indicated when 10 year absolute risk of cardiovascular morbidity or mortality ≥ 20% - Patients with CVD, DM, familial dyslipidemia and patients with SBP ≥ 180 or DBP ≥ 100 mmHg: always start medication
Target of treatment	DBP < 90 mmHg	DBP < 90 or SBP < 160 mmHg	SBP < 140 (160 in healthy patient of 60 years and older without other risk factors) and DBP < 90 mmHg
Type of treatment	No protocol, choice doctor-patient Decision based on co-morbidity, costs and adverse drug events	Protocols for patients with and without co-morbidity Without co-morbidity: 1. Diuretic; 2. β-blocker; 3. Calcium channel blocker Patients with DM: Start ACE-inhibitor	Protocol for patients with and without co-morbidity Without co-morbidity: 1. Diuretic; 2. β-blocker; 3. ACE-inhibitor Patients with DM: protocol as without co-morbidity

DBP = diastolic blood pressure;
SBP = systolic blood pressure;
CVD = cardiovascular disease;
DM = diabetes mellitus;
ACE = angiotensin converting enzyme

Table 2. Characteristics of study population (at time of diagnosis hypertension)

	Cohort 1 (1992-1996) n=285	Cohort 2 (1998-2002) n=508	Cohort 3 (2004-2006) n=112
Age, mean (SD), years	54.8 (12.3)	59.2 (12.1)	60.3 (12.9) †
Sex, %			
Female	58.6	55.5	56.2
Male	41.4	44.5	43.8
BMI, mean (SD), kg/m^2	27.6 (4.1)	28.5 (4.9)	28.1 (5.2)
Diabetes, %	3.2	15.9	11.6
SBP, mean (SD), mmHg	175.1 (19.8)	179.0 (19)	175.1 (15.7)
DBP, mean (SD), mmHg	105.7 (7.4)	101.7 (9.7)	98.7 (8.8) †

BMI = body mass index;
SBP = systolic blood pressure;
DBP = diastolic blood pressure;
† p < 0.0001 for difference between cohorts

Table 3. Two-year course of blood pressure per cohort

	Cohort 1 (1992-1996) n=285	Cohort 2 (1998-2002) n=508	Cohort 3 (2004-2006) n=112
SBP diag, mean, mmHg	175.1	179.0	175.1
SBP 2 yr, mean, mmHg	150.8	149.9	148.2
Δ SBP diag – 2 yr, mmHg	24.3	29.1	26.8
% Δ SBP diag – 2 yr	13.3 ‡	15.7	14.9
DBP diag, mean, mmHg	105.7	101.7	98.7
DBP 2 yr, mean, mmHg	88.8	85.6	85.3
Δ DBP diag – 2 yr, mmHg	16.8	16.1	13.4
% Δ DBP diag – 2 yr	15.6	15.4	13.3 †

SBP = systolic blood pressure;
DBP = diastolic blood pressure;
‡ p = 0.002 compared to cohort 2, p = 0.190 compared to cohort 3;
† p = 0.02 compared to cohort 1, p = 0.027 compared to cohort 2

Table 4. Type of initial drug choice in patients who have started on mono therapy

Type of drug	Cohort 1 (1992-1996) n=241	Cohort 2 (1998-2002) n=392	Cohort 3 (2004-2006) n=85
ACE-inhibitor	17.0	19.9	10.6
ARB	0	0.3	5.9
β-blocker	43.6	37.0	36.5†
CCB	12.9	3.8	3.5
Diuretic	26.6	37.8	43.5‡
Other	0	1.3	0

ACE = angiotensin converting enzyme;
ARB = angiotensin receptor blocker;
CCB = calcium channel blocker;
† p = 0.121 for difference between cohorts;
‡ p = 0.001 for difference between cohorts

Table 5. Mono-duo-triple therapy per cohort at time of diagnosis and after two years of treatment (in % of patients)

	Cohort 1 (1992-1996) n=285		Cohort 2 (1998-2002) n=508		Cohort 3 (2004-2006) n=112	
	tdiag	2 years	tdiag	2 years	tdiag	2 years
No of antihypertensive drugs						
0	0	7	0.2	4.3	1.8	0.9
1	84.6	32.6	77.2	31.1	75.9	44.6
2	15.1	36.8	19.9	42.1	19.6	32.1
≥ 3	0.4	23.4	2.8	22.4	2.7	22.3

tdiag = time of diagnosis

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Chapter 3

Thirty-minute compared to standardised office blood pressure measurement in general practice

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Abstract

Background: Although blood pressure measurement is one of the most frequently performed measurements in clinical practice, there are concerns about its reliability. Serial, automated oscillometric blood pressure measurement has the potential to reduce measurement bias and 'white coat effect'.

Objective: To study agreement of 30-minute office blood pressure measurement (OBPM) with standardised OBPM, and to compare repeatability.

Methods: In a method comparison study executed in two general practices, 30-minute and standardised OBPM was carried out with the same, validated device in 83 adult patients. The procedure was repeated after 2 weeks. During 30-minute OBPM, blood pressure was measured automatically every 3minutes, with the patient in a sitting position, alone in a quiet room. Agreement between 30-minute and standardised OBPM was assessed by Bland–Altman analysis. Repeatability of the blood pressure measurement methods after 2 weeks was expressed as the mean difference in combination with the standard deviation of difference (SDD).

Results: Mean 30-minute OBPM readings were 7.6/2.5mmHg (95%confidence interval [CI] = 6.1 to 9.1/1.5 to 3.4mmHg) lower than standardized OBPM readings. The mean difference and SDD between repeated 30-minute OBPMs (mean difference = 3/1mmHg, 95%CI = 1 to 5/0 to 2mmHg; SDD 9.5/5.3mmHg) were lower than those of standardised OBPMs (mean difference = 6/2mmHg, 95%CI = 4 to 8/1 to 4mmHg; SDD 10.9/6.3mmHg).

Conclusion: Thirty-minute OBPM resulted in lower readings than standardised OBPM and had a better repeatability. These results suggest that 30-minute OBPM better reflects the patient's true blood pressure than standardised OBPM does.

Introduction

In everyday practice, blood pressure measurements are often of poor quality, mostly resulting in overestimation of the patient's blood pressure.[1] But, even when performed according to the 'state of the art', blood pressure measurements in the office may not be representative of the patient's true blood pressure status because the phenomenon 'white-coat effect' can introduce an additional level of bias.[2] Overestimation of blood pressure leads to overprescribing of antihypertensive drugs, with avoidable side effects and costs. Until recently, observer bias and 'white-coat effect' could be eliminated sufficiently only with the ambulatory blood pressure measurement techniques like home blood pressure monitoring and ambulatory blood pressure monitoring (ABPM).[3,4] However, these advantages of ambulatory techniques come with a price. ABPM is not very patient friendly,[5] and is associated with disturbed sleep.[6] Home blood pressure measurements may be inaccurate because of poor measurement technique[7] and report bias.[8] These aspects make ABPM techniques less suitable for routine use in daily practice.

Serial automated blood pressure measurement, without a doctor or nurse present, also has the potential to eliminate observer bias and reduce 'white-coat effect'.[9–12] Compared to ambulatory techniques, this could be used much more easily in routine practice. The results are available during a single consultation, and the procedure appears to be more patient friendly than ABPM. In a recent study, 30-minute automated blood pressure measurement (30 minute OBPM) agreed well with daytime ABPM and classified normotension, 'white-coat hypertension', masked hypertension, and sustained hypertension similarly to daytime ABPM.[13] The aim of this study was to compare 30-minute OBPM with standardised OBPM in general practice. The level of agreement between both methods was studied and the repeatability compared.

Method

Design

A method-comparison study was performed to investigate how 30-minute OBPM agreed with standardised OBPM. As part of the method comparison, a repeatability study of 30-minute OBPM compared to standardised OBPM was carried out.[14]

Participants and setting

The study took place in two general practices of the academic practice-based research network[15] of the Radboud University Nijmegen Medical Centre. Each consecutive patient who attended the practice with a main reason for encounter that warranted blood pressure measurement was invited by the practice assistant to participate in the study. Patients gave written informed consent before participation. Exclusion criteria were atrial fibrillation, documented heart valve disease, complete axillary lymph node excision on the right side, and upper arm circumference more than 35 cm. Smoking, diabetes, cardiovascular disease, and medication were recorded.

Blood pressure measurements

Both standardised OBPM and 30-minute OBPM were taken with the same, validated, automated oscillometric device, the Mobil- O-Graph NG (IEM GMBH, Stolberg, Germany).[16] The devices are calibrated annually. Different bladder sizes were used to match the different arm circumferences.

Two researchers were trained to perform the OBPMs according to a detailed protocol (available on request) based on the recommendations of the European Society of Hypertension[17] and the American Heart Association.[18] The key elements of this protocol are listed in Boxes 1 and 2.

Box 1. Key elements of blood pressure measurement

Key elements of standardised office blood pressure measurement

- *No talking*
- *Temperature in the room22 degrees Celsius*
- *Right arm*
- *Placement of the cuff: 2 cm above antecubital fossa*
- *Position of patient: sitting, back supported, feet flat on the floor, middle of cuff on level on right atrium*
- *5 minutes' rest in the absence of the observer before office blood pressure measurement*
- *3 readings with 30 seconds in between, first reading discarded*

Key elements of 30-minute automated office blood pressure measurement

- *Same position of patient and cuff as in standardised office blood pressure measurement*
- *30 seconds after standardised office blood pressure measurement, observer checks first*
- *measurement, then leaves the room. Patient stays in same position*
- *11 measurements every 3 minutes, first measurement discarded*

Box 2. Overview of study method

Time			
Retrospectively	*Usual blood pressure*		
Visit 1, T = 0	*Standardised OBPM*	*30-minute OBPM*	
Visit 2, T = 2 weeks	*Standardised OBPM*	*30-minute OBPM*	*Standardised OBPM*

During visit 1, standardised OBPM was carried out after a 5-minute rest period in the absence of the observer. The measurement consisted of three readings. Immediately afterwards, 30-minute OBPM followed, consisting of 11 measurements, of which 10 were made in the absence of the researcher. The position of the patient and cuff were not altered. The result of the first measurement of both standardised and 30-minute OBPM was discarded. After 2 weeks, the measurements were repeated by the same researcher in the same room at the same time of the day (visit 2). To assess whether the measurement order influenced the results, an additional standardised OBPM was performed after the second 30-minute OBPM. The last noted usual

blood pressure measurement was collected, to compare with the study's standardised procedure (Table 1). The last 'usual blood pressure' was not included if there had been a medication change between this measurement and the start of the study.

Sample size

A priori, a difference in blood pressure of 5mmHg or more was deemed to be clinically relevant. To detect such a difference with a power of 90%, a significance level of 5%, and assuming a standard deviation of the difference (SDD) of 14mmHg, 82 patients would be needed. Considering a drop-out of 20%, the study aimed to recruit 110 participants.

Statistical methods

All data were registered and analysed in SPSS (version 16). Data were excluded for analysis if there was a change of medication type or doses between the two visits, or if fewer than nine measurements were valid during the 30-minute OBPM. The level of agreement between standardised OBPM and 30-minute OBPM was assessed by Bland and Altman's approach of difference-against-mean plots.[19] Because the difference increased with increasing blood pressure (positive rank correlation between the standard deviation [SD] and mean of the two blood pressure measurement methods), data were logarithmically transformed.[14] The back-transformed limits of agreement were added to Bland–Altman plots on the original scale.[20] For comparison of means, 95% confidence intervals (CIs) were presented. For evaluation of the repeatability, the mean difference was used in combination with the SDD. The repeatability of the two methods was compared by performing the Wilcoxon signed-rank test on the difference of the SD of the (logarithmically transformed) standardised OBPMs and of the SD of the 30-minute OBPMs.

Results

Participants

A total of 105 patients agreed to participate in the study. Twenty-two patients were excluded from analysis, 10 because fewer than nine measurements of 30-minute OBPM were valid, six because of medication change between the two visits, two because they felt unwell during the measurements, two because they altered the position of their arm during the measurements, and two because they were unable to come for the second visit. The characteristics of included patients are shown in Table 1.

Agreement between 30-minute OBPM and standardised OBPM

Mean 30-minute OBPM readings were significantly lower than standardised OBPM readings, with a mean (absolute) difference of 7.6/2.5mmHg (Table 2).

Figure 1a and 1b shows Bland–Altman plots of systolic and diastolic blood pressures during the first visit. These plots show the differences between 30-minute and standardized OBPM against their mean. As the difference increased with increasing blood pressure, the diverging limits of agreement were based on back transformation of results of logarithmically transformed data. The median difference in systolic blood pressure between standardised OBPM and 30-minute

OBPM was 6% (95% limits of agreement ranging from -4% to 15%). The median difference in diastolic blood pressure between standardised OBPM and 30-minute OBPM was 3% (95% limits of agreement from -7% to 13%).

Repeatability of standardised and 30-minute OBPM

Table 2 gives an overview of the data on visit 1 and 2 for both measurement methods. The mean difference between the first and second visit of 30-minute systolic OBPM is about half the mean difference of standardised OBPM. In addition, SDDs of repeat 30-minute OBPM were smaller than SDDs of repeat standardised OBPM. The Wilcoxon signed-rank test demonstrated that repeatability was significantly better for 30-minute OBPM than for standardized OBPM ($P<0.01$ for systolic and diastolic blood pressure).

Figures 2a and 2b presents Bland–Altman plots of the repeatability of systolic blood pressure for standardised and 30- minute OBPM respectively. The 95% limits of agreement are wider for standardized than for 30-minute systolic blood pressure (for data on the repeatability of diastolic blood pressure see Table 2; a figure is available on request).

Measurement order

Comparing blood pressures measured by standardised OBPM before (128.4/81.8mmHg) and after (128.3/82.1) the second 30-minute OBPM (visit 2) demonstrated that the order of measurement did not influence the results (difference (0.1/–0.3mmHg; 95 % CI = –1.6 to 1.9/–1.2 to 0.6mmHg) [SDD 7.9/4.0 mmHg]).

Discussion

Summary

In this study, mean 30-minute OBPM readings were significantly lower than standardised OBPM readings, with a difference of 7.6/2.5mmHg. The repeatability in 2 weeks was better for 30-minute OBPM than for standardised OBPM: the difference and the SDD in both systolic and diastolic blood pressure between the two visits were significantly lower for 30- minute than for standardised OBPM.

Strengths and limitations

This study has several strengths. It was carried out in a general practice setting, where most hypertension management takes place. It is the first study to perform serial automated OBPM (AOBPM) in general practice, with a common 24-hour ambulatory device. The advantage is that many practices already own one of these devices, and they are likely to be standard equipment in all general practices in the near future. With one type of device (and consequently just one type of software), practices can then run both office and ambulatory measurement protocols. The presentation of data on repeatability is of additive value in judging serial AOBPM in the office.

This study did not randomise the measurement order, which would have been methodologically more accurate. To study whether any time effect would bias the results, a second standardised OBPM was added after 30-minute OBPM. Standardised office blood pressure before and after

30-minute OBPM did not differ, so random measurements appear to have had no significant effect on the results. By introducing 30-minute OBPM, the study aimed to reduce the 'white-coat effect' by leaving the patient alone in a room. The practice setting, which is also part of the 'white-coat effect', may still contribute to a blood pressure rise. Thirty-minute OBPM takes less time from a healthcare professional than the 8–12 minutes required for a standardized OBPM.[1] However, it takes organizational skills and a spare room to implement 30-minute OBPM in daily practice. Previous research suggests that a duration of 30 minutes may not be necessary.[13] A shorter measurement time may help to overcome organisational problems. Results were presented both absolutely and relatively. The data in Table 2 were presented in absolute figures. However, it is important to realise that the presented results depend on the height of the blood pressure. Therefore, a relative measure is, strictly speaking, more appropriate. Most data were analysed in this relative form (after log transformation) as can be seen in the Bland–Altman plots, but to facilitate interpretation and enable comparison with other studies, absolute figures are presented in Table 2.

Comparison with existing literature

The study data support abundant evidence on the difference between usual blood pressure measurement and standardized OBPM based on measurement bias.[1,21] In real life, the difference between office blood pressure measurement and 30-minute OBPM will be greater than the difference found in this study, as lack of measurement technique in daily practice will lead to higher blood pressure results.

The mean last noted usual systolic blood pressure was 18mmHg higher than standardised OBPM (Tables 1 and 2). With the choice to compare 30-minute OBPM with standardised OBPM, measurement, bias was eliminated as potential (confounding) cause for a difference in blood pressure. It is therefore hypothesised that the presented difference in blood pressure is a result of the reduction of the 'white-coat effect' with 30-minute OBPM. The fact that standardised OBPMs before and after 30-minute OBPM were the same, underlines that a fall in blood pressure during 30-minute OBPM is influenced by the absence of the healthcare professional (and, less so, caused by a long rest period or regression to the mean). Other studies also demonstrated that repeated automated measurements with the patient alone in an examining room give lower results than standardized measurements. Recently, Myers et al found a difference of 5.4/2.1 mmHg between automated office blood pressure and conventional manual office blood pressure.[22] These findings, which point in the same direction of lower results of automated measurements, are interesting, as their approach differed from the present one in two aspects: the researchers followed a shorter measurement procedure (10 minutes) and they used routine — not standardised — OBPM as the reference. It would be valuable to establish the repeatability of Myers et al's short procedure. Considering the wide limits of agreement in relation to awake ambulatory blood pressure (limits of agreement –31.9 to 36.6 mmHg,[22] where 30-minute OBPM compared to daytime ambulatory blood pressure revealed limits of –19 to 19 mmHg[13]), one may assume that the repeatability of their short procedure will not be as good as the present longer procedure. The differences between automated measurements with the patient alone in an examining room and standardized measurements seem to depend on the baseline blood pressure level of the study population; mean automated blood pressure was

142/80 mmHg in an outpatient clinic population (difference 20/5mmHg)[10] and 115/71 mmHg in an open population study (difference 3/3 mmHg).[23] The mean automated blood pressure of the present study population (134/84mmHg) was intermediate compared to the abovementioned studies, with the differences also intermediate. This is in line with the observation in the present study that differences are related to blood pressure level (Figures 1a and b). To the authors' knowledge, data on the repeatability of any serial AOBPM were lacking until now. This is unfortunate because study of repeatability should be part of every validation procedure.[14] The relevance of repeatability was underlined recently by Palatini et al, who reported that ABPM only predicted end-organ damage in subjects with reproducible recordings.[24] In the absence of data on the repeatability of serial AOBPM, data in the present study were compared with reproducibility studies of 24-hour ABPM. In a study in 508 hypertensive patients,[24] the SDD of 24-hour ABPM was 8.3/6.4 mmHg. Stergiou et al reported an SDD of 8.3/5.6 mmHg for 24-hour ABPM; the SDD of the awake 24-hour ABPM was 10.0/6.6.[25] In this last-mentioned article, the SDD for clinic blood pressure measurement was 11.0/6.6 mmHg,[25] comparable to the SDD reported in the present study for standardised OBPM (10.9/6.3 mmHg). This study revealed that 30-minute OBPM had a good repeatability, as the difference between visits 1 and 2 was less than 5 mmHg and the SDD (9.5/5.3 mmHg) was in agreement with above-mentioned studies concerning the repeatability of 24-hour ABPM.

Implications for practice and research

The results of this study demonstrate the potential of 30-minute OBPM to reduce measurement bias and 'white-coat effect' in the office, without the need for ambulatory techniques. Combined with the authors' previous work, a 30-minute OBPM is suggested to be a valid, office-based alternative to daytime ABPM or home blood pressure measurement, in attempting to determine one's true blood pressure status. Meanwhile, the authors realise that 30- minute OBPM cannot replace several, relevant features that are unique for 24-hour ABPM, like measurement of blood pressure variability and nighttime blood pressure. Myers has already suggested how to implement the use of serial AOBPM in daily practice.[26] He advocates using the same reference value for the diagnosis of hypertension as in home blood pressure monitoring or daytime ABPM (135/85 mmHg). The author's previous finding that 30-minute OBPM outcome agreed well with daytime values of ABPM supports our proposal.[13] Further research should focus on the comparison of serial AOBPM with home blood pressure measurement and on the optimal measurement duration. In addition, implementation studies on cost-effectiveness are required. In conclusion, 30-minute office blood pressure measurement resulted in lower readings than standardised office blood pressure measurement and had a better repeatability. The favourable repeatability and the lower values of 30-minute OBPM are promising for its value in blood pressure management in general practice.

Acknowledgements

We would like to thank the doctors, nurse practitioners, assistants, and patients of the general practices in Berghem and Schaijk (The Netherlands) for their cooperation.

Table 1. Characteristics of subjects

Characteristic	
Number (male/female)	83 (32/51)
Age, mean (SD), y.	62.1 (10.7)
Last noted blood pressure in GP record, mean (SD), mmHg, n = 78	
Systolic	152.8(16.5)
Diastolic	82.0 (10.0)
On antihypertensive drugs, n (%)	69 (83)
Smoker, n (%)	10 (12)
Cardiovascular disease, n (%)	17 (20)
Diabetes mellitus type 2, n (%)	9 (11)

Table 2. Blood pressure results (Δ = difference)

	Mean blood pressure (SD) in mmHg		Mean difference
	Visit 1	Visit 2	Δ visit 1—visit 2 (95% CI) [SDD]
Standardised OBPM (n = 83)			
Systolic	134.4 (16.4)	128.4 (14.8)	6.0 (3.6 to 8.3) [10.9]
Diastolic	84.1 (10.8)	81.8 (10.7)	2.3 (1.0 to 3.7) [6.3]
30-minute OBPM (n = 83)			
Systolic	126.8 (14.1)	123.8 (13.3)	3.0 (0.9 to 5.1) [9.5]
Diastolic	81.6 (10.1)	80.6 (10.5)	1.0 (–0.1 to 2.2) [5.3]
	Mean difference in blood pressure (95%CI) [SDD] in mmHg		
Δ standardised OBPM - 30-minute OBPM (n = 83)			
Systolic	7.6 (6.1 to 9.1) [6.8]	4.6 (3.2 to 6.1) [6.7]	
Diastolic	2.5 (1.5 to 3.4) [4.5]	1.2 (0.3 to 2.0) [3.7]	

OBPM = office blood pressure measurement;
SD = standard deviation;
SDD = standard deviation of the difference

Figure 1a. Comparison of systolic blood pressures: Bland and Altman plot of difference between standardized systolic office blood pressure and 30-minute systolic office blood pressure against their mean (first visit)

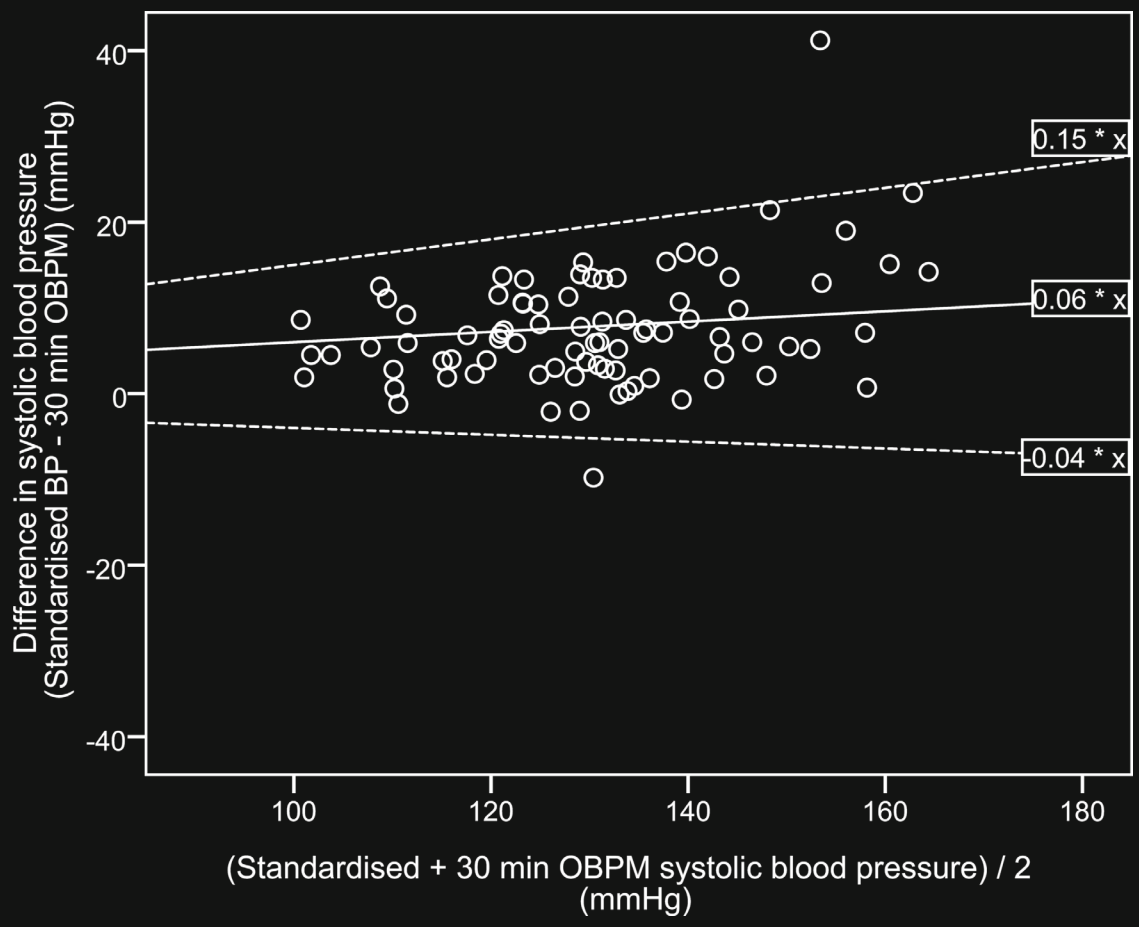


Figure 1b. Comparison of diastolic blood pressures: Bland and Altman plot of difference between standardized diastolic office blood pressure and 30-minute systolic office blood pressure against their mean (first visit)

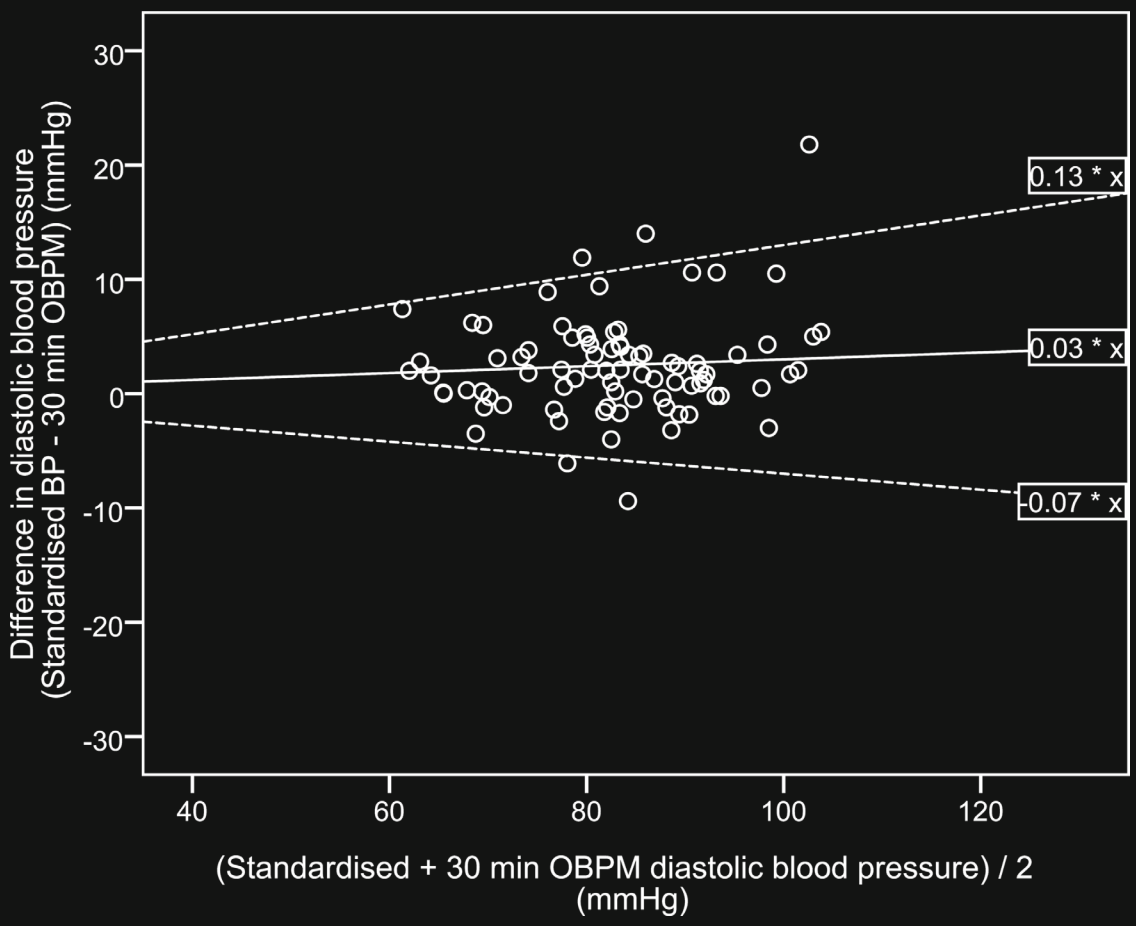


Figure 2a. Repeatability of standardized OBPM: Bland and Altman plot of difference between standardized systolic office blood pressure of visit 1 and 2 against their mean

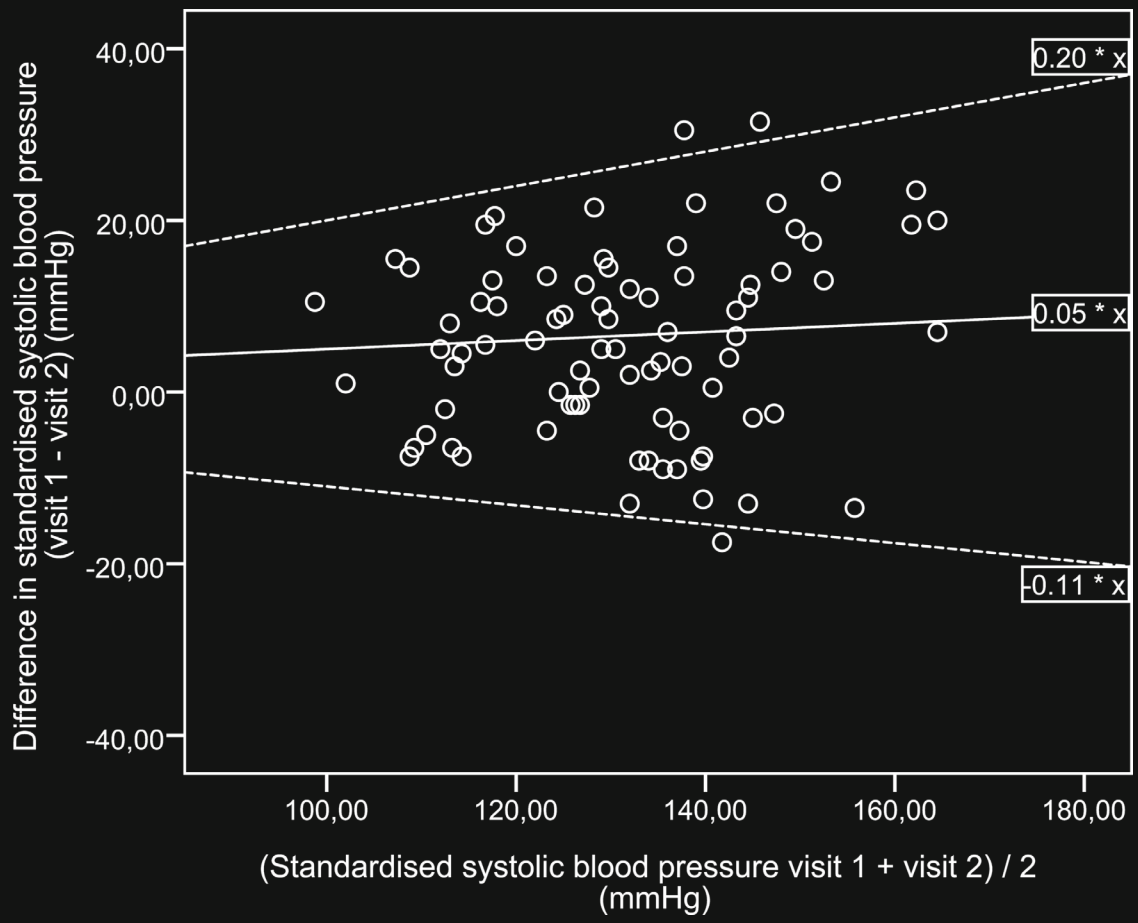
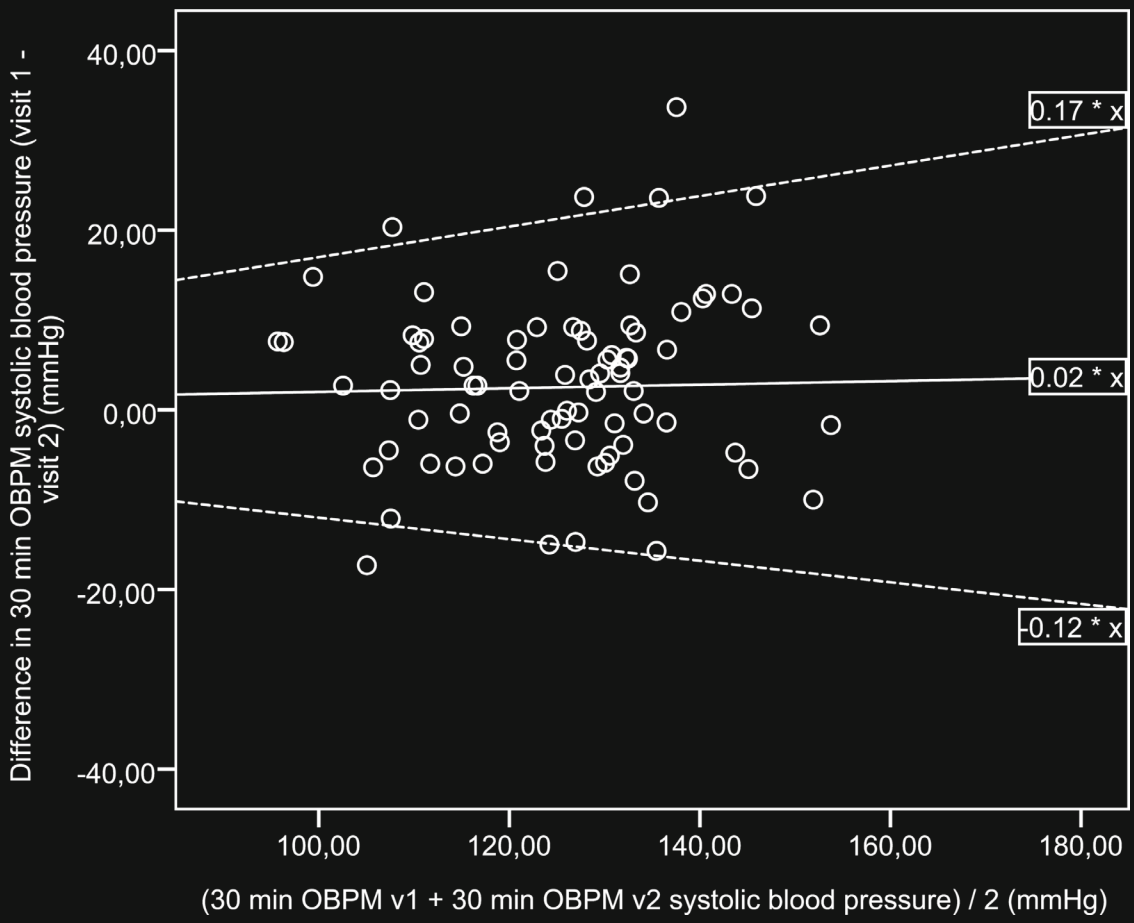


Figure 2b. Repeatablity of 30-minute OBPM: Bland and Altman plot of difference between 30-minute systolic office blood pressure of visit 1 and 2 against their mean



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Chapter 4

A Novel Approach to Office Blood Pressure Measurement: 30-Minute Office Blood Pressure vs Daytime Ambulatory Blood Pressure

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Abstract

Background: Current office blood pressure measurement (OBPM) is often not executed according to guidelines and cannot prevent the white-coat effect. Serial, automated, oscillometric OBPM has the potential to overcome both these problems.

Objective: To validate a 30-minute OBPM through a method comparison with daytime ambulatory blood pressure.

Methods: Patients referred to a primary care diagnostic center for 24-hour ambulatory blood pressure monitoring (ABPM) had their blood pressure measured using the same validated ABPM device for both ABPM and 30-minute OBPMs. During 30-minute OBPM, blood pressure was measured automatically every 5 minutes with the patient sitting alone in a quiet room. The mean 30-minute OBPM (based on t = 5 to t = 30 minutes) was compared with mean daytime ABPM using paired t tests and the approach described by Bland and Altman on method comparison.

Results: We analyzed data from 84 patients (mean age 57 years; 61% female). Systolic and diastolic blood pressures differed from 0 to 2 mm Hg (95% confidence interval, −2 to 2 mm Hg and from 0 to 3 mm Hg) between mean 30-minute OBPM and daytime ABPM, respectively. The limits of agreement were between −19 and 19 mm Hg for systolic and −10 and 13 mm Hg for diastolic blood pressures. Both 30-minute OBPM and daytime ABPM classified normotension, white-coat hypertension, masked hypertension, and sustained hypertension equally.

Conclusion: The 30-minute OBPM appears to agree well with daytime ABPM and has the potential to detect white-coat and masked hypertension. This finding makes 30-minute OBPM a promising new method to determine blood pressure during diagnosis and follow-up of patients with elevated blood pressures.

Introduction

The Framingham and the SCORE (systematic coronary risk evaluation) risk functions, both developed to assess the risk of cardiovascular disease, are based on standardised office blood pressure measurements (OBPMs).[1,2] Despite guidelines that advocate the relevance of well-executed, standardised OBPM to prevent several forms of bias,[3,4] it is well known that most caregivers do not execute OBPM strictly according to these guidelines.[5,6] In addition, up to one-quarter of patients is prone to the white-coat effect (in which patients exhibit elevated blood pressure in a clinical setting but not in other settings), which influences cardiovascular risk profiling as well.[7,8] This white-coat effect cannot be overcome by standardised OBPM. As a consequence, the determined cardiovascular risk will be incorrect in an estimated 25% of patients and may lead to under- or overtreatment. To enable a more precise determination of cardiovascular risk, OBPM should be free from (observer) bias and the white-coat effect. The measurement should be uniform, easy to execute correctly for all types of health care personnel (doctors, practice assistants, practice nurses, research assistants, etc), and straightforward to implement in daily practice. Fortunately, since the introduction of automated, oscillometric blood pressure measurement devices, this ideal can be met. Oscillometric devices are readily available in primary care and are used for 24-hour ambulatory blood pressure monitoring (ABPM) and home blood pressure monitoring.[1,3] Guidelines have started to recommend the use of 24-hour ABPM and home blood pressure monitoring primarily for the detection of the white-coat effect.[1,4] Although both these types of monitoring eliminate most types of observer bias and the white-coat effect, 24-hour ABPM is costly and not suitable for all types of patients; up to 50% of patients report it is a nuisance or results in disturbed sleep.[9] With home blood pressure monitoring, patients are reported to be noncompliant with measurements or self-report of blood pressures.[10] There is a small but growing body of evidence to support a new method of office measurements in which a series of automated measurements is taken with the patient sitting alone in a quiet room (serial automated OBPM). The scarce, available research comes predominantly from one research group that used a validated oscillometric office blood pressure device able to be set at measurement intervals of 1 minute or more for a duration of 5 to 10 minutes. With this protocol the white-coat effect was practically eliminated.[11,12]

Meanwhile we developed a protocol that enables practices or primary care diagnostic centers to use a 24-hour ABPM device for serial automated OBPM. To our knowledge no previous research has studied using this protocol. A growing number of practices and diagnostic centers already possess 1 or more 24-hour ABPM devices. Using a 24-hour ABPM device for serial automated OBPM can be cost saving, and the device is user friendly, as clinic staff are already familiar with it. Validating our protocol may contribute to further acceptance of serial automated OBPM. As a first step in the process of validation, using a study sample of patients drawn from a family medicine population, we compared blood pressures determined using a protocol of serial measurements while patients were sitting for a mean of 30 minutes (30-minute OBPM) with their mean daytime ABPMs.

Methods

Design, Setting, and Participants

We invited all patients aged 18 years or older who were referred by their family physician from October 2008 until February 2009 for a 24-hour ABPM to a diagnostic center that primarily supports family practices to participate in this comparative study. Reasons for referral were obtained from routinely used referral forms. Known atrial fibrillation, irregular pulse, pregnancy, and night shift work were exclusion criteria. After informed consent a 30-minute OBPM took place directly before a 24-hour ABPM. Ethics approval was not required, as declared by the local Medical Ethics Committee of the RUNMC (Central Committee on Research involving Human Subjects, Arnhem-Nijmegen, the Netherlands).

Blood Pressure Monitors and Measurements

A Welch Allyn Cardioperfect 6100 oscillometric blood measurement device (Welch Allyn Protocols, Inc, New York, New York) was used for both the 30-minute OBPM and the 24-hour ABPM. This device is equivalent to the validated SunTech Medical Oscar 2 device (SunTech Medical, Inc, Morrisville, North Carolina, and Eynshm, Oxfordshire, England; declaration of equivalence form[13] available upon request).[14] For each patient, the same device was used for both measurements. The devices are calibrated annually. All 30-minute measurements took place between 11 AM and 3 PM in a quiet room at the diagnostic center. The patient was sitting still 5 minutes before and during the 30-minute OBPM. The patient sat in a chair with a supported back, arm at heart level, and both feet resting flat on the floor. Blood pressure was measured on the nondominant arm at 5-minute intervals for a total of 8 measurements. The first measurement was a test measurement during the installation of the patient. The second measurement was the start of the 30-minute period; the researcher (I.E.B.) left the room after this measurement proved to be successful (no error reading). Previous research has shown that in serial measurements blood pressure can decline substantially in the first 10 minutes before it stabilizes.[15,16] We therefore chose to exclude the first 2 measurements for the determination of the mean 30-minute OBPM. Thus we define 30-minute OBPM to be the mean blood pressure calculated from the 6 measurements taken at 5-minute intervals from $t = 5$ to $t = 30$ minutes. If more than 1 of these 6 measurements was erroneous (defined as an “error” reading given by the device), the entire case was excluded for analysis. To underpin our choice for a 30-minute period of measurements, we compared the mean 30-minute OBPM with the means of several shorter time periods, using the acquired data on 30-minute OBPM and recalculated these data to means based on 2 to 5 measurements. We then compared these means with the mean 30-minute OBPM using paired t tests. The 24-hour ABPM was set at 20-minute intervals from 7 AM to 11 PM and at 1-hour intervals from 11 PM to 7 AM. Blood pressure was monitored on the same arm as during the 30-minute OBPM. Patients were instructed to perform their usual daily activities but to stop moving and be silent during measurements. The mean daytime ABPM was calculated from the readings of 9 AM to 9 PM.[3] Only patients with 15 or more successful daytime readings were included. Patient instructions and application of the monitors were performed by the same experienced researcher (I.E.B.), trained in the procedures of blood pressure measurement, using a standardised protocol based on the American Heart Association guidelines.[4]

Classification of Hypertension Subtype

As an indication for the diagnostic value, we compared the 30-minute OBPM with the daytime ABPM in classifying 4 groups of blood pressure subtypes: normotension (office blood pressure <140/90 mm Hg and daytime ABPM or 30-minute OBPM <135/85 mm Hg); white-coat hypertension (office blood pressure ≥140/90 mm Hg and daytime ABPM or 30-minute OBPM <135/85 mm Hg); masked hypertension (office blood pressure <140/90 mm Hg and daytime ABPM or 30-minute OBPM ≥135/85 mm Hg), and sustained hypertension (office blood pressure ≥140/90 mm Hg and daytime ABPM or 30-minute OBPM ≥135/85 mm Hg). In the absence of usual care office blood pressure measurements, we defined office blood pressure as the mean of the first 2 measurements of the 30-minute OBPM.

Sample Size

In the absence of international consensus criteria, we deemed a mean difference of 5 or more mm Hg between both types of measurements in the same patient to be of clinical relevance. Detection of blood pressure differences smaller than 5 mm Hg is seriously hampered by the biologic variation of blood pressure.[17,18] With a 2-sided α of .05, a power of 90%, and a standard deviation of the difference of 15 mm Hg, a sample size of 81 would allow detection of a difference of 5 mm Hg or more.

Statistical Analysis

We calculated the difference between the mean daytime ABPM and the mean 30-minute blood pressure, as well as the standard deviation of the difference. Results are presented for systolic and diastolic blood pressure and for mean arterial pressure. Although mean arterial pressure is not a measure commonly used in primary care, we present it because it is measured by oscillometric devices to calculate the values of the systolic and diastolic blood pressure. The means of the daytime ABPM and the 30-minute blood pressures were compared using a paired t test. Bland-Altman plots were constructed to further evaluate agreement of both means. The limits of agreement in these plots were derived from the standard deviation of the mean difference between both measurements using the following formula: mean difference +/- 1.96 × standard deviation of the mean difference.[19]

Pearson's correlation was determined to study whether a difference between the means would relate to the magnitude of the blood pressure. Log transformation would be applied in case of dependence.[20] We applied McNemar-Bowker test to determine whether the same patients who were categorised by 30-minute OBPM into 1 of the 4 subgroups of the hypertension classification were similarly categorised by the mean daytime ABPM. We used the SPSS version 14.0 software package (SPSS Inc, Chicago, Illinois) for all analyses.

Results

Of 117 patients asked to participate, 18 patients declined, and 3 patients were excluded (2 with known atrial fibrillation, and 1 with irregular pulse at examination). Of 96 patients included, 6 measurements exceeded the predefined number of erroneous readings; in 5 patients a problem occurred with cuff fitting during the 24-hour ABPM, and 1 patient was disturbed during the 30-minute OBPM, leaving 84 patients for the final analysis. The characteristics of these patients

are shown in Table 1. Figure 1 shows that systolic blood pressure declines substantially in the first 15 minutes before reaching a plateau phase. We observed exactly the same course for diastolic blood pressure (data not shown). The mean 10-minute OBPM (mean of third and fourth measurements) is modestly but not significantly higher than the mean 30-minute OBPM (142/84 mm Hg vs 141/84 mm Hg; P = .1 and .7, respectively). No differences were found for mean 15-, 20-, and 25-minute OBPMs compared with the mean 30-minute OBPM. The mean blood pressure levels, the difference between the means, and the standard deviation of the difference of the daytime ABPM and the 30-minute blood pressure levels are depicted in Table 2. The limits of agreement were between –19 and 19 mm Hg for systolic blood pressure, between –10 and 13 mm Hg for diastolic blood pressure, and between –13 and 16 mm Hg for mean arterial pressure.

Figures 2a, 2b, and 2c plot the difference between the 30-minute OBPM and the daytime ABPM against mean blood pressure. The difference proved to be related to the magnitude of the mean blood pressure for systolic blood pressure, but not for mean arterial pressure and diastolic blood pressure (Pearson correlation coefficient r = 0.27, P = .01; r = 0.17, P = .13; and r = 0.05, P = .64, respectively).

As shown in Table 3, the 30-minute OBPM classified patients into the 4 subgroups of hypertension (as mentioned in the method section) similarly to daytime ABPM. There was no significant difference in classification of patients between both measurements (P = .22); 87% of patients were classified similarly.

Discussion

We have reported a difference of less than 2 mm Hg, with a standard deviation of the difference of less than 10 mm Hg for mean arterial pressure and systolic and diastolic blood pressure of the mean 30-minute OBPM compared with the mean daytime ABPM using the same blood pressure monitoring device for both types of measurement. The limits of agreement were comparable to other blood pressure method comparison studies. In addition, 30-minute OBPM seems to be able to detect white-coat hypertension as well as daytime ABPM does.

Our Results in Perspective of Previous Research

Although in our study no clinical relevant systematic difference was detected between 30-minute OBPM and daytime ABPM, the limits of agreement show that at the individual level, substantial, clinical relevant differences can occur (Figures 2a-c). Ideally in comparative studies the reference measurement has an excellent reproducibility.[20] In blood pressure measurement, however, this reproducibility is always limited by the relatively large intrapersonal biologic variation of blood pressure. Consequently, any comparative study on blood pressure measurements will result in relatively wide limits of agreement. The limits of agreement in our study did not exceed even those of well-executed reproducibility studies (eg, with 24-hour ABPM).[18,21] Accordingly, 30-minute blood pressure readings are preferred to other types of office-based blood pressure measurements.[22] Although it is known that conventional OBPMs executed in complete accordance with guidelines may reach results similar to those of ABPMs,[23] daily practice over the last decades has proved that one can be skeptical about ever bridging the gap between

theory and daily practice. No previous studies have aimed at comparing mean 30-minute blood pressures with mean daytime ambulatory blood pressure in a primary care setting using the same measurement device for both types of measurement.

There has been some research showing that mean 4- to 10-hour blood pressure was comparable to mean daytime ambulatory blood pressure.[24,25] In a recent study, Culleton et al reported on the use of a mean 25-minute (4-minute interval) oscillometric blood pressure measurement to reduce white-coat effect.[26] Mean 25-minute blood pressure appeared to be 10 mm Hg lower than daytime ABPM. Differences, however, in the primary objective of the study, the study population, and the period of rest before start of measurement obstruct reasonable comparison with our results.

Our results are in agreement with data from Myers et al, where the automated office measurement proved to be 2 mm Hg lower than daytime ABPM.[12] Their study population was almost similar to ours, but their blood pressure measurement protocol differed considerably (5 or 10 minutes, apparently without a prior rest period). In contrast to Myers et al, we used 1 device for both the office and the ambulatory measurement. In this way, we excluded a potential source of bias when comparing the 2 measurement methods. We purposely chose to validate a protocol with the use of an ABPM device because we anticipate that in most industrialized countries these devices will soon become standard equipment in family physicians' offices. With the 30-minute protocol, practices can than use 1 type of device (and 1 type of software) for both office and ambulatory measurements. The 5-minute measurement interval in our protocol was chosen because the minimum measurement interval of most, if not all, ambulatory devices can be set at least at 5 minutes. As a consequence, with the same number of measurements, this minimum interval results in a longer measurement period than the 10 minutes studied by Myers et al. Our results showed, however, that serial measurements for 10 minutes after a 5- to 10-minute rest period may be sufficient; future research is needed to underline this possibility.

Strengths and Limitations

Our study has several strengths. It was performed in a primary care setting—the setting where high blood pressure is most often diagnosed and managed. Blood pressure measurements were executed according to clear and well-described protocols that can be easily implemented in daily practice using existing blood pressure measurement devices. For logistic reasons we were unable to randomize the order in which 30-minute OBPM and ABPM took place. As a consequence, a regression to the mean could have influenced the results of our study. The 30-minute OBPM, however, was not used as a selection criterion to undergo 24-hour ABPM, and the mean 30-minute measurement was determined excluding the first measurement.

Our definition of a successful daytime ABPM was more lenient than the consensus-based definitions of most guidelines. To understand whether this discrepancy would influence results, we reanalyzed our data from 64 patients using the cutoff as defined by O'Brien et al[3] and found the results to be consistent with those reported here (data not shown). The study population consisted of hypertensive patients in usual care family practice, some of whom were taking antihypertensive medications. Although in theory treatment for hypertension may have had an effect on the study outcome, in their method comparison study, Little et al found that, in a family practice–based population, treatment does not bias results.[22] The mean difference

between 30-minute OBPM and daytime ABPM was related to the magnitude of the blood pressure. This relation is common in blood pressure research, and if this relation is strong, it seems reasonable to report conclusions separately for both hypertensive and normotensive patients. In our study, however, the observed correlations were very small and do not affect our conclusions. We realize that the outcome of our study depends in part on the population under study, its sample size, and the setting. For instance, that our 30-minute OBPM was executed in a single primary care diagnostic center rather than in actual family practices may have affected the results, because of a potential difference in white-coat effect between settings. Recently, however, Ogedegbe et al showed that although setting can be a factor, the role of the physician is most relevant.[27]

Future Perspectives

Currently, detection of the white-coat effect is the main and most evidence-based indication for the use of 24-hour ABPM or home blood pressure monitoring, and guidelines formulate with caution about other possible indications.[1,3-4] We believe that automated OBPM (such as the 30-minute OBPM) is a valid, useful, office-based alternative to daytime ABPM or home blood pressure monitoring for this indication. Moreover and contrary to the more laborious home blood pressure monitoring and 24-hour ABPM, 30-minute OBPM could be a convenient way to follow up high blood pressure findings. Although 30-minute OBPM and home blood pressure monitoring are theoretically interchangeable with regard to indication and interpretation, the same cannot be said for 24-hour ABPM. Twenty-four hour monitoring gives unique information about the diurnal blood pressure pattern (dipping or nondipping), blood pressure variability, and mean night blood pressure. It is unclear, however, whether these data can be used to improve cardiovascular risk management, and if so, how these variables should be used and interpreted in family medicine. Improvement of office measurement techniques can already benefit patients substantially, particularly in family medicine. Very recently an algorithm has been proposed for diagnosing hypertension using serial automated OBPM.[24]

The 30-minute OBPM agrees well with daytime ABPM and has limits of agreement comparable to other method comparison studies of blood pressure. It appears to classify blood pressure status of patients as well as daytime ABPM. Accordingly, this new method of office blood pressure measurement can potentially enable family physicians to overcome well-known problems when measuring usual blood pressure, such as observer bias and the white-coat effect. Additional research is needed to determine the reproducibility of the 30-minute OBPM and its agreement with usual office and home-based blood pressure measurements.

Acknowledgment

We would like to thank the primary care based diagnostic center Stichting Huisartsenlaboratorium Oost (location Velp) for their help in data acquisition.

Table 1. Characteristics of Study Population

Variables	
Population studied, No.	84
Age, mean (SD), y	57 (13.9)
Sex, %	
Female	61
Male	39
Body mass index, mean (SD)	26.5 (4.3)
Smoker, %	17
Antihypertensive medication, %	
Yes	51
No	49
Reason of referral for 24-hour ABPM, %	
Suspected white-coat hypertension	45
Diagnosis of hypertension	38
Treatment evaluation	12
Other	5

ABPM = 24-hour ambulatory blood pressure monitoring

Table 2. Blood Pressure Levels for Daytime ABPM and 30-Minute OBPM

Measurement	30-min OBPM (SD)	Daytime ABPM (SD)	Δ 30-min OBPM–ABPM (95% CI)	SDD
MAP (mmHg)	104 (12)	103 (11)	2 (0 to 3)†	7
SBP (mmHg)	141 (17)	141 (14)	0 (–2 to 2)	10
DBP (mmHg)	84 (11)	82 (11)	2 (0 to 3)‡	6

ABPM = ambulatory blood pressure monitoring;
CI = confidence interval;
DBP = diastolic blood pressure;
MAP = mean arterial pressure;
OBPM = office blood pressure measurement;
SBP = systolic blood pressure;
SDD = standard deviation of the difference of the mean;
† P = .03; ‡ P = .008;
Note: Because of rounding, figures may not add up correctly

Table 3. Comparison of the number of patients classified by hypertension subtypes between 30-minute OBPM and daytime ABPM

Subtype	30-min OBPM	Daytime ABPM
Normotensive	18	15
White coat hypertension	13	13
Masked hypertension	1	4
Sustained hypertension	52	52

HT = hypertension;
WCH = white coat hypertension
Note: There were 87% of patients similarly classified by both 30-min OBPM and daytime ABPM

Figure 1: Course of mean systolic blood pressure during 30 minutes of measurement

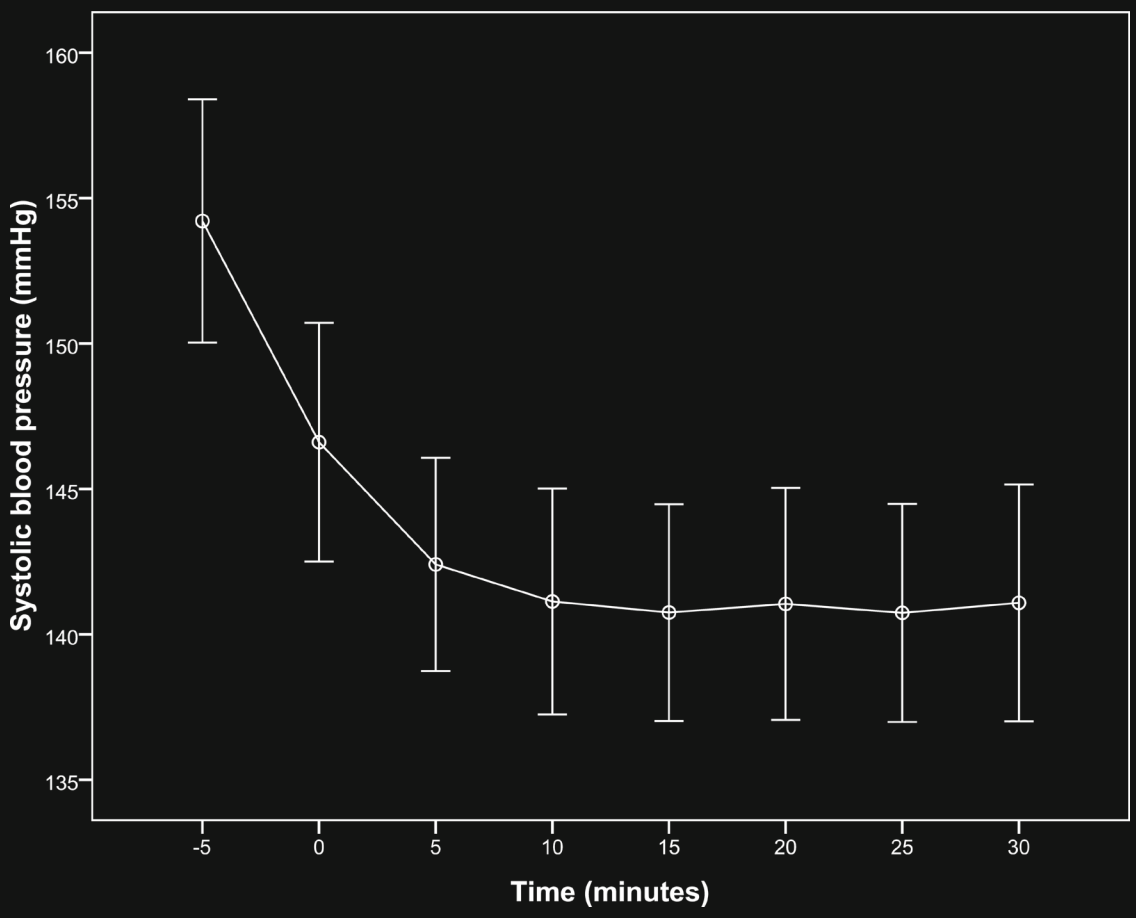


Figure 2a. Bland-Altman plot of difference in mean arterial pressure between 30-minute OBPM and daytime ABPM against mean mean arterial pressure

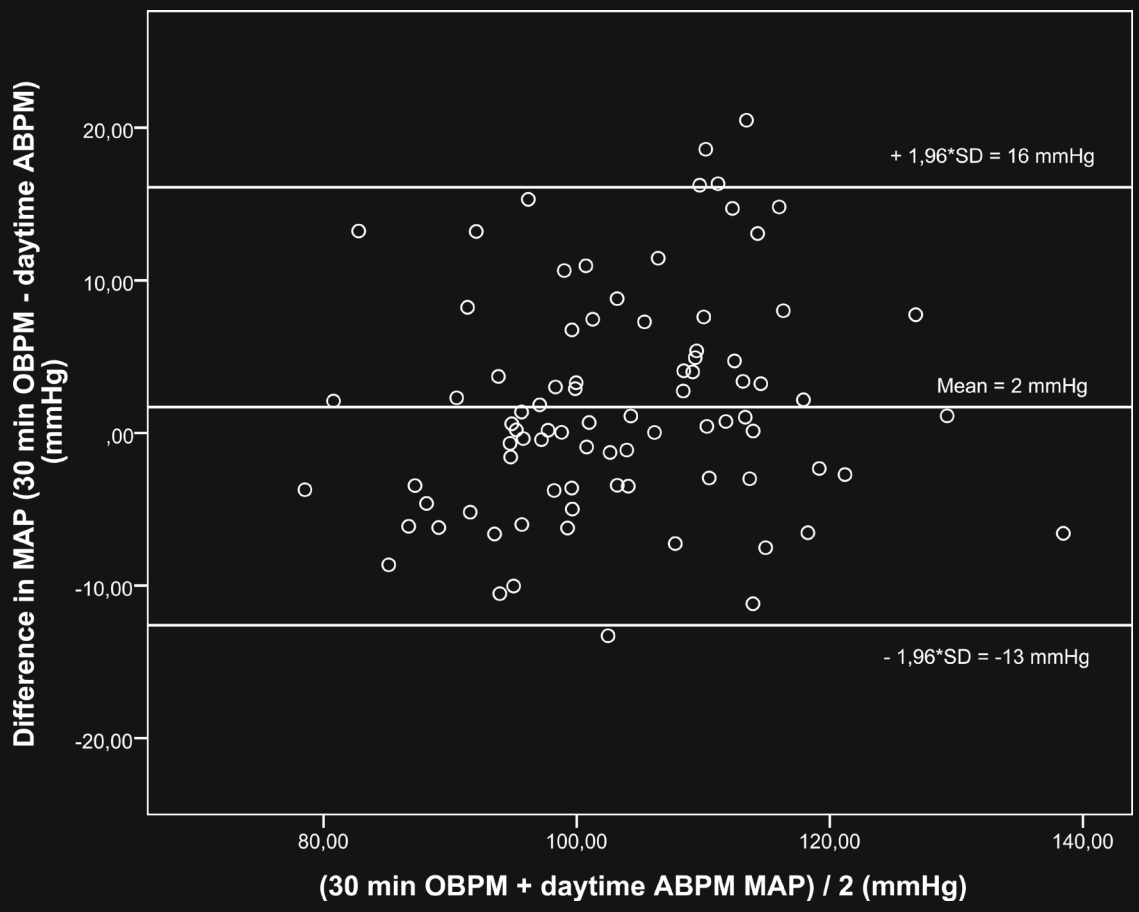


Figure 2b. Bland-Altman plot of difference in systolic blood pressure between 30-minute OBPM and daytime ABPM against mean systolic blood pressure

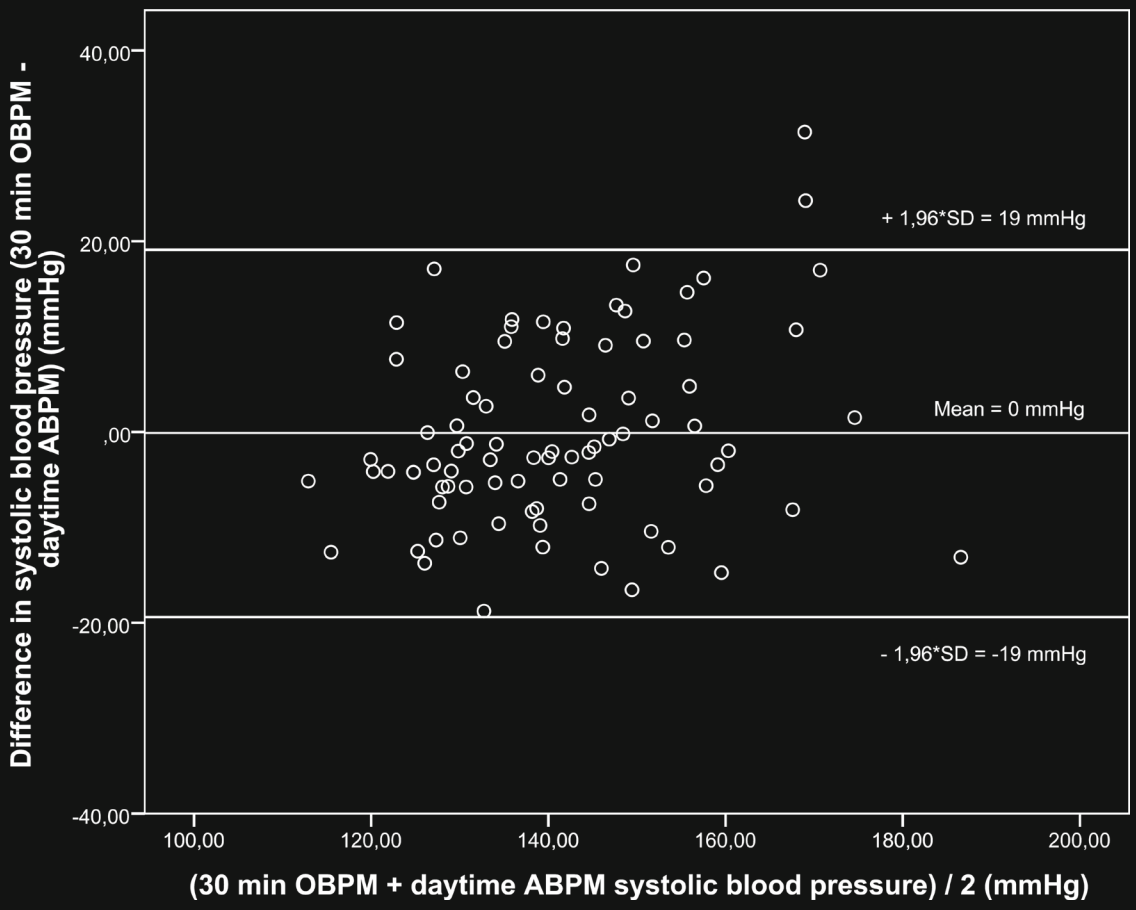
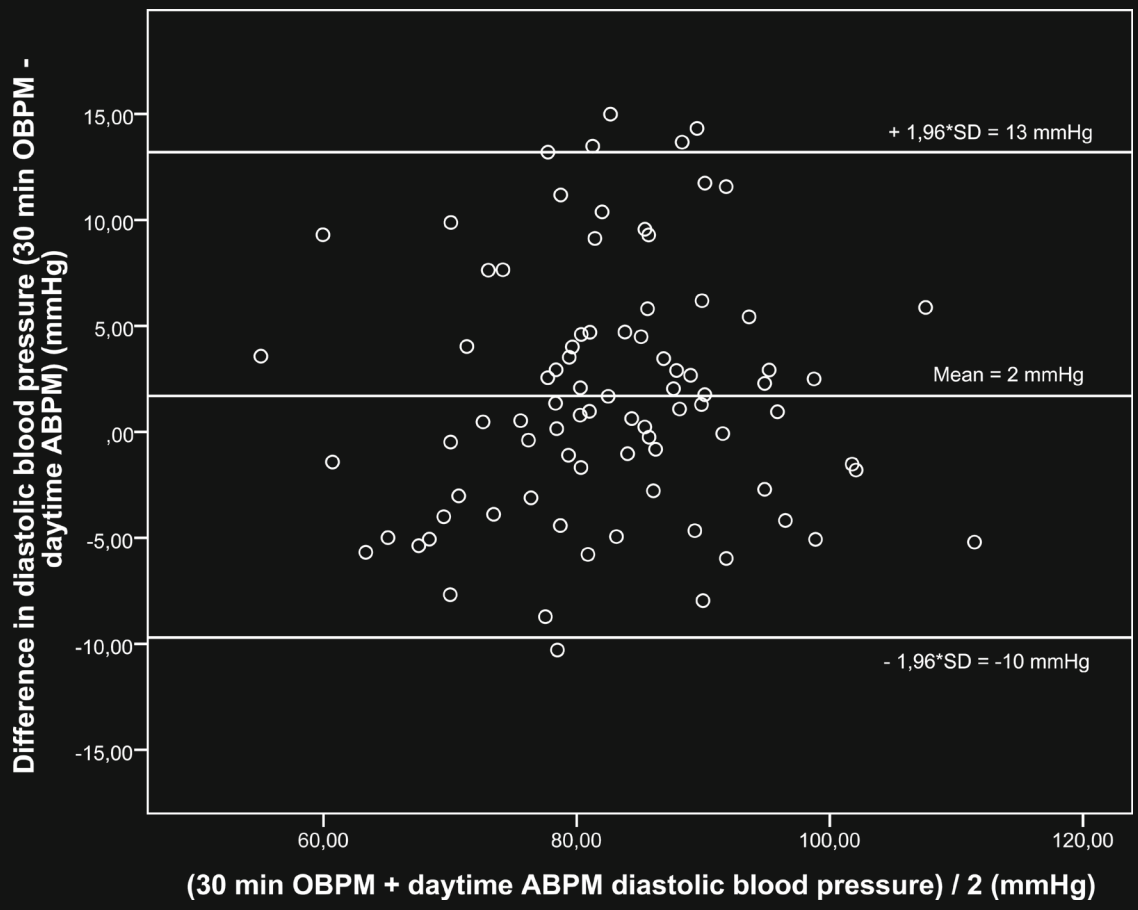


Figure 2c. Bland-Altman plot of difference in diastolic blood pressure between 30-minute OBPM and mean daytime ABPM against mean diastolic blood pressure



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Chapter 5

Comparison between supine, 30 minute, serial, automated office blood pressure and ABPM

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Abstract

Background: Recently it was demonstrated that sitting 30-minute automated office blood pressure measurement (30-min OBPM) agreed well with daytime ABPM and classified subtypes of blood pressure similarly. Until now it is unclear if supine 30-min OBPM could be considered as an alternative for sitting 30-min OBPM.

Objective: To validate a supine 30-minute OBPM through a method comparison with daytime ambulatory blood pressure.

Methods: In patients referred to two primary care diagnostic centers for 24-hour ambulatory blood pressure monitoring (ABPM) we used the same, validated ABPM device for both measurements. During supine, 30-min OBPM blood pressure was measured automatically every five minutes, with the patient lying still, alone in a quiet room. Mean 30-min OBPM (based on t=5 to t=30 minutes) was compared with mean daytime, nighttime and 24-hour ABPM using paired t-tests and the approach described by Bland and Altman on method comparison.

Results: Data of 96 patients (mean age 60 years; 58% female) were analyzed. Systolic blood pressure differed -1 (-4 to 2), 17 (14 to 20) and 2 (-1 to 4) mmHg between supine 30-min OBPM and daytime, nighttime and 24-hour ABPM respectively (95% CI). Supine 30-min OBPM classified normotension; white coat hypertension; masked hypertension and sustained hypertension equal to daytime ABPM.

Conclusions: Supine 30 min OBPM agreed well with daytime ABPM also in classifying subtypes of blood pressure like white coat and masked hypertension. 30 minutes supine blood pressure does not resemble blood pressure while sleeping. Although we prefer sitting 30-min OBPM, the results of this study suggest that supine 30-min OBPM presents an alternative method to determine blood pressure in the office and can be used when patients' preference or physical condition would make it more appropriate.

Introduction

There is a small but growing body of evidence that demonstrates the value and relevance of serial automated office blood pressure measurements (AOBPM).[1, 2]
For AOBPM, measurement devices can be used that are purposely built for this task (e.g. BPTru, Microlife WatchBP Office). These devices are capable to measure blood pressure with relatively small time intervals down to 15 seconds.[3, 4]
We hypothesized that ambulatory blood pressure devices could also be convenient to use for AOBPM. In a validation project consisting of three studies we validated an AOBPM with duration of 30 minutes (30-min OBPM). In two studies we demonstrated that sitting 30-min OBPM agreed well with both daytime ambulatory and standardized office blood pressure measurement. Reproducibility proved to be better than that of standardized office BPM.[5, 2] This paper reports the validation of supine 30-min OBPM.
While in older guidelines supine and sitting blood pressure measurements were considered to be interchangeable [6-8] in most recent guidelines the position of supine measurements is no longer mentioned [9, 10], or considered for certain subgroups.[11] Predominantly in hospital settings, however, supine AOBPM is used as primary blood pressure measurement. Reasons to maintain supine measurements are tradition, inability for subgroups of patients to sit (still) for several minutes, better standardisation of the arm position and management of the patient flow in outpatient clinics. One could argue that supine blood pressure measurements may compare with nighttime blood pressure levels and would thus underestimate true daytime blood pressure. As part of the validation of 30-min OBPM we therefore studied how supine 30-min OBPM agrees with daytime and nighttime ABPM.

Methods

Design, setting and participants
In this comparative study patients aged 18 years or older who, over a six month period, were referred to two primary care based diagnostic centers for 24-hour ambulatory blood pressure monitoring (24-hour ABPM) by their family physician were invited to participate. Reasons for referral were obtained from routinely used referral forms.
Known atrial fibrillation, irregular pulse, pregnancy, working in night-shifts and four or more alcohol consumptions in the evening prior to the 24-hour ABPM were exclusion criteria. After informed consent a 30-min OBPM took place directly prior to 24-hour ABPM. Ethics approval was not required, as declared by the local Medical Ethics Committee of the RUNMC (Central Committee on Research involving Human Subjects, Arnhem-Nijmegen, The Netherlands).

Blood pressure monitors and measurements
OSCAR 2 (SunTech Medical Inc, Morrisville, USA) oscillometric blood pressure measurement devices were used for both the 30 min OBPM and the 24-hour ABPM.[12] For each patient, the same device was used for both measurements. The devices used are calibrated annually.
All 30 minutes measurements took place between 1.00 and 4.00 p.m. in a quiet room at the diagnostic centre. The patient was lying in supine position with a small neck rest five minutes prior to and during the 30-min OBPM. The patient was instructed to lie still for the entire

measurement period and leave both arms parallel to the body. Blood pressure was measured at the non-dominant arm with a five minutes interval for a total of seven measurements. The first measurement (t=0) was after 5 minutes of rest; the researcher (LL or FD) left the room after this measurement proved to be successful (no error reading). We have defined 30-min OBPM to be the mean blood pressure calculated from the six measurements taken at 5 minutes intervals from t=5 to t=30 minutes.[2] If more than one of these six measurements was erroneous (defined as an "error" reading given by the device), the entire case was excluded for analysis. Although we know of at least one ABPM device with a minimum measurement interval of as little as two minutes, we have chosen for five minute intervals to increase generalisability and validate a protocol that can be executed by several types of ABPM devices.
The 24-hour ABPM was set at 20 minutes intervals from 7 a.m. to 11 p.m. and at a one hour interval from 11 p.m. to 7 a.m. Blood pressure was monitored at the same arm as during 30-min OBPM. Patients were instructed to perform their usual daily activities but to stop moving and be silent during measurements. The mean daytime ABPM was calculated from the readings of 9 a.m. to 9 p.m.; mean nighttime ABPM from the readings between 0 a.m. and 6 a.m. and mean 24-hour ABPM from all available readings.[13, 14] Patient instructions and application of the monitors were performed by the same experienced researchers (LL, FD), trained in the procedures of blood pressure measurement, using a standardised protocol based on the AHA guidelines.[15]

Classification of hypertension subtype
In the current study we did not obtain standardized office blood pressure measurements. To enable an indication of the diagnostic value of supine 30-min OBPM we therefore defined office blood pressure to be the first measurement of the 30-min OBPM. Subsequently, we compared supine 30-min OBPM with daytime ABPM in classifying four groups of blood pressure subtypes: normotension (office blood pressure <140/90 mmHg and daytime ABPM or 30-min OBPM <135/85 mmHg); white coat hypertension (office blood pressure ≥ 140/90 mmHg and daytime ABPM or 30-min OBPM < 135/85); masked hypertension (office blood pressure < 140/90 mmHg and daytime ABPM or 30-min OBPM ≥ 135/85 mmHg) and sustained hypertension (office blood pressure ≥ 140/90 mmHg and daytime ABPM or 30-min OBPM ≥ 135/85).

Sample size
We deemed a mean difference of five or more mmHg between both types of measurements in the same patient to be of clinical relevance. Detection of blood pressure differences smaller than five mmHg is seriously hampered by the biological variation of blood pressure.[16, 17] With a two-sided α of 0.05, a power of 90%, and a standard deviation of the difference (SDD) of 15 mmHg a sample size of 81 would allow detection of a difference of 5 mmHg or more.

Statistical analysis
The difference between 30-min OBPM and daytime, nighttime and 24-hour ABPM was calculated, as well as the SDD. The means of daytime, nighttime and 24-hour ABPM and 30-min OBPM were compared using a paired t-test. Bland-Altman plots were constructed to further evaluate agreement.

The limits of agreement in these plots were derived from the standard deviation of the mean difference between both measurements using the formula: mean difference +/- 1.96 * standard deviation of the mean difference.[18] We applied McNemar-Bowker test to determine whether the patients, categorized by 30-min OBPM in one of the four subgroups of the hypertension classification, were similarly categorised with mean daytime ABPM. We used SPSS version 14.0 software (SPSS, Inc) package for all analyses.

Results

We asked one hundred and twenty consecutive patients to participate; 14 patients declined, no patients were excluded. Of 106 included patients three 30-min OBPM and three 24-hour ABPM's exceeded the predefined number of erroneous readings, in 3 patients ABPM data were not stored/saved correctly and turned out to be missing and in one patient a problem occurred with cuff-fitting leaving 96 patients for the final analysis. The characteristics of these patients are shown in Table 1. Mean blood pressure levels and the differences between the ambulatory and 30-min OBPM means are depicted in table 2. While differences between 30-min OBPM and daytime or 24- hour ABPM are within 2 mmHg, nighttime ABPM was between 10 and 20 mmHg lower than 30-min OBPM.

Figures 1a, b and c plot the mean difference of systolic blood pressure between the 30-min OBPM and daytime, night time and 24-hour ABPM against the mean blood pressure. The limits of agreement were between -25 and +23 mmHg; -12 and 46 mmHg and -22 and 26 mmHg for figures 1a-c respectively. Plots for diastolic blood pressure and MAP show a similar pattern (data not shown).

In table 3 it is shown that 30-min OBPM classified patients in the four subgroups of hypertension (as mentioned in the method section) similar to daytime ABPM. There was no significant difference in classification of patients between both measurements ($p = 0.37$); 82% of patients were classified similarly.

Discussion

Systolic and diastolic blood pressure did not differ between supine 30-min OBPM and daytime ABPM (mean differences smaller than 2 mmHg). In contrast, the difference with nighttime ABPM was substantial (17/13 mmHg; $p < 0.001$). Supine 30-min OBPM classified normotension; white coat hypertension; masked hypertension and sustained hypertension equal to daytime ABPM.

Results in context of previous research

We are unaware of previous publications dealing with supine serial automated OBPM. Several publications of Myers et al have demonstrated the relevance of serial automated OBPM in sitting position, but data on lying patients are lacking.[19-21]

Compared to our findings with sitting 30-min OBPM [2] we could not observe a clinically relevant difference neither in the blood pressure readings nor in the classification of blood pressure in different subtypes (like white coat hypertension). Although a direct comparison between sitting and supine 30-min OBPM is lacking, our current findings at least suggest that sitting and supine measurements are interchangeable.

The number of studies dealing with the influence of body and arm position on blood pressure is small and seems to be inconclusive. Netea et al demonstrated that with the arm exactly positioned at heart level systolic and diastolic supine oscillometric blood pressure was 6 and 5 mmHg higher than sitting blood pressure respectively.[22] In studies where the arm position was not corrected sitting was (almost) equal to supine systolic blood pressure (0-2 mmHg higher). Sitting diastolic blood pressure could differ from supine in a range from +2 to -6 mmHg.[23-26] In the last decade only two studies of sufficient quality dealt with supine measurements. One study demonstrated that supine blood pressure was 9/3 mmHg higher than sitting, but information about arm position was lacking and there was no correction for the fixed sequence of measurements.[27] Braam et al showed that blood pressure was 3/1 mmHg higher in supine than in sitting patients with arms exactly at heart level, and 2 mmHg higher systolic but 2 mmHg lower diastolic with arms not positioned at heart level.[28] From the presented data we conclude that body position influences blood pressure independently from arm position but this influence is small and appears to be of minor clinical relevance.

It is well described that blood pressure has a diurnal rhythm which is not based on an underlying circadian rhythm but more so on arousal and (sympathetic) activity.[29-31] In our study the difference between supine 30-min OBPM and nighttime ABPM was considerable, while it was very small with daytime ABPM. This suggests that a 30 minute period of measurement during the day could be regarded more as part of normal daily activities than as the basal situation during sleep. Previous research already demonstrated that resting during daytime is not similar to sleep. In bed ridden patients due to a leg cast blood pressure was 25% higher during the day than during the night.[32]

Limitations

Supine blood pressure is not advocated in most guidelines and most prognostic data are based on sitting BP measurements. However, as discussed, consensus about the influence of body position on blood pressure appears to be lacking.

In our study we did not monitor whether patients fell asleep during supine 30-min OBPM. Our results, however, showed that mean 30-min OBPM agreed well with daytime and poor with nighttime blood pressure. Agreement with daytime ABPM was similar to the agreement of daytime ABPM with sitting 30-min OBPM.[2] In the unlikely event that a patient would have fallen asleep directly after the observer left the room and in addition slept constantly to re-entry of the observer 30 minutes later, in theory the patient could have reached sleeping stage 2 which is reported to result in maximum 10% lower blood pressures than during wakefulness. This is half of the decline that occurs during sleeping stage 3-4.[33, 34]

For logistic reasons we were unable to randomize the order in which 30-minute OBPM and ABPM took place. As a consequence, a regression to the mean effect could have influenced the results of our study. However, the 30-minute OBPM was not used as a selection criterion to undergo 24-hour ABPM, and the mean 30-minute measurement was determined excluding the first measurement.

Despite some methodological limitations we still have chosen to determine hypertension subtypes, because we value to demonstrate practical implications of our findings. We used

the first measurement of 30-min OBPM as normal office measurement, which is likely to be not perfectly similar. In addition we classified white coat and masked hypertension in a population that was in part under antihypertensive treatment. The presented data should therefore be seen as indicative only.

Future perspectives

Although body position influences blood pressure this effect appears to be very small and of minor clinical relevance. In accordance with the most recent guidelines we prefer sitting blood pressure measurements over supine. If a supine measurement is nevertheless method of choice (e.g. because of patient inability or preference) supine 30-min OBPM seems to be a valid alternative for sitting 30-min OBPM.

When combining the findings of this study with the results of sitting OBPM we can now conclude that 30-min OBPM is a robust method to measure blood pressure, with high potential for use in general practice. This makes it particular relevant to establish its clinical value in daily practice.[21] In future studies we would like to establish the minimum and optimum requirements, with regard to a priori rest period, measurement interval and measurement time for a serial automated OBPM protocol and thus stimulating implementation of automated OBPM irrespective of the device used. In addition, data on the cost effectiveness of 30-min OBPM is needed.

Acknowledgement

We would like to thank the primary care based diagnostic centres Stichting Huisartsenlaboratorium Oost (location Velp) and Diagnose for U (Eindhoven) for their help in data acquisition.

Table 1. Characteristics of study population

Variables	
Population studied, No.	96
Age, mean (SD), y	60 (13.6)
Sex, %	
Female	58
Male	42
Body Mass Index, mean (SD)	26.6 (4.1)
Smoker, %	14
Antihypertensive medication, %	
Yes	61
No	39
Reason of referral 24-hour ABPM, %	
Suspected white-coat hypertension	12
Diagnosis hypertension	47
Treatment evaluation	40
Other	1

ABPM = 24-hour ambulatory blood pressure monitoring

Table 2. Mean blood pressures for 30-min OBPM, daytime, nighttime and 24-hour ABPM and mean differences between 30-min OBPM and ABPM

	SBP	DBP	MAP
30-min OBPM (SD)	140 (16)	80 (11)	101 (12)
Daytime ABPM (SD)	141 (15)	80 (11)	101 (11)
Nighttime ABPM (SD)	123 (16)	67 (10)	86 (12)
24-hour ABPM (SD)	138 (15)	78 (10)	99 (11)
Δ 30-min – day ABPM (95% CI)	- 1 (-4 to 2)	0 (-2 to 1)	-1 (-2 to 1)
Δ 30-min – night ABPM (95% CI)	17 (14 to 20) †	13 (11 to 15) †	15 (12 to 17) †
Δ 30-min – 24-hour ABPM (95% CI)	2 (-1 to 4)	2 (0 to 3) ‡	2 (0 to 4) ‡

ABPM = ambulatory blood pressure monitoring;
OBPM = office blood pressure measurement;
SBP = systolic blood pressure;
DBP = diastolic blood pressure;
MAP = mean arterial pressure;
CI = confidence interval; † $p < 0.001$; ‡ $p < 0.05$

Table 3. Comparison of the number of patients classified in the hypertension subtypes between 30-min OBPM and daytime ABPM

	30-min OBPM	Daytime ABPM
Normotensive	14	12
WCH	21	21
Masked HT	1	3
Sustained HT	63	63

HT = hypertension;
WCH = white coat hypertension;
82% of patients are similarly labeled by both 30-min OBPM and daytime ABPM

Figure 1a. Bland-Altman plot of difference between supine 30-min OBPM and daytime ABPM systolic blood pressure against mean systolic blood pressure

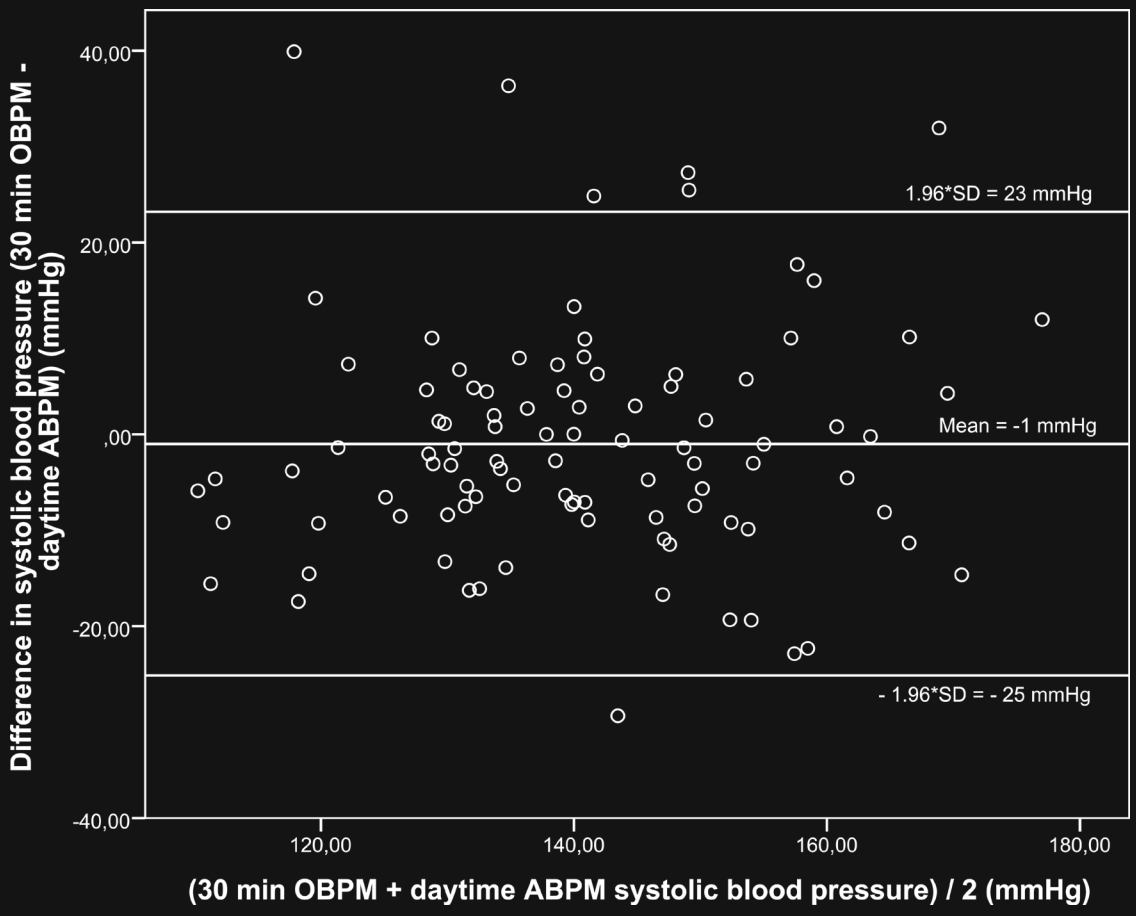


Figure 1b. Bland-Altman plot of difference between supine 30-min OBPM and nighttime ABPM systolic blood pressure against mean systolic blood pressure

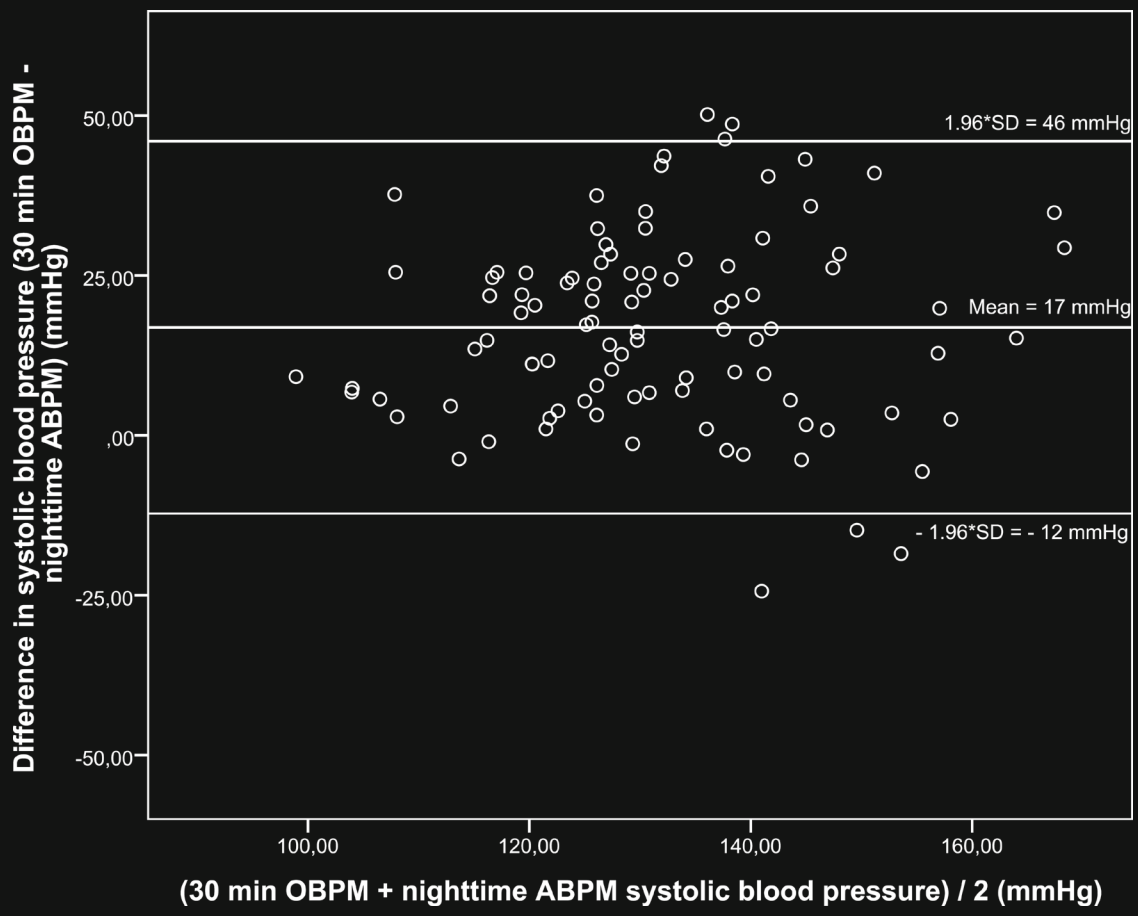
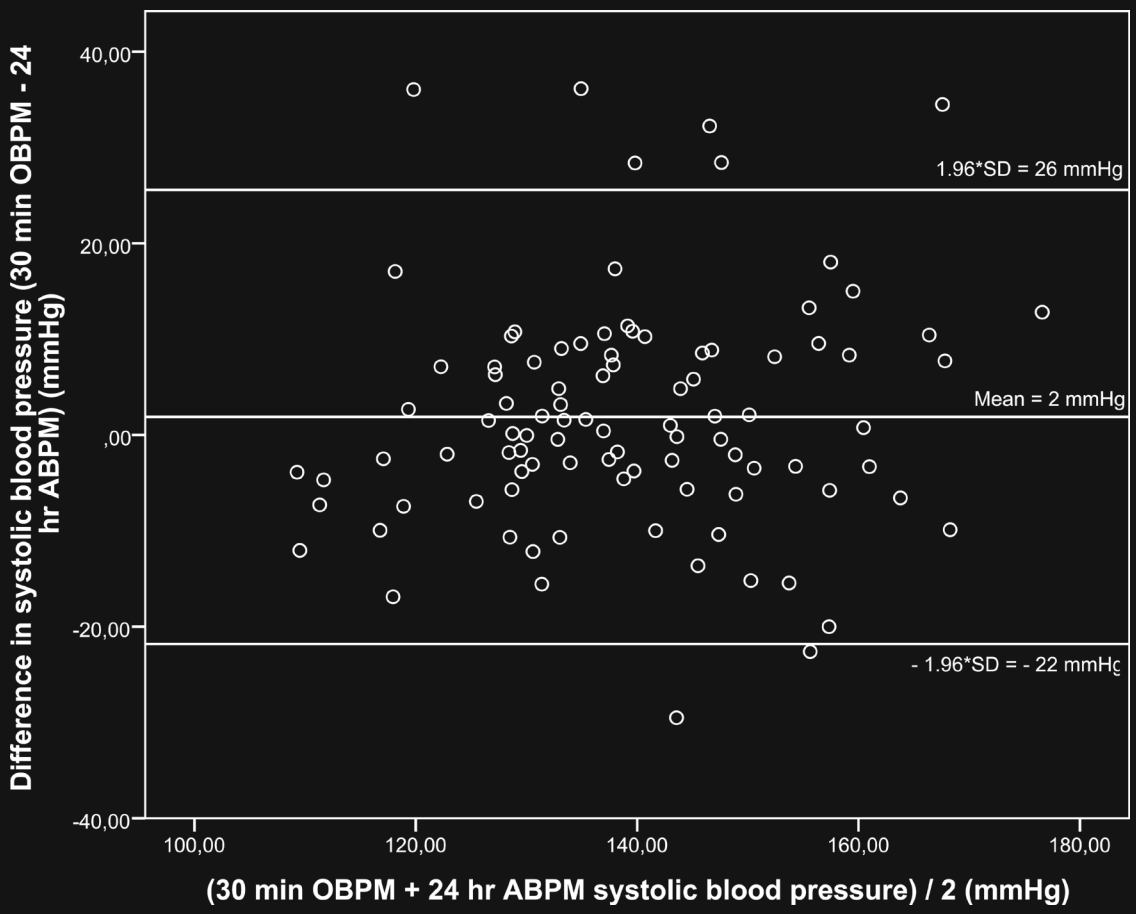


Figure 1c. Bland-Altman plot of difference between supine 30-min OBPM and 24-hour ABPM systolic blood pressure against mean systolic blood pressure



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Chapter 6

Patient characteristics do not predict the individual response to antihypertensive medication: a cross-over trial

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Abstract

Background: Population based hypertension control is suboptimal, despite widely available, cheap and effective treatment options. Patient tailored initiation of treatment may improve hypertension control rates. Previous studies exploring the use of patient characteristics as predictors of treatment response came with several methodological limitations and are not well transferable to everyday general practice – the setting were most patients with hypertension are diagnosed and treated.

Objective: To study potential predictive patient characteristics to the response of two classes of antihypertensive drugs with different mechanisms of action in patients with newly diagnosed hypertension in primary care.

Methods: We conducted a prospective, open label, blinded endpoint crossover trial in ten, Dutch general practices. 120 patients with a new diagnosis of hypertension identified in usual general practice entered the study. Most important exclusion criteria were use of antihypertensive medication and presence of cardiovascular co-morbidity. 98 patients (52% female; mean age 52 yrs) were eligible for per-protocol-analysis. Patients received 4 weeks of 12.5 mgr hydrochlorothiazide once daily and 4 weeks of 80 mgr valsartan once daily, each followed by a 4 week washout. The sequence of drugs was randomized. Age, sex and menopausal state were recorded at run in and 24-hour ambulatory blood pressure, office blood pressure, plasma renin concentration, NT-proBNP, potassium, estimated glomeral filtration rate, urinary albumin, body mass index and waist circumference at each regimen change. Blood pressure response was determined by 24-hour ambulatory blood pressure monitoring.

Results: Besides BMI -which was significantly related to the effect of valsartan (ß -0.63, $p = 0.04$) - the studied variables were not predictive for blood pressure response. Individual systolic blood pressure response ranged from an increase by 18 mmHg to a decrease of 39 mmHg.

Conclusions: We did not find predictors that could support personalised hypertension treatment in uncomplicated essential hypertension. Our findings are not in agreement with the theoretical framework used to support the current treatment recommendation of the NICE guideline on hypertension.

Introduction

Recent meta-analyses have demonstrated that on average all known classes of antihypertensive medication are equally effective in reducing blood pressure.[1;2] However, several studies have confirmed what clinicians experience in daily practice: in individual patients treatment response can differ substantially from one antihypertensive class to the other.[3;4]

This finding supports the attractive possibility that predictive factors can be identified that determine the success rate of an antihypertensive drug. Application of such a predictive therapeutic strategy, able to predict the hypotensive response, might reduce polypharmacy, enhance treatment adherence and reduce costs.[5;6]

Research in animals and humans suggests that several patient characteristics may have predictive qualities. All international guidelines on hypertension management advise to initiate treatment in patients of African or Caribbean descent with a diuretic or calcium channel blocker (CCB), because renin-angiotensin-aldosterone-system (RAAS) activity is relatively low in most of these patients.[7-9] Besides ethnicity, other potential factors are plasma renin [4;10;11], NT-proBNP [3;12], potassium [13], estimated glomeral filtration rate (eGFR), urinary albumin, waist circumference [14], BMI [15], sex [16;17], age [18;19] and menopause.[20]

Because hypertension is diagnosed and managed most often in general practice, studies on individual treatment response should ideally be performed in general practice based populations and reflect an age around 55-60 years, in which diagnosis is commonly made.[21;22] Selection of predictive characteristics should preferably be based on the actual feasibility of implementation in daily general practice. Several clinical studies have tried to identify predictors of the individual blood pressure response to different classes of antihypertensive medication.[3;4;11;23;24] However, extrapolation to current general practice is seriously limited for a number of reasons: some studies examined only patients younger than 55 years [3;4]; all included predominantly male patients [3;4;11;23;24]; some studies used only supine blood pressure measurements[3;4] or studied diastolic blood pressures.[3;11;23;24] In addition, in some studies identification of predictors was not the primary objective.[3;4;24]

We therefore decided to set up a study with the primary objective to identify predictors to the blood pressure response of two classes of antihypertensive drugs with different mechanisms of action (angiotensin receptor blocker (ARB) and diuretic) in a representative general practice population and with a set of potential predictors that are feasible to implement in the general practice setting.

Methods

Patients, design and setting

Patients with newly diagnosed hypertension, aged 18 – 65 years and listed in 10 general practices affiliated with the Radboud University Nijmegen Medical Centre [25] were screened for eligibility to participate in a prospective open label blinded end point (PROBE) [26] crossover study. Patients in whom the diagnosis of hypertension was confirmed and who gave written informed consent were included in the study. Exclusion criteria were use of antihypertensive medication, blood pressure higher than 210/110 mmHg, inability to speak or understand Dutch and presence of cardiovascular co-morbidity (diabetes mellitus, peripheral arterial disease,

ischemic heart disease, stroke, transient ischemic attack and atrial fibrillation). We excluded this last group because hypertension treatment algorithms differ from those in uncomplicated patients.[7-9]

After a two week run-in period, patients used four weeks of hydrochlorothiazide 12.5 mg once daily and four weeks of valsartan 80 mg once daily. The sequence of medication was randomized and each medication period was followed by a 4 week washout period (figure 1). At the run in and at the start and end of each medication or washout period we measured 24 hour ambulatory blood pressure (24-hour ABP), office blood pressure (OBP), plasma renin concentration, NT-proBNP, plasma potassium concentration, eGFR, urinary albumin excretion, body mass index (BMI) and waist circumference. At the run in also age, sex and menopausal state were recorded.

The study was approved by the local Medical Ethics Committee of the RUNMC (Central Committee on Research involving Human Subjects, Arnhem-Nijmegen, The Netherlands) and registered in clinicaltrials.gov under NCT00457483.

Blood pressure measurements

During the eligibility screening performed by the local staff of the general practices a confirmed diagnosis of hypertension (≥ 140/90mmHg) was based on the mean of blood pressure measurements taken at three different office visits. All practices were provided with two validated oscillometric office monitors (Stabil-O-Graph, I.E.M. GMBH, Stolberg, Germany).[27] These monitors were exclusively used for study patients and were re-calibrated every two years. The office blood pressure measurements during the study were taken by practice nurses who were trained in the methodology of standardised blood pressure measurement.

All 24-hour ABP recordings were taken on week days and patients were asked to keep a standardised diary of daily activities. Practices used the same, validated 24-hour ABPM device (Mobil-O-Graph, I.E.M. GMBH, Stolberg, Germany).[28] The measurement interval was 20 minutes from 7 a.m. to 11 p.m. and 1 hr from 11 p.m. to 7 a.m. We defined the mean day ABPM from 9 a.m. to 9 p.m. and we used this measure as our primary blood pressure outcome. Only recordings with 70 % or more valid readings were used. Using the software of the ABP device, the display of the device was set not to show blood pressure values. Ambulatory blood pressure values were not communicated to the patient, prescribing physician and researcher until after completion of the study protocol.

Study variables and study medication

We selected demographic and biochemical variables that general practitioners commonly use or that are easily implemented in daily practice. All blood and urine samples were collected in the morning (before 12.30 pm) and analyzed at one primary care orientated diagnostic centre. Sample analyses were performed batch wise. The following laboratory tests were used: creatinine (CREA plus, Roche Diagnostics), renin (DSL-25100 ACTIVE Renin IRMA kit, Diagnostic Systems Laboratories), NT-proBNP (Elecsys, Roche Diagnostics), potassium (ISE Indirect, Roche Diagnostics), urine albumine (COBAS, Roche Diagnostics).

Based on literature about equipotence, patients used 80 mg valsartan once daily and 12.5 mg hydrochlorothiazide once daily.[29] These dosages also are in agreement with recommendations

of the Dutch guideline on cardiovascular risk management.[30] Following the PROBE design, medication was not blinded for both patients and the prescribing general practitioners. We recorded compliance and adverse events with the use of standardised questionnaires.

Statistical analyses and sample size calculation

First, we applied descriptive statistics to compare baseline patient characteristics of patients who completed the study with those who were lost to follow up. We used Pearson's test for correlation to study the relation between the individual blood pressure responses of both medications. To visualise intra-individual responses of blood pressure to both medications we plotted all individual responses and linked the results of each patient.

Next, we performed mixed model analyses (using a compound symmetry correlation matrix) to determine whether relevant carry-over, period and treatment effects occurred.

In the final step, according to a per protocol analysis on those patients that had minimally completed the second medication period, we used univariate followed by manual forward multiple regression analysis with mean systolic blood pressure response (blood pressure at start of treatment minus blood pressure after 4 weeks of treatment) to either hydrochlorothiazide or valsartan as primary dependent variables. A negative blood pressure response implies a rise in blood pressure after treatment. Renin and NT-proBNP were modelled after log transformation.

Although our study was not primarily powered for (post-hoc) subgroup analyses, we explored how results would alter in subgroups based on sex, the age used in the NICE guideline (<55 years; or ≥ 55 years) and on renin and NT-proBNP tertiles.

In all analyses we considered a two sided p-value of < 0.05 to be significant. Statistical test were performed with SPSS version 16 (SPSS Inc, Chicago, Illinois). With 10 variables that in theory could all be part of the multiple regression model and with a minimum requirement of at least 10 observations per variable [31] a sample size of 100 patients was needed for final analyses. Taking loss to follow up in account we planned to include 140 patients.

Results

Of 159 patients formally assessed for eligibility, 120 patients signed informed consent and 98 patients were included in final analysis. Patient flow and loss to follow up are visualized in figure 2. In Table 1 the main patient characteristics at baseline (start of the first medication period) are depicted. Figure 3 depicts the difference in systolic blood pressure response for each patient. This response ranged from -18 to 34 mmHg and -17 to 39 mmHg for hydrochlorothiazide and valsartan respectively. There was no correlation between the response to hydrochlorothiazide and valsartan ($r = 0.02$, $p = 0.88$). Repeated measures analyses demonstrated that there was no significant difference between the daytime ambulatory blood pressure values at the start of the first medication period and at the end of each washout period (figure 1). There was no difference in carry- over effect between both sequences of study medication. For systolic blood pressure we found no period effect, while for diastolic blood pressure the period effect was significant (1.8 mmHg, $p = 0.04$). Valsartan reduced blood pressure on average by 3/2 mmHg more than hydrochlorothiazide ($p = 0.03$).

We did not find a single study variable to predict the systolic blood pressure response to hydrochlorothiazide (table 2). Table 3 depicts that with increasing BMI the response to valsartan decreased. Results were similar for diastolic blood pressure (data not shown).
Post hoc analysis (table 4) demonstrated that mean blood pressure reduction by valsartan in patients of 55 years and older was exactly the same as in younger patients ($p = 0.99$). Hydrochlorothiazide appeared to reduce blood pressure better in patients of 55 years and older, but the difference with younger patients was not significant ($p = 0.17$) In young patients valsartan reduced blood pressure significantly more than hydrochlorothiazide; in older patients a similar pattern was seen but the difference was not significant. Both study medications tended to reduce blood pressure more in women than in men. In women valsartan reduced blood pressure significantly more than hydrochlorothiazide; in men this difference was not significant. Although not significant, for each tertile of higher plasma renin concentration valsartan tended to reduce blood pressure more than hydrochlorothiazide. The effect of both medications did not differ significantly between tertiles.

Discussion

In this study with newly diagnosed hypertensive patients in general practice plasma renin concentration, age, NT-proBNP, potassium, eGFR, urinary albumin, waist circumference, sex and menopausal state were not predictive for the response to either valsartan or hydrochlorothiazide. BMI weakly but significantly predicted the response to valsartan.
Our study underlines results of previous crossover trials that were also unable to find convincing evidence for the use of predictors in antihypertensive management.[3;4;23] While one study could not identify predictors (including plasma renin activity, catecholamines, age) for blood pressure response at all [3], another only found plasma renin activity to be a weak predictor ($r = -0.40$) for ACE-inhibition but not for ß blockade.[4] Finally, in another trial plasma renin concentration and blood pressure response to ACE inhibitor were not related, while a weak association ($r = 0.32$) with a ß-blocker existed.[23] Our study is the first to suggest a predictive role for BMI. However, the inverse relation with the response to valsartan is opposite to what we expected based on pathophysiological grounds.[14;15] We do not exclude that our finding may be based on chance.
We hypothesised that we would find considerable intra-individual differences in blood pressure response to both study drugs, but that the mean blood pressure reduction of valsartan and hydrochlorothiazide would be the same. However, in our study sample valsartan was slightly more effective in reducing blood pressure then hydrochlorothiazide.
In an attempt to understand this difference, results from post-hoc analysis suggested that plasma renin concentration does not affect response to valsartan; that part of the difference depends on sex and that valsartan is equally effective in patients younger than 55 compared to those of 55 years and older.
Rather than valsartan to be less effective in older patients it is hydrochlorothiazide that seems to be less effective in younger patients. This conclusion is in agreement with one study that demonstrated that treatment success for diastolic blood pressure (data of systolic blood pressure were not presented) of captopril was similar in young and old white patients (cut-off 60 years) and that in old whites treatment response of captopril was similar to hydrochlorothiazide.

Only in young whites hydrochlorothiazide appeared to be less effective.[11] However when scrutinizing the source of the data of this study [24], systolic blood pressure response to captopril and hydrochlorothiazide in white patients did not differ between age groups for each medication nor between both medications.

Since 2006 the NICE/BHS guideline recommends to stratify treatment in uncomplicated essential hypertension based on race and age. [9;32] In patients younger than 55 years, treatment should start with an ACE inhibitor or ARB whereas in patients of 55 years and older CCB's should be the first choice medication (AB/CD rule). The NICE recommendation is based on the pathophysiological assumption that at least part of the patients with uncomplicated essential hypertension can be divided in low renin (salt sensitive) and high renin (vasoconstrictive) hypertension.[18;33] This concept combined with the finding that plasma renin activity declines with age was used as the foundation of the modified Cambridge AB/CD rule.[9;18;32] In this rule age and race are regarded as surrogates for plasma renin and as such as predictors of treatment response. Unfortunately, a prospective study proving the cost-effectiveness of the AB/CD rule is lacking. Meanwhile, with regard to age and renin the results of our study do not support the theoretical frame work used to formulate the AB/CD rule. Data from two crossover trials [3;4] and one randomised controlled trial [24] constitute the core evidence for the Cambridge rule. However, as pointed out in the introduction these studies have several limitations. More importantly, if age and renin are indeed key elements in predicting treatment response how can it be explained that in all studies, including the current one age and renin were never convincingly found to be predictive?

One answer might be that in the age range when hypertension is diagnosed most frequently, the pathofysiological mechanism of the development of essential of hypertension is a mixed bag were the model of high versus low renin hypertension only applies to a very small minority. Our results do show that in some individuals differences in blood pressure response are very large, most likely due to a predominant mechanism. Unfortunately, our study suggests that it is not possible to tell beforehand what the predominant mechanism is in an individual patient.

Strengths and limitations

Although our study findings can be generalised to everyday general practice with newly diagnosed patients in the age range when diagnosis of (essential) hypertension is most common, there are several limitations.

We included a rather homogenous group of patients in a relevant age range larger than previous crossover studies. However, lack of sufficient elderly patients (older than 65 years) may have contributed to the fact that we could not identify age as predictor of blood pressure response. Low and high renin hypertension are likely to be present more frequently in the extremes of the age distribution but less so in the age range when hypertension is diagnosed most.

The objective of our study was not to study the efficacy of the studied drugs. In such studies usually a protocol with intention to treat analysis is preferred. We used a per protocol analysis in those patients with full data at least including the second treatment period. It is unlikely that intention to treat analysis with the 22 patients lost to follow up would alter our conclusions. Not only were these patients in baseline characteristics similar to the study sample, more importantly already seven of them stopped before the first treatment either because of human

error in study protocol or because patients disliked 24hr ABPM at run in.
Assessment of urinary sodium excretion [10;11;33] would have enabled improved subtyping of patients in different sorts of essential hypertension as opposed to our pragmatic approach with tertiles of plasma renin concentration. However, we decided not to study sodium excretion because of its patient unfriendliness and erratic results it is unlikely that this variable is easily implemented in general practice. We aimed to use equipotent doses of both studied drugs [29], but a minor difference in equipotence may explain the mean difference in response between valsartan and hydrochlorothiazide.

Considerations for future research
In the search for improved hypertension control, more research on the identification of predictors of blood pressure response in an attempt to enable personalised hypertension management probably will have very limited value. Our results do not support a role for age as surrogate for plasma renin and for renin as predictor itself. Prospective clinical trials evaluating the use of the AB/CD rule versus the management protocol of the ESH guideline and studies evaluating renin driven initiation of treatment versus usual care could help end the ongoing controversy with regard to this topic. If such trials prove to be inconclusive or even reject a useful role for renin or age in the initiation of treatment than the improvement of hypertension control needs better alternatives than patient tailored strategies.

Conclusion
We did not find predictors that support a personalized hypertension treatment strategy in uncomplicated essential hypertension. We did find large intra individual differences in treatment response which in our view justifies initiation of mono therapy and switch to another mono therapy when the first proved to be unsuccessful. The choice of the first drug should be based on costs, anticipated adverse events, co-morbidity and patient opinion.

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Table 1. Baseline characteristics (SD) for patients who completed both medication periods compared to the subgroup of patients lost to follow up

	Completed	Loss to follow up
Population studied, No.	98	22
Age, mean (SD), y.	52 (9)	53 (8)
Sex, % females	52	55
Menopause, % of females	49	64
DayABPM SBP, mean (SD)	152 (12)	150 (14)
DayABPM DBP, mean (SD)	95 (8)	97 (11)
OBPM SBP, mean (SD)	155 (16)	155 (14)
OBPM DBP, mean (SD)	97 (11)	96 (10)
Body Mass Index, mean (SD)	28.2 (4)	27.1 (3)
Waist Circumference	96 (12)	96 (11)
Renin (median)	12.0 (13)	9.3 (14)
NT-proBNP (median)	5.0 (9)	5.0 (7)
Potassium	4.4 (0.3)	4.5 (0.3)
eGFR (MDRD)	84.3 (14)	85.4 (15)
Urine albumin	16.7 (25) [a]	8.1 (6) [b]

DayABPM = daytime ambulatory blood pressure measurement;
SBP = systolic blood pressure;
DBP = diastolic blood pressure;
OBPM = office blood pressure measurement;
BNP = brain natriuretic peptide;
eGFR = estimated Glomerulal Filtration Rate;
MDRD = modification of diet in renal disease; a n=89 ; b n=14

Table 2. Univariate linear regression analyses with systolic blood pressure response to hydrochlorothiazide as dependent variable

	Univariate	
	β	p
Age	0.08	0.395
Sex	-1.41	0.402
Menopause		
Yes	2.45	0.238
No	0.48	0.818
BMI	-0.03	0.904
Waistcircumference	-0.02	0.741
logRenin	-0.55	0.628
logBNP	0.98	0.222
Potassium	-2.80	0.252
eGFR (MDRD)	0.07	0.251
Urinary albumin	-0.01	0.690

BMI = body mass index;
BNP = brain natriuretic peptide;
eGFR = estimated Glomerulal Filtration Rate;
MDRD = modification of diet in renal disease.
We used p=0.05 as cut off for inclusion of variables in the next step of the model;
waistcircumference excluded from model because of collinearity with BMI

Table 3. Univariate and multiple linear regression analyses (manual forward selection procedure) with systolic blood pressure response to valsartan as dependent variable

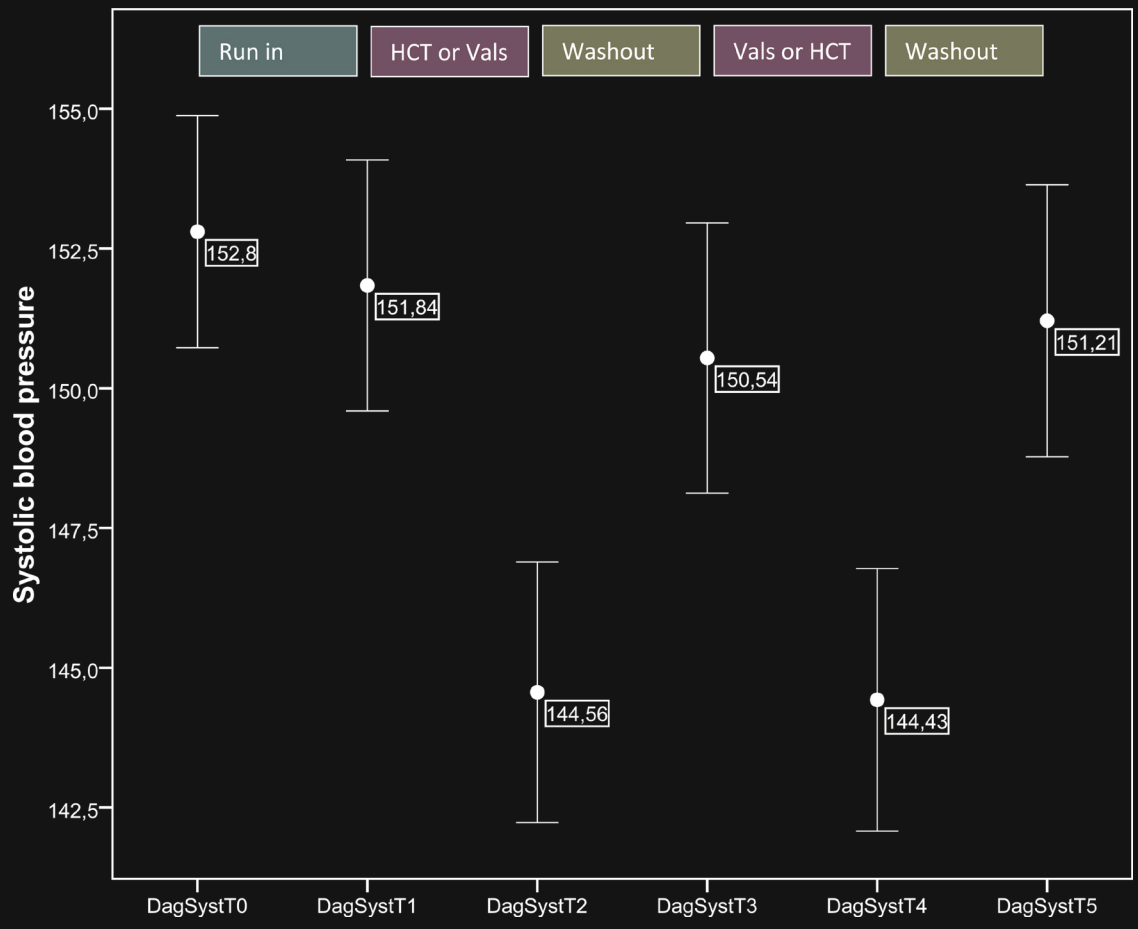
	Univariate		*ModelBMI*	
	β	p	β	p
Age	-0.10	0.434	-0.11	0.378
Sex	-2.95	0.205	-3.08	0.182
Menopause				
Yes	0.61	0.831	0.97	0.741
No	5.30	0.064	4.98	0.078
BMI	-0.63	0.040	-	
Waistcircumference	-0.21	0.039	n.a.	
logRenin	1.38	0.373	1.39	0.363
logBNP	1.36	0.222	1.12	0.314
Potassium	-0.41	0.903	1.12	0.738
MDRD	-0.03	0.751	-0.03	0.757
Urinary albumin	-0.01	0.837	-0.00	0.950

BMI = body mass index;
BNP = brain natriuretic peptide;
eGFR = estimated Glomerulal Filtration Rate;
MDRD = modification of diet in renal disease.
We used p=0.05 as cut off for inclusion of variables in the next step of the model;
waistcircumference excluded from model because of collinearity with BMI

Table 4. Effect size of mean systolic blood pressure reduction by hydrochlorothiazide (HCT) and valsartan for subgroups based on age, sex and plasma renin tertiles

	Effect HCT	Effect Valsartan	p-value
Total	5.0 (8)	8.2 (12)	0.03
Age < 55 yrs (n=59)	4.0 (8)	8.2 (11)	0.02
Age ≥ 55 yrs (n=43)	6.3 (10)	8.2 (13)	0.43
Male (n=49)	4.3 (9)	6.7 (12)	0.25
Female (n=53)	5.7 (8)	9.7 (12)	0.05
Renin 1st tertile	5.2 (9)	8.3 (9)	0.21
Renin 2nd tertile	5.6 (8)	8.0 (13)	0.34
Renin 3rd tertile	4.2 (11)	8.5 10)	0.12

Figure 1. Study design and time course of mean daytime ambulatory systolic blood pressures



Error bars represent standard error of the mean

Figure 2. Patient flow and loss to follow up

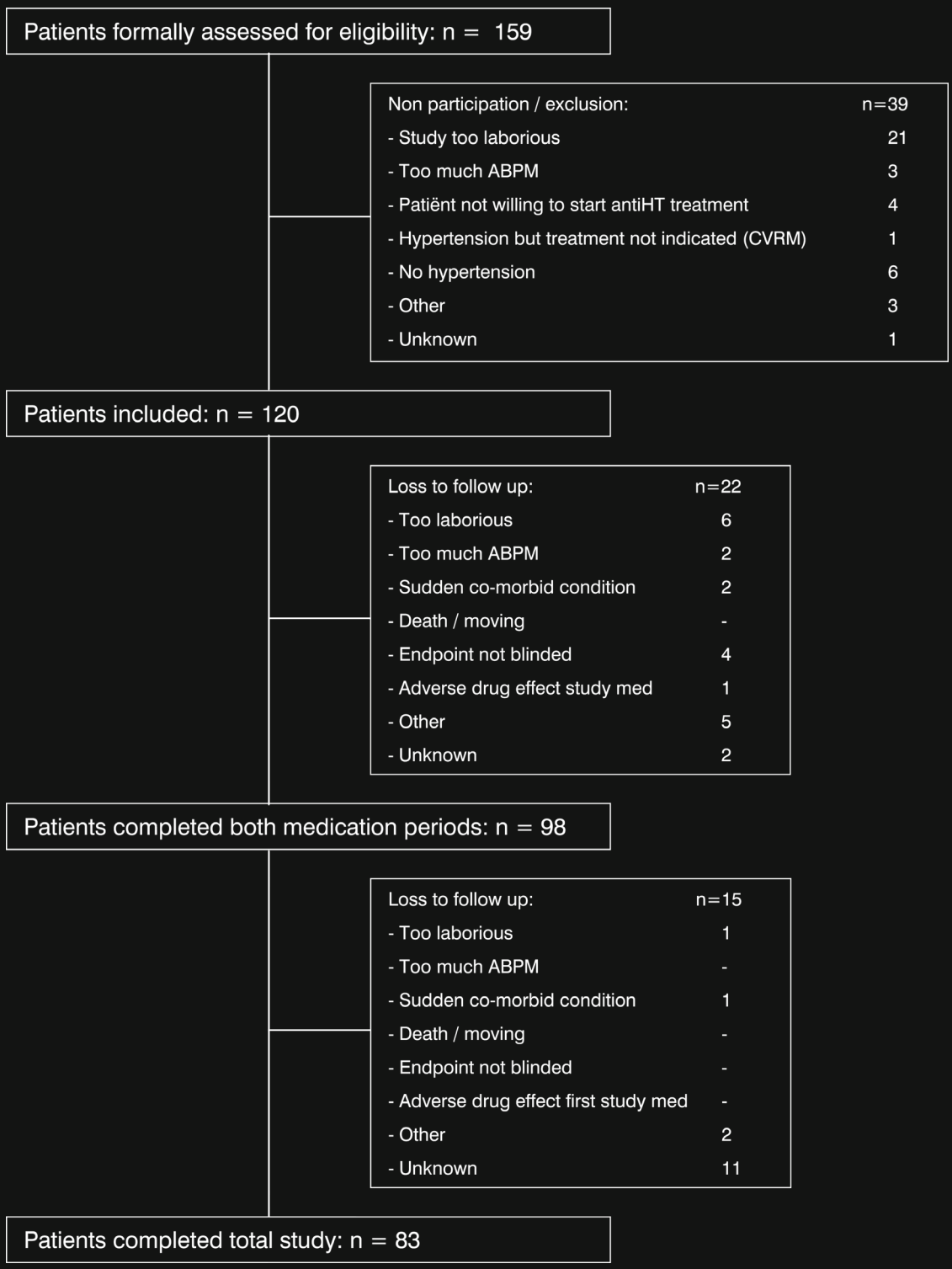
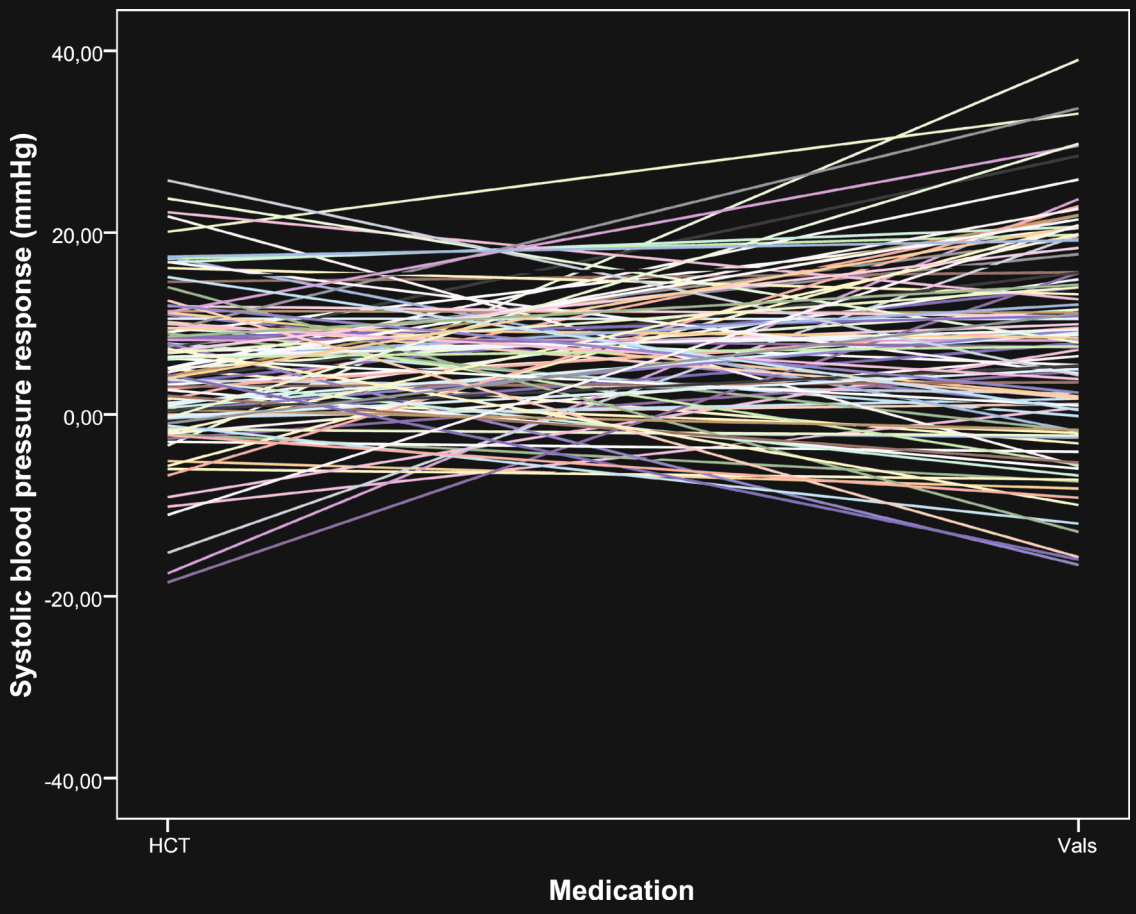


Figure 3. Intra-individual systolic blood pressure response to both study medications



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Chapter 7

General Discussion

In essence

This thesis dealt with two topics, both with the objective to improve hypertension management in primary care.
First, we clinically validated a novel approach of office blood pressure measurement (OBPM) to minimize measurement bias and to overcome the white coat effect: 30 minute serial, automated office blood pressure (30-min AOBPM). In three different sets of patients we demonstrated that sitting 30-min AOBPM readings are lower than readings with standardized OBPM; that the reproducibility of 30-min AOBPM is better than standardized OBPM and that both sitting and supine 30-min AOBP agreed well with daytime ambulatory blood pressure measurement (ABPM). This first phase of validation justifies exploration of the implementation of 30-min AOBPM in usual care.
Second, in a representative sample of newly diagnosed hypertensive patients in primary care we searched for predictors of the response to either a diuretic or an angiotensin receptor blocker. If predictors exist, these could tailor treatment to the individual patient and as such increase the efficient use of medication and resources. Although we found large intra-individual differences in treatment response to both studied drugs, we were unable to identify such predictors.

30-min AOBPM

Methodological considerations
We would like to highlight two aspects of 30-min AOBPM that warrant discussion:

- The influence of the (clinical) setting of blood pressure measurement on the white coat effect
- The duration of AOBPM

The first issue has a direct link with the perceived mechanism of white coat effect. While it has been described that within a clinical setting this effect is mainly attributable to the observer taking the blood pressure[1;2], the question remains whether –independent of the presence of the observer- the clinical setting itself also contributes to the white coat effect and if this contribution is clinically relevant. If the clinical setting itself plays a substantial role in the development of white coat effect, than 30-min OBPM would lose part of its appeal.
Unfortunately, research on the etiology of white coat effect is scarce and its mechanism remains poorly understood. Until now patient-related psychological effects are regarded to be the most important contributor to the white coat effect. Research demonstrating blood pressure to be higher when taken by a senior compared to a junior doctor or between doctor and nurse supports this[3;4], as well as research suggesting that patient's perception of being hypertensive contributes to the development of white coat effect.[5] It is theorized that part of the patients will either conscious or subconsciously associate the doctor and her office with pain, sorrow, miscommunication or unfavorable medical treatment with an anxious state including a rise in blood pressure as a consequence.[2] Also, anticipation or curiosity about the blood pressure to be measured could be of relevance.
To our knowledge only one study provides some data about the contribution of setting (both non-clinical and clinical) versus the role of the doctor in the development of the white coat

effect.[1] Results from this study showed that anxiety increased going from the non-clinical environment to the waiting room of the clinic. Blood pressures were higher in the waiting room than in the non-clinical setting for all four subgroups (sustained, white coat, masked, normotension) of hypertension. This difference in blood pressure was considerably smaller than that introduced by the presence of the doctor. The main conclusion was that the conditioned response to a doctor taking the blood pressure was the most powerful influence on the patient's blood pressure. Although we did not formally study the effect of setting on the results of 30-min AOBPM, based on the above-mentioned research[1] and based on our findings that 30-min AOBPM agreed well with the measurements taken outside the clinic using ABPM we conclude that 30-min AOBPM is able to quantify most if not all of the white coat effect.

Even though 30-min AOBPM takes considerably less time than 24-hour ABPM or HBPM, office management clearly benefits from even shorter interventions; it simply serves more patients per day. Results of the research group of Myers using the purpose built BpTRU blood pressure measurement device for their AOBPM suggest that measurement times of as little as 5-10 minutes (with a 1 minute measurement interval) give reliable results.[6] We chose to start with 30 minute measurement duration for a theoretical and a pragmatic reason. First we based our measurement time on data from several studies suggesting that in a time course of blood pressure measurements blood pressure does not reach a plateau phase within the first 10 minutes.[7-9] Results as presented in this thesis underline this assumption. Second, we used a 24-hour ABPM device with –at the time of the research- a minimum measurement interval of 5 minutes. To facilitate a mean of at least 5 measurements we needed a measurement time of thirty minutes.
Myers demonstrated similar agreement between his protocol of 5 to 10 minutes of measurement and daytime ABPM. However, scrutinizing the previous work of Myers showed that in those studies with data available on the comparison of AOBPM with daytime ABPM the standard deviation of the difference (SDD) proved to be around 15mmHg[10-12] while in our studies the SDD was around 9 mmHg, which is similar to SDD's as reported in 24-hour ABPM reproducibility studies.[13-16] This implies that agreement between 5-10 minute AOBPM and daytime ABPM is inferior to that between 30-min AOBPM and daytime ABPM, involving differences more than can be explained by biological variation alone. This poorer agreement could be a consequence of error caused by blood pressure not yet reaching its plateau phase combined with the fact that the protocol of Myers calculates a mean blood pressure based on five measurements compared to six in 30-min AOBPM. To obtain optimal results we therefore conclude that a measurement period of 30 minutes and a minimum of five measurements are to be preferred.

Future research
Evaluation of the perception of patients and health care staff about the use, feasibility and patient friendliness of 30-min AOBPM compared to HBPM and daytime ABPM could further support the implementation in daily practice. Moreover, it would help acceptance of AOBPM if we can further elucidate the mechanism of white coat effect and confirm that clinical setting itself only contributes modestly (if not at all) to this phenomenon. Next, in a clinical trial, use of 30-min AOBPM in the diagnostic workup of patients with elevated blood pressures should

provide evidence for its cost-effectiveness. The question whether early advanced diagnostic workup indeed reduces the number of "diagnostic visits" to the general practices before a doctor confirms the diagnosis hypertension could be answered in such a trial, just as it will enable insight in the number of patients "saved" from an unjust diagnosis of hypertension and unjust initiation of medication. Finally, it will tell whether this reduction in unnecessary diagnosis and treatment balances the investment in the use of 30-min AOBPM.

Clinical implications and future prospects

Unfortunately results of serial AOBPM cannot be used directly in cardiovascular risk functions like the one based on the Framingham study or the European SCORE risk function.[17;18] After all, these functions are based on data derived from standardized office measurements. This disadvantage is not unique for serial AOBPM but also hampers applicability of ABPM and HBPM and can be partly overcome in a similar way to the interpretation of additional risk factors that are not part of the risk function (like family history, obesity, sedentary life, etc). While guidelines encourage physicians to take these additional risk factors into account by increasing the calculated risk with an estimated guess[19;20], a diagnosis of relevant white coat effect could be used as argument to reduce this risk.

The successful first steps of validation of 30-min AOBPM as novel approach in office blood pressure management, in combination with the available data of other research groups working on AOBPM has stimulated us to formulate how 30-min AOBPM may fit in current hypertension diagnostic work up. The proposed flow of diagnostic evaluation is depicted in figure 1. This proposition needs to be validated by data as described earlier in "Future research".

As shown in this figure it is at the discretion of the doctor and the patient what type of additional blood pressure measurement (HBPM, ABPM or 30-min AOBPM) is preferred. If information on true blood pressure status suffices than the choice will depend on patient's preference and abilities, available type of blood pressure measurement devices and local setting. If additional information like night time blood pressure or dipping status is required than the choice will be limited to ABPM. If only information on true blood pressure status is needed our preference lies with the use of 30-min AOBPM. Compared to HBPM and daytime ABPM this type of measurement is the most standardized type of measurement, which is a major advantage in the interpretation of follow up measurements.

For the near future we foresee a further increase in the use of HBPM and 24-hour ABPM. The very recent publication of the new version of the Dutch multidisciplinary guideline on Cardiovascular risk management has introduced extensive sections with regard to indication, use/implementation and interpretation of these types of measurements, which will stimulate evidence based application of these type of measurements.[20]

The recent publication of the British NICE guideline on hypertension management has gone even one step further and now recommends that for the purpose of identification of white coat effect 24-hour ABPM or HBPM should be in the standard work up of each patient with elevated office blood pressures.[21] The evidence base for this recommendation is subject to heated debate.[22] In contrast to the current NICE guideline we think doctors should be allowed OBPM follow up without 24-hour ABPM, HBPM or 30-min AOPBM in case elevated blood pressure is perceived to be a consequence of a temporarily stressful period in a patient's life.

NAMI study

Methodological considerations

The results of the NAMI study form a small weight that will probably not tip the scale and end the controversy about the use of predictors in hypertension management. Although the body of knowledge that has accumulated over the last decades appears to be quite substantial, a systematic evaluation of the type of knowledge may help to understand why the controversy remains. For this systematic evaluation we first formulated the methodological / epidemiological requirements needed to draw firm conclusions about the predictive qualities of a studied variable (Box 1).

Box 1. Requirements for a variable to be a convincing predictor

1. *A theory (mechanistic, etiologic, pathophysiologic, etc) why a variable could have predictive power*
2. *A valid method of measurement of the variable*
3. *Prospective study in relevant population that demonstrates an association between variable and outcome*
4. *Verification of this finding in additional patient cohorts*
5. *Randomised clinical trials demonstrating that predictor based treatment is more cost-effective than usual care*

Step 1: Theory for predictors

Although not without debate, this first step seems to be fulfilled with the model based on RAAS as described in the Introduction chapter of this thesis. However, the complex regulation of blood pressure involves more than RAAS and entails a variety of organ systems (central nervous system, cardiovascular system, kidneys and adrenal glands) and regulatory mechanisms that are all intricately linked.

Multiple types of feedback loops with both acute and chronic adaptation to different haemodynamic states add to the complexity.[23;24] It is not unreasonable to assume that the proposed model is too much of a simplification, which then may lead to inconclusive evidence. In addition, according to the model, low renin patients should have excessive extracellular and plasma volume and although several studies have demonstrated this relationship [25;26], several others did not.[27-29]

What may be interfering with the robustness of all suggested models is the fact that patients with essential hypertension are a very heterogeneous group. This heterogeneity may be of such an extent that it will limit the possibility to predict response to treatment.[28;30]

Step 2: Valid method of measurement

To validate the renin model a reliable assay to determine plasma renin is essential and preferably there should be one international standard. Unfortunately, an international standard is lacking and both assays determining plasma renin activity and plasma renin concentration

are used. As pointed out previously until recently the quality and interpretation of plasma renin activity assays was subject of debate.[29;31] In summary, although current assays seem to fulfil the conditions of this second step, a substantial part of the previous work on predictors was a source of controversy due to less reliable renin assays.

Step 3 & 4: Prospective data demonstrating association between predictor and outcome
With doubts about meeting the conditions of step 1 and 2 it is not surprising that prospective data on potential predictors were conflicting (table 1, Introduction). In addition, the methodological limitations with regard to study design, sample size, sex distribution and patient selection further restrain interpretation of results. The NAMI study was set up in an attempt to overcome these obstacles.

Step 5: RCT demonstrating cost effectiveness of predictor based treatment
To our knowledge only one proof of concept study has compared a predictor (plasma renin) guided treatment algorithm with usual care.[32] The sample was small with only 57 patients, patient selection included treated, but uncontrolled patients selected from hypertension clinics and costs were not studied. Taking the uncertainties as described in the first four steps into account, it is not surprising that fundibg this final 5th step has been a challenge and that until now this research is missing. A recent comment on controversies in hypertension management suggests that the 5th step is underway.[33]

Clinical implications
Despite the controversial evidence base for the use of predictors in hypertension management and in contrast with the European and American guidelines [17;35], the British NICE guideline on hypertension management recommends the use of an AB/CD treatment algorithm. In this algorithm "A" stands for ACEi, "B" for ß blocker, "C" for CCB and "D" for diuretic. Age –regarded as surrogate for renin- is used at a cut off of 55 years: in younger patients ACE (or ß blocker) should be started, in older patients CCB (or diuretic).[21] The recent Dutch multidisciplinary guideline on cardiovascular risk management has followed this recommendation with the minor adjustment to use a cut off of 50 years.[20] The rationale for this algorithm was based on the interpretation of a selection of evidence in four steps.[21;36]

1. Studies demonstrating the inverse relation between plasma renin activity and age.[37]
2. Crossover trials demonstrating intra-individual differences in treatment response.[38;39]
3. Crossover trials and one RCT suggesting that in young patients ACEi and ß blockers work better, in older patients CCB and diuretics.[38-40]
4. Primary and posthoc analyses of large RCT's on the efficacy of antihypertensive medication demonstrating that CCB and diuretic are more effective in older patients.[41-44]

After scrutinizing the studies that were used to come to the NICE recommendation we do not share the conclusions put forward in the last two steps. While the crossover trials referred to in step 3 did not include patients older than 55 years and included less than 50 patients, data from the RCT clearly show that systolic blood pressure reductions for old and young white patients (similar to the NAMI population) for both diuretic and ACEi were similar.

The conclusion in step 4 was undermined by a recent meta-analysis which concluded that both blood pressure reductions and cardiovascular event rates are similar in old and young patients for the different drug classes.[45] In addition, also the results from the NAMI study do not support this theoretical framework. We therefore advocate physician driven best estimated guess for first choice treatment taking patient's context, co-morbidity, preferences and costs into account.

Future research

From a purely scientific point of view and based on the current evidence it seems reasonable to conclude that predicting response to different classes of antihypertensive treatment in patients with essential hypertension is not possible and that further research exploring this topic is of little use without new knowledge with regard to the first two steps of Box 1.

From a pragmatic point of view it could be worthwhile to end the controversy about the use of predictors by setting up a methodologically sound RCT to explore whether renin driven initiation of treatment is a cost effective approach of hypertension management.

Research on how to improve hypertension control should focus on ways to improve treatment adherence of both doctors and patients. Telemedicine/e-medicine to stimulate patient self management [34] and expert systems integrated in the electronic medical file of physicians could be useful interventions to improve hypertension control. Moreover, research is needed to evaluate whether instant initiation of combination treatment outweighs trial and error initiation of different classes of mono therapy.

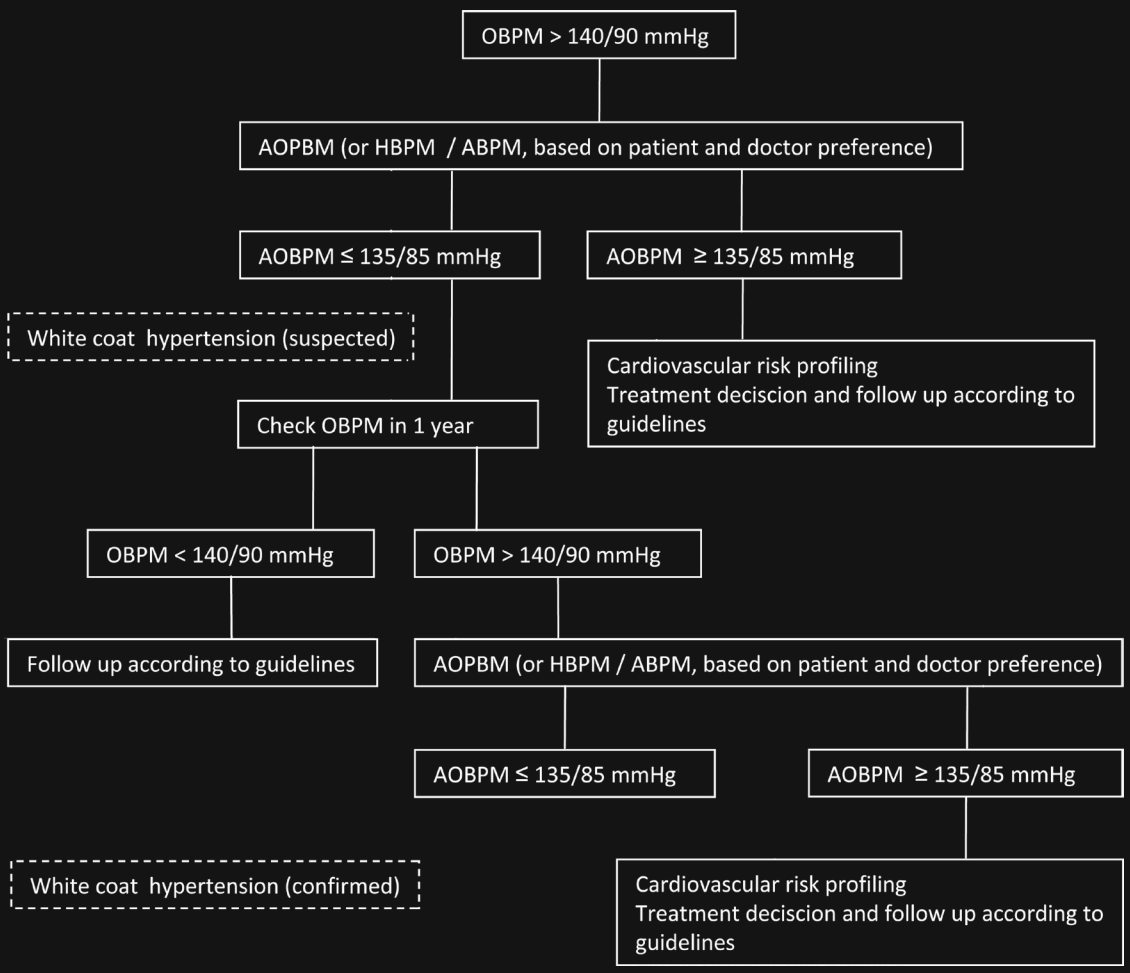
Final remarks

Both research topics in this thesis dealt with hypertension which, as an important risk factor, is part of cardiovascular risk management. This type of management is aimed at prevention of the first event or the recurrence of cardiovascular disease.

Prevention has gained increasing attention by policymakers as part of the solution to deal with the deficit between available resources in health care and the expected progressive increase in demand. While prevention and public health have a lot to offer, the current focus on prevention may have the undesirable side effect of fuelling the perception of people that perfect health is in one's own hand [46], even to an extent where suffering a myocardial infarction despite a low cardiovascular risk is still regarded as one's own fault.[47] In addition some preventive measures will inevitably lead to over diagnosis and over treatment.[48]

As a general practitioner I am worried that our profession is about to lose what I believe to be a powerful asset: the art of parsimony. Several factors contribute to this development of which the focus on prevention is only one. In the final part of this thesis together with several others I have addressed this concern. It explores how less can be more and how physicians need to stand for their ability to wisely do less.

Figure 1. Proposed work up of patient with elevated office blood pressure



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Epilogue

The art of parsimony in delivering care

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Submitted

The art of parsimony

Medicine is about to lose a powerful asset that has become difficult to put into practice: the art of parsimony. Previously described as watchful waiting or quaternary prevention [1], it stands for an active role for the doctor to reach an agreed upon alternative for an initial patient's wish for diagnostic workup or medical treatment, which from a medical viewpoint seems unnecessary or harmful.[2]

Here we describe why this art is important for medicine, what is needed to practice it, the threats to practising it, and our suggestions how to maintain it.

Why is it important?

Parsimony makes sense simply because it is efficient; producing better health for fewer healthcare costs.[3] Case reports [4], primary research [5], and overviews [6;7] have demonstrated the harm of overutilization of diagnostic tests and treatment. Harm can be caused by adverse events but also by negative socio-psychological consequences of (falsely) labelling disease.[8]
If practiced well the art of parsimony will strengthen the patient-doctor relationship (by requiring the doctor to better understand and manage the patient's expectations) [9] and thereby enhance quality of care and satisfaction, of both patient and doctor.
Of course parsimony is not a goal in itself. Not only will it then increase missed diagnoses and undertreatment, it would also risk raising the suspicion of our patients that we are more interested in saving money than caring for them. Rather parsimony aims to protect our patients from harm or overuse, promote self-reliance in health, and judiciously use available resources.

What is needed?

A prerequisite to be parsimonious is the doctor's ability to combine medical expertise and excellent communication skills with self-knowledge and a holistic view of the patient. This will enable building a patient-doctor relationship based on trust.[10;11] Doctors are then set to predict the added value of interventions against the natural course of the health problem, to weigh the patient's perspective, to judge the time frame for eventual reassessment, and to identify indicators against which to (re)assess.[11]

Threats to medical parsimony: societal and medical changes

The medical profession has itself contributed substantially to lack of parsimony. Doctors have contributed to 'medicalisation' of once-normal aspects of the human condition. Patients can now be pre-hypertensive [12], and are no longer sad but are suffering from 'moderately severe depression' requiring drug treatment and psychological intervention.[13]

Another contributing factor is the notion of 'anti-litigation practice', the ordering of tests or offering treatments not so much to benefit patients as to protect doctors. Medico-legal criticism of individual cases tend to focus more on underuse (failing to test or treat) than overuse, (especially in prevention), perhaps reflecting the difficulty we have in practising medical parsimony.

Also the constant pressure on time experienced by most doctors will hamper parsimony. This stimulates ordering futile diagnostics, because it is quicker to offer overmanagement than to explain why not. For all these reasons doctors have "trained" their patients in the desire for more instead of fewer interventions.

Society itself has changed in several ways. People (including doctors) have become hyper-vigilant to risks in life and appear to have increasing difficulty to deal with uncertainty.[14] Values like individual autonomy and personal freedom have become important and coincide with a decrease in 'social capital' consequent on our being less religious and less part of tight-knit social networks.[15] 'God's will' or 'destiny' is replaced by a demand for medicine to eliminate uncertainty and fix illness or distress. Patients increasingly expect this fixing to be done immediately, perfectly, and with minimal effort from themselves.

The organisation of health care has changed from one primarily based on the value of solidarity, to a market orientated organization, increasingly based on individual responsibility.[16] This change supports the role of patients as consumers of health care, rather than 'responsible for one's own health' in a sensible way. The conjoint restructuring of health care finance has introduced incentives for doctors to perform diagnostic workup and start treatment (pay for performance). Unfortunately, this will rather support over- than underuse of medical services.
Next to our intuitive affinity with trust as an important contributing factor to parsimony, research has clearly demonstrated the quality of care and cost effectiveness of high trust patient-doctor relationships.[11;17;18] Ironically, despite this evidence the societal, political and even medical world appears to be navigating away from it.[19;20] Medical misconduct and increased media exposure have contributed substantially to this process.

Furthermore, medical information is now available to the public through a variety of sources (friends, media, virtual communities, wiki's, government, doctors, etc) with –through its multitude– a considerable chance of being conflicting.[21] Data from the swine flu (H1N1) epidemic have shown that conflicting information was the major cause of the significant decrease in confidence in the Dutch government during the progress of the epidemic.[22]

This decline in confidence has induced a steady increase of measures of accountability that seem to evolve in a direction where confidence is replaced by protocol.[20] We foresee these developments to also negatively influence trust on the level of the individual patient-doctor relationship. Bensing and co-authors recently demonstrated that in 15 years time consultations have indeed become more protocolised, without an increase in shared decision making.[23]

Other factors that influence the role of trust in the patient-doctor relationship have to do with the changed image of doctors in society. From a "magician", part of an elite minority with exclusive knowledge on health and disease, he has changed into a peer, a person who "merely" executes protocols and guidelines which are readily available to the public with the use of internet. He has become part of, and is dependent on, a team of health care workers, and for a growing number of patients is trained at a similar, academic level.

A priori trust has therefore decreased and trust has more than ever to be earned just like in any other interpersonal relationship. The above-mentioned threats are strongly interrelated and seem to feed each other in a synergistic way, which has now put more pressure on parsimonious medicine than ever before.

Suggestions how to maintain the art of parsimonious medicine

The factors outside our control (related to societal perception) need something outside our profession. However as doctors there are things we can do:

- Take a stand against moves towards a market-driven health industry; instead we should focus on maintaining and enhancing the patient-doctor relationship. Experiments are needed to find payment methods that promote prudent use of resources.
- Invest not only in our own quality of care, but in that of our colleagues as well. Trust increasingly depends on the patient-health care team relationship, and we need to better understand how this can happen. Together with Stange we foresee that continuous personal connections remain of utmost importance.[11]
- Use of social media and internet based networking, to communicate better with younger generations.[15;24] This may seem somewhat ironic given the fact that new media also feed patients with all kinds of incorrect information, which can cause distress and medical consumerism. However, using these types of media to communicate, facilitate the process of care and create or direct to reliable evidence-based sources of medical information may help counteract this.[21] More research is needed to inform this process.
- Medico-legal reform. Doctors have to develop forms of intelligent accountability that enable them to work in the best interest of patients without the fear of unfair penalty if an error is made unintentionally and in good faith.[10] This has to be seen as scrupulously fair, and probably should be governed external to professional control, to gain the trust of the community.
- Medical parsimony should be part of every doctor's critical thinking. This will require continuous education by strong role models from the beginning of medical training onwards.
- Performance indicators are almost exclusive directed at what doctors do, not at what they do not do.[25] However, they should also reflect parsimony. Comparisons between clinics or hospitals can identify overuse of diagnostic and treatment options. Doctors seem to be willing to reduce overuse by learning from comparison with colleagues on efficient use of resources.[26]

Policy makers face the challenge of dealing with a continuous growth of health care demand with a paucity of well-trained medical staff and limited financial resources. Part of this growth can be explained by excessive use of resources. Counter intuitive as it may be, to stop the growth of medical overutilization, more than anything else, investments in an optimal patient-doctor relationship are needed. Only then the art of parsimony can be practised.

Box 1. Medical Parsimony: Problems and Solutions

1. *Doctors create disease and practice defensive medicine; Continuous education of students and doctors about harm by overuse. Reconsider the position in guideline committees of medical opinion leaders tied to pharmaceutical companies. Doctors and patients together need to be actively involved in the creation of intelligent accountability.*
2. *Increased difficulty to deal with uncertainty; Doctors have to be authentic and consistent in their information and management. Doctors should be well trained in risk communication.*
3. *The societal claim for perfect health; Guidelines need to clearly state the boundaries of where evidence ends and wisdom begins and if possible include numbers needed to treat and harm. Doctors have to invest time to explain patients the limitations of medicine and the chances on harm from testing or treatment; this will only work in relations with trust.*
4. *A market driven organization of health care; Restrict pay for performance to evaluated care. Create incentives for doctors and health care teams that demonstrate high quality of care with low consumption.*
5. *Inability to built trust between patient and doctor; Research whether trust in health care teams is as effective as trust in individual doctors. Evaluate the use of social media and internet networking to built trust in modern ways. Building trust takes time; prevent downsizing of actual consultation time.*

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Summary

This thesis addressed the suboptimal control of hypertension, focussing on a new type of office measurement that could improve diagnosis of hypertension and on the use of predictors of treatment response to different classes of antihypertensive medications.

In Chapter 1 the rationale and objectives of this thesis are described. Even though multiple effective and affordable medications to treat hypertension exists and the relevance of adequate treatment is without debate hypertension control remains suboptimal. Guidelines were developed to help general practitioners to improve this suboptimal control. However, it is unclear if the content of these guidelines actually is translated to changes in daily general practice.
In this thesis we describe our study of two different strategies to improve hypertension control. First of all we studied a new type of office blood pressure measurement (OBPM). OBPM is subject to different types of measurement error and often overestimate true blood pressure status. Blood pressure measurements outside the office using 24-hour ambulatory blood pressure measurement (24-hour ABPM, automated measurements at regular intervals with device coupled to patient) or home blood pressure measurement (HBPM, protocol guided self measurement at home) are more reliable than OBPM but both come with several disadvantages. Second, we studied whether personalised medicine could be used in the treatment of newly diagnosed hypertensive patients without cardiovascular co-morbidity. So far data on this subject were inconclusive. While some results suggested that patient characteristics like age, sex and plasma renin predict the response to different classes of antihypertensive medication, others do not. In our view, several, relevant methodological and epidemiological limitations of these previous studies exist.

The objectives of these thesis were:

1. *To study the impact of guideline revisions on the process and outcome of hypertension management in primary care*
2. *To validate the concept of a 30 minute serial automated office blood pressure measurement (AOPBM) in a primary care population using an ambulatory blood pressure measurement device.*
3. *To identify patient characteristics that predict blood pressure response to two classes of antihypertensive drugs, each interfering with a different pathophysiological pathway of hypertension.*

In chapter 2 we describe results of a descriptive study on the impact of the Dutch guideline on hypertension management and two subsequent revisions on the process and outcome of hypertension management in general practice. Three cohorts of patients were defined, each managed during a period with a different version of the guideline available. The mean age of patients in these cohorts rose from 55 years (1992-1996) to 60 years (2004-2006). Mean blood pressure at initiation of treatment remained similar (175-179/99-106 mmHg).

The relative two year systolic and diastolic blood pressure decline (13.3 – 15.7% systolic) differed only modestly between cohorts. Mean two year follow up blood pressure ranged from 148-151/85-89 mmHg. The percentage of patients with three or more antihypertensive drugs remained equal (22-23%). In agreement with revisions in the guidelines, the use of diuretics as first-choice drugs increased significantly from the first to the last cohort. We concluded that general practitioners achieve substantial and prolonged blood pressure reduction. However, guideline revisions do not seem to influence the amount of reduction, despite clear formulation of stricter treatment goals.

Chapter 3 presents data of a method comparison study between blood pressure measured with sitting 30-minute AOBPM compared to standardised OBPM and data on the reproducibility of 30-minute AOBPM. Mean 30-minute AOBPM readings were 8/3 mmHg lower than standardized OBPM readings. The mean difference and standard deviation of the difference (SDD) between repeated 30-minute AOBPMs (mean difference = 3/1mmHg, 95% CI = 1 to 5/0 to 2mmHg; SDD 10/5 mmHg) were lower than those of standardised OBPM (mean difference = 6/2mmHg, 95% CI = 4 to 8/1 to 4mmHg; SDD 11/6 mmHg). In conclusion, these results suggested that 30-minute AOBPM better reflects true blood pressure status than standardised OBPM and with better reproducibility.

Next, in chapter 4 we describe our study of the agreement between sitting 30-minute AOBPM and daytime ABPM. Mean systolic and diastolic blood pressures differed 0 to 2 mm Hg respectively (with limits of agreement between between -19 and 19 mm Hg for systolic and -10 and 13 mm Hg for diastolic blood pressures) between 30-minute AOBPM and daytime ABPM. Both 30-minute AOBPM and daytime ABPM classified normotension, whitecoat hypertension, masked hypertension, and sustained hypertension equally. We concluded that 30-minute AOBPM agreed well with daytime ABPM and had the potential to detect white-coat and masked hypertension.

Chapter 5 reports on a similar study as described in chapter 4 but in a different set of patients and now with a comparison of supine 30-minute AOBPM and daytime ABPM. Systolic blood pressure differed -1 (-4 to 2), 17 (14 to 20) and 2 (-1 to 4) mmHg between supine 30-minute AOBPM and daytime, nighttime and 24-hour ABPM respectively (95% CI of error). Supine 30-minute AOBPM classified normotension; white coat hypertension; masked hypertension and sustained hypertension equal to daytime ABPM. We concluded that similar to sitting also supine 30-min AOBPM agreed well with daytime ABPM, but that we prefer a sitting measurement.

Chapter 6 describes the results of the NAMI study, a crossover design to identify patient characteristics that could predict the response to either a diuretic or angiotensin receptor blocker. We studied age, sex, menopausal state, plasma renin concentration, NT-proBNP, potassium, estimated glomeral filtration rate, urinary albumin, body mass index and waist circumference as potential predictors and used daytime ABPM as main outcome measure for the blood pressure response. Besides BMI -which was significantly related to the effect of valsartan (ß -0.63, p = 0.04) - the studied variables were not predictive for blood pressure response. Individual

systolic blood pressure responses ranged from an increase by 18 mmHg to a decrease of 39 mmHg. In conclusion, we did not find clinical relevant predictors that could substantiate personalised hypertension treatment in uncomplicated essential hypertension. This conclusion does not support the British NICE hypertension guideline treatment algorithm were age is used as predictor for treatment response.

In chapter 7 we discuss the main findings of this thesis, address several methodological issues and point out clinical implications and future research.
With regard to 30-minute AOBPM we concluded that the first steps of validation were successful and that for assessment of true blood pressure status this type of measurement can be used in daily practice. To substantiate implementation in daily practice study on the perception of patients and health care staff about the use, feasibility and patient friendliness of 30-min AOBPM compared to HBPM and daytime ABPM is needed. In addition, a clinical trial is required to study whether use of 30-min AOBPM in the diagnostic workup of patients with elevated blood pressures is indeed cost-effective.
Results of our crossover study to identify potential predictors of the efficacy of antihypertensive medication points out that personalised medicine in patients with essential hypertension but without cardiovascular co-morbidity with the current knowledge is unlikely to be successful. In a systematic approach we have formulated what is needed for a potential predictor to be recognised as such and did we try to unravel what has caused the current contradictory results in research on predictors in hypertension treatment.
With our current knowledge we conclude that predicting response to different classes of antihypertensive treatment in patients with essential hypertension is not possible and that further research exploring this topic is of little use.
We therefore advocate physician driven best estimated guess for first choice treatment taking patient's context, co-morbidity, preferences and costs into account. Research to demonstrate whether searching for the best fit mono therapy versus direct start with combination treatment is needed.

We end this thesis with an Epilogue that puts the results of this thesis in the perspective of changes in society and the medical profession. Our research tried to contribute to reduction of overdiagnoses and overtreatment of hypertension. However, we have noticed that medico-legal changes, pay for performance in health care, focus on prevention, societal perception on health, autonomy and risk seems to put pressure on doctors to overdiagnose and overtreat rather than vice versa. In our essay we propose a change for the better.

Samenvatting

Dit proefschrift behandelt onderzoek dat kan bijdragen aan het verbeteren van de zorg voor patiënten met een hoge bloeddruk. We rapporteren over een nieuwe manier van bloeddruk meten in de huisartspraktijk die de diagnostiek van hypertensie kan verbeteren. Daarnaast beschrijven we of er patiëntkenmerken bestaan die de respons op twee verschillend werkende bloeddrukverlagende medicijnen kunnen voorspellen. Hiermee zou de behandeling van hoge bloeddruk aanmerkelijk geoptimaliseerd kunnen worden.

In Hoofdstuk 1 geven we een onderbouwing voor de geformuleerde doelen en de verrichte onderzoeken zoals beschreven in dit proefschrift. Het is uitvoerig bekend dat een aanzienlijk deel van de mensen met hypertensie onvoldoende behandeld wordt. Er zijn richtlijnen over hypertensie opgesteld onder meer om deze onderbehandeling te voorkomen. Het is echter niet duidelijk wat de invloed van deze richtlijnen op het handelen van huisartsen is.
Bij het meten van de bloeddruk in de huisartspraktijk is door verschillende soorten van meetfouten vaak sprake van overdiagnostiek van hypertensie. Een 24-uurs bloeddrukmeting, waarbij een meter die de patiënt permanent bij zich draagt twee tot vier keer per uur automatisch de bloeddruk meet, of het op geprotocoliseerde wijze door de patiënt zelf een week lang meten van de bloeddruk thuis, geven een betrouwbaarder beeld van de ware bloeddruk van de patiënt dan een gewone praktijkmeting. Echter, beide meetmethoden kennen een aantal beperkingen en daarom hebben we een nieuwe meetmethode gevalideerd voor gebruik in de huisartspraktijk.
Tenslotte hebben we onderzocht of het mogelijk is om behandeling op maat te starten bij patiënten met een terecht gestelde diagnose hypertensie. Voorgaand onderzoek op dit terrein resulteerde in tegenstrijdige bevindingen. Sommige studies suggereren dat leeftijd, geslacht en plasma renine de reactie op verschillende soorten antihypertensiva kunnen voorspellen, maar weer andere studies laten het tegendeel zien. Omdat de meeste van de studies behoorlijke methodologische beperkingen hadden en slechts beperkt of niet vertaalbaar bleken naar de populatie van mensen met hoge bloeddruk die bij de huisarts komen, hebben we zelf een studie naar mogelijke voorspellers verricht.

Dit proefschrift heeft dan ook de volgende doelstellingen:

1. *Bestuderen van de invloed van richtlijnen op het proces en de uitkomsten van hypertensiebeleid in de huisartspraktijk*
2. *Valideren van een 30 minuten, seriële, automatische praktijkbloeddrukmeting (30-min APBDM), gemeten in de huisartspraktijk met een 24-uurs bloeddrukmeter*
3. *Identificeren van patiëntkenmerken die de bloeddruk respons op twee verschillende soorten bloeddrukverlagende medicijnen, elk met een eigen pathofysiologisch werkingsmechanisme, kunnen voorspellen*

In Hoofdstuk 2 geven we de resultaten weer van een beschrijvende studie naar de impact van de eerste Nederlandse huisartsenrichtlijn over hypertensie en de twee daaropvolgende revisies op het proces en de uitkomst van hypertensiebeleid in de huisartspraktijk. We definieerden 3 cohorten van nieuw gediagnosticeerde patiënten steeds in de periode van 1 jaar na het verschijnen van de richtlijn tot aan de introductie van een nieuwe revisie. De gemiddelde leeftijd van patiënten in deze cohorten steeg van 55 jaar in het eerste cohort (1992-1996) tot 60 jaar in het derde cohort (2004-2006). De gemiddelde bloeddruk waarop met medicatie gestart werd verschilde niet significant tussen de drie cohorten (175-179 / 99-106 mmHg). Ook de procentuele bloeddrukdaling na 2 jaar behandelen verschilde weinig tussen de cohorten (variërend van 13,3 tot 15,7% systolisch). De gemiddelde bloeddruk na 2 jaar was 148 – 151 / 85-89 mmHg. Het percentage patiënten met drie of meer antihypertensiva bleef vrijwel gelijk (22-23%) in de 3 cohorten. Passend bij het veranderd advies in de gereviseerde richtlijnen nam het gebruik van diuretica als 1e keus medicatie significant toe. Wij concludeerden dat huisartsen en patiënten in staat zijn om klinisch relevante en aanhoudende bloeddrukverlaging te bereiken. Echter de twee richtlijn revisies lijken de mate van bloeddrukverlaging niet te verbeteren ondanks beter geformuleerde en strengere behandeldoelen.

Hoofdstuk 3 rapporteert over onderzoek naar de overeenkomst tussen zittend 30-min APBDM in vergelijking met een gestandaardiseerde praktijkbloeddrukmeting en naar de reproduceerbaarheid van 30-min APBDM. De gemeten 30-min praktijkbloeddruk bleek gemiddeld 8/3 mmHg lager dan bij een gestandardiseerde praktijkbloeddrukmeting. Het gemiddelde verschil en de standaard deviatie van het verschil (SDD) tussen twee opeenvolgende 30-min APBDM's (3/1 mmHg, 95% CI 1 tot 5/0 tot 2 mmHg; SDD 10/5mmHg) was kleiner dan tussen twee opeenvolgende gestandaardiseerde praktijkmetingen (6/2 mmHg, 95% CI 4 tot 8/1 tot 4 mmHg; SDD 11/6 mmHg). We concludeerden hieruit dat 30-min APBDM beter de ware bloeddruk status van een patiënt weergeeft en beter reproduceerbaar is dan een gestandaardiseerde praktijkmeting.

Vervolgens geven we in Hoofdstuk 4 de resultaten weer van de vergelijking tussen zittend 30-min APBDM en de gemiddelde dagwaarde van een 24-uurs bloeddrukmeting. Het gemiddelde verschil tussen beide methoden was respectievelijk 0 en 2 mmHg voor de systolische en diastolische bloeddruk (met "limits of agreement" tussen -19 en 19 mmHg systolisch en -10 en 13 mmHg diastolisch). Patiënten werden zowel door een zittend 30-min APBDM als de dagwaarde van de 24-uursmeting vergelijkbaar geclassificeerd in 4 soorten bloeddrukcategorieën (normotensief, witte jassen hypertensie, gemaskeerde hypertensie en structurele hypertensie). Wij concludeerden uit dit onderzoek dat 30-min APBDM goed overeenkomt met de dagwaarde van een 24-uurs meting en dat het de potentie heeft om witte jassen hypertensie en gemaskeerde hypertensie op te sporen.

Hoofdstuk 5 beschrijft tenslotte een vergelijkbaar onderzoek als in hoofdstuk 4 maar nu met de 30-min APBDM liggend uitgevoerd. De systolische bloeddruk verschilde -1 (-4 tot 2), 17 (14 tot 20) en 2 (-1 tot 4) mmHg tussen liggend 30-min APBDM en respectievelijk de dagwaarde, de nachtwaarde en het 24-uurs gemiddelde van een 24-uurs bloeddrukmeting (95% BI).

De diastolische waarden vertoonden een vergelijkbaar beeld. Patiënten werden zowel door liggend 30-min APBDM als de dagwaarde van de 24-uursmeting vergelijkbaar geclassificeerd in 4 soorten bloeddrukcategorieën (normotensief, witte jassen hypertensie, gemaskeerde hypertensie en structurele hypertensie). Onze conclusie was dat vergelijkbaar met zittend ook liggend 30-min APBDM goed overeenkomt met de dagwaarde van de 24-uursmeting, maar dat zittend meten onze voorkeur heeft.

In Hoofdstuk 6 rapporteren we over de resultaten van de NAMI-studie, een cross-over onderzoek met als doel om patiëntkenmerken te achterhalen die de respons op een diureticum (hydrochloortiazide) of een angiotensine receptor antagonist (valsartan) zouden kunnen voorspellen. We bestudeerden leeftijd, geslacht, menopauze, plasma renine concentratie, NT-pro BrainNatriureticPeptide, kalium, nierfunctie, urine albumine, body mass index (BMI) en middelomtrek als mogelijke voorspellers. De bloeddruk respons bepaald met de dagwaarde van de 24-uurs meting was de primaire uitkomstmaat. De intra-individuele systolische bloeddruk respons varieerde tussen een daling van 39 mmHg en een stijging van 18 mmHg. BMI bleek in bescheiden maar significante mate de respons op valsartan te voorspellen (ß -0,63; p = 0,04), de overige variabelen bleken niet voorspellend. In onze studie vonden we onvoldoende aanwijzingen voor het gebruik van patiëntkenmerken bij het optimaliseren van de behandeling van ongecompliceerde essentiële hypertensie. Deze resultaten zijn niet in overeenstemming met de theoretische onderbouwing voor het behandelschema van de Britse NICE richtlijn over hypertensie waarbij leeftijd wordt gebruikt als voorspeller van de behandeling.

Hoofdstuk 7 staat in het teken van een kritische beschouwing van de beschreven resultaten in dit proefschrift en beschrijft tevens de klinische implicaties en mogelijkheden voor vervolgonderzoek. Met betrekking tot 30-min APBDM concluderen we dat deze meetmethode valide lijkt om de ware bloeddrukstatus van de patiënt in de huisartspraktijk te kunnen bepalen. Voor de implementatie in de dagelijkse huisartspraktijk is een haalbaarheidsstudie wenselijk waarbij zowel het perspectief van zorgverleners en patiënten over gebruiksgemak en toepassing vergeleken wordt met thuismetingen en 24-uursmetingen. Daarnaast zal een trial met als doel de kosteneffectiviteit vast te stellen van het gebruik van 30-min APBDM ten opzichte van nu gebruikelijke zorg in het diagnostisch proces van hoge bloeddruk wenselijk zijn. De resultaten van de NAMI studie suggereren dat op de patiënt toegesneden starten met antihypertensieve therapie bij ongecompliceerde hypertensie niet mogelijk is met de door ons bestudeerde set van mogelijke voorspellers van het effect van behandeling. We hebben een vijftal voorwaarden geformuleerd waaraan een variabele moet voldoen om als succesvol voorspeller beschouwd te kunnen worden. Aan de hand van deze voorwaarden proberen we de resultaten van de NAMI studie te duiden en een verklaring te geven voor de huidige tegenstrijdige resultaten op het gebied van onderzoek naar voorspellers voor de behandeling van hypertensie. Met de huidige stand van kennis concluderen we dat het niet zinvol lijkt om vervolgonderzoek te verrichten naar de voorspellende waarde van de door ons bestudeerde variabelen. Voor de dagelijkse praktijk pleiten we er daarom voor om bij de eerste keus voor een antihypertensivum bij ongecompliceerde hypertensie zonder cardiovasculaire comorbiditeit de context van de patiënt, zijn of haar voorkeur en de medicatiekosten mee te wegen. Daarnaast lijkt het zinvol

om te bestuderen of het kosteneffectief is om bij een patiënt middels “trial and error” het best werkende eerste keus middel te vinden dan wel om direct te starten met combinatietherapie.

Dit proefschrift wordt afgesloten met een Epiloog waarin we de resultaten van ons onderzoek proberen te plaatsen in de context van recente veranderingen in de maatschappij en de medische professie. Ons onderzoek probeert bij te dragen aan een reductie van overdiagnostiek en overbehandeling van hypertensie. Echter, wij vinden dat veranderingen in medische wetgeving, verkeerde marktwerking in de zorg, een overschatting van de voordelen van preventie en het huidige maatschappelijke perspectief op maakbaarheid van gezondheid, individualisering en omgaan met risico’s druk op artsen uitoefent om juist overmatig te diagnosticeren en behandelen. In deze epiloog beschrijven we een aantal manieren om dit te voorkomen.

Dankwoord

En dan nu een veel gelezen stukje proefschrift. Daarom heb ik tussen de regels door de kern van mijn onderzoek subliminaal verpakt. Lees het en je weet het, al is het maar onbewust.
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Allereerst wil ik alle deelnemende patiënten bedanken voor hun bijdrage aan ons onderzoek. Je moet het maar willen, eerst een half uur stil blijven zitten of liggen zonder iemand om mee te kletsen om daarna ook nog eens 24 uur lang door zo'n bloeddrukmeter lastig gevallen te worden. Of nog erger: binnen 18 weken 6 keer (!!) zo'n 24uurs meting.

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En ik maar denken dat internisten droge, vervelende betweters waren. Uit mijn n=3 ervaringsstudie heb ik geconcludeerd dat dit geheel niet het geval is, ook al blijven het natuurlijk wel een beetje vreemde vogels:

Theo, je kennis over bloeddruk is indrukwekkend en met jouw ervaring was ook het historisch perspectief nooit ver weg. Ik zal onze dinsdagochtendsessies met Carel gaan missen, er was naast serieus werken altijd wat te lachen. Ik vind het geweldig dat je plaatsvervangend rector magnificus wilt zijn tijdens de verdediging van mijn proefschrift.

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Beste Jaap, jij bent een generalist met passie voor patiënten en kennis van veel. Op je poli zag ik dat je eigenlijk huisarts bent. Echter zoals jij bloeddruk snapt, gaat mij nooit lukken. Je beheerst de kunst van het afdwalen als geen ander, en je kon er mijn ongeduld wel eens mee tarten. Andersom leverde het afdwalen ook vaak relativiteit, humor of een nieuw idee op. Ik kon altijd bij je terecht, dank je wel daarvoor.

Beste Carel, lieve Carel, ik schrijf dit in de wetenschap dat je er waarschijnlijk niet meer bent als ik ga promoveren. Je bent een vaderfiguur voor mij geweest en mijn verdriet is groot.
Gelukkig is de weg zelf de bestemming. Onze weg was vol mooie, inspirerende en meestal

vrolijke herinneringen. Van ellenlange discussies over CVRM registratie, tot bier drinken op WONCA Singapore, van samen racefietsen langs de Ijssel of in de Elzas, tot samen nascholing geven of een modern KetenzorgInformatieSysteem ontwikkelen. Je nimmer aflatende nieuwsgierigheid en open staan voor anderen en hun ideeën was jouw voeding voor je rol als wetenschapper. Meer nog dan wetenschapper was je volgens mij mentor en onderwijzer. Jij leert me –en je bent me daarin ver vooruit- om werkelijk te luisteren, om bescheiden te kunnen zijn, niet te snel te oordelen, om het naadje van de kous te weten (en soms dus even te vertragen i.p.v. te versnellen) en om je te blijven verwonderen. Wat ga ik je missen.

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About the author

Mark Christian van der Wel was born on the 1st of August, 1974 in Nieuw-Lekkerland and grew up in Ermelo until he started his university studies in Nijmegen. After he completed his Masters degree in Biomedical Health Sciences at the Radboud University Nijmegen Medical Centre (RUNMC) in 1998 he decided to continue his “education permanente” by becoming a medical doctor. He completed his training in the year 2000 finishing with a 3 month residency in Rubya, Tanzania. He then worked in several health care settings before he started in 2003 with his family medicine residency training which from 2004 onwards he combined with research. The subject of his research project was cardiovascular risk management (CVRM) with a focus on innovations in hypertension management. He became a family physician in 2006 and after one year of combining work as a locum in the practice of Carel Bakx in Doesburg and Marie Jose Metz in the multidisciplinary health centre Wijkgezondheidscentrum Lindenholt, he since then continued to work in Lindenholt. The health centre is one of nine that form the Academic Nijmegen Practice Based Research Network (NMP).

Together with Carel Bakx he intiated a ZonMw funded project to implement the “Zorgstandaard Vitale Vaten”. This project formed the basis for the new CVRM programs of the zorggroep Arnhem (Huisartsenzorg regio Arnhem) and Nijmegen (Organisatie voor Chronische Eerstelijns Zorg). Mark is now member of the working group CVRM of the OCE.
In 2010, together with Tim olde Hartman (The Netherlands), Greg Irvin (UK) and Karen Falloon (New Zealand) he has founded MINERVA (Montreal INitiative de Education et Recherche Voacationale Academique) to build an international network that stimulates and facilitates combined family medicine residency and PhD training programmes. He chaired the scientific committee of the annual congress of the Dutch College of General Practitioners in 2012 which dealt with the future of family medicine.

Mark and his girlfriend Esther have a beautiful daughter Ella.